Chemotherapy related cognitive impairment in colorectal cancer patients

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DEDICATION

To my parents, Freda and Leon Dwek. Special thanks to mum for her continuous and unwavering belief in me.

DECLARATION

FEBRUARY 2019

Signed declaration

I, Marie-Rose Dwek, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. I grant powers of discretion to the University Librarian to allow the thesis to be copied in whole or in part without further reference to the author. This permission covers only single copies made for study purposes, subject to normal conditions of acknowledgement.

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ABSTRACT

The aim of this thesis was to establish the extent of objective and subjective cognitive impairment in patients with resected colorectal cancer who required adjuvant chemotherapy treatment compared to those who did not. Specific objectives were to i) identify the extent and nature of cognitive impairments ii) explore changes in cognitive function over time and iii) identify relationships between cognitive function and psychosocial outcomes. The qualitative study aimed to further evaluate the lived experience of patients diagnosed with colorectal cancer undergoing adjuvant chemotherapy treatment over time.

A mixed method longitudinal comparative study was conducted to address these objectives'. A convenience sample of 98 patients with resected colorectal cancer were recruited from 5 London based NHS Trusts. Participants consisted of 63 patients scheduled for 6 months adjuvant chemotherapy treatment and 35 patients who did not require any further systemic treatment. Each participant completed a neuropsychological test battery and psychosocial self-report questionnaires and/or a semi structured interview prior to the start of the treatment, during and 3 months after the end of treatment.

The results showed objective cognitive impairment in a statistically significant ($p<0.01$) proportion (ranging from 42% -60% depending on the definition used) of participants in both patient groups at all assessment time points (from before chemotherapy treatment to 3 months after it finished); with very little change over time (small to medium effect sizes). Verbal memory, motor function and executive function were most affected in both groups. There was no significant association between overall objective cognitive impairment and fatigue, anxiety/depression or quality of life. All psychosocial outcomes were all highly correlated with cognitive symptoms at every time point. Cognitive symptoms (such as memory lapses and word findng problems) were also reported at every time point by participants in the interview study, which corroborated the results of the quantitative analysis.

The results of this study address a gap in the literature and highlight the extent of cognitive impairments in patients with colorectal cancer. The clinical implications of the findings are discussed.

LIST OF ABBREVIATIONS

A&E	Accident and emergency department
AJCC	American Joint Committee on Cancer
Barts	Barts and the London NHS Trust
BC	Breast cancer
BVRT	Benton Visual Retention Test
CI	confidence interval
CIPN	Chemotherapy-induced peripheral neuropathy
CNS	Colorectal Nurse Specialists
COWA	The Controlled Oral Word Association Test
CRC	colorectal cancer
CRCI	Chemotherapy-related cognitive impairment
CT	Chemotherapy treatment
CT	Computerised Tomography scan
DVT	Deep vein thrombosis
EF	Emotional functioning
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life core questionnaire
FACT Cog	The Functional Assessment of Cancer Therapy—Cognitive Function Instrument
FACT Cog Oth	FACT comments from others
FACT Cog PCA	FACT perceived cognitive abilities subscale
FACT Cog PCI	FACT perceived cognitive impairment subscale
FACT Cog QoL	FACT quality of life
FACT C	Functional Assessment of Cancer Therapy-Colorectal
FACT C: EWB	FACT Emotional well-being

FACT C: FWB	FACT Functional wellbeing
FACT C: PWB	FACT Physical wellbeing
FACT C: SWB	FACT Social well-being
FACIT Fatigue	Functional Assessment of Chronic Illness Therapy –fatigue
FOBT	the faecal occult blood test
GP	family doctor
GP dom	Grooved Pegboard Test, dominant hand
GP non dom	Grooved Pegboard Test, non-dominant hand
HADS:	Hospital and Anxiety Scale
HRQoL	health related quality of life
HVLT R	Hopkins Verbal Learning Test – Revised
ICCTF	International Cognition and Cancer Task Force
Imperial	Imperial NHS Trust
MCI	mild cognitive impairment
MDT	multi-disciplinary team
MLM	Multilevel modelling
MoCA	Montreal Cognitive Assessment
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
NP	neuropsychological
OCI	Objective cognitive impairment
OR	odds ratio
PF	physical functioning
POCD	post operative cognitive dysfunction
PPI	patient and public involvement
QoL	quality of life
R&D	Reasearch and Development

Royal Free	Royal Free London NHS Foundation Trust
SCI	Subjective cognitive impairment
SD	Standard Deviations
SE	Standard Error
SF	social functioning
SCI	subjective cognitive impairment
SDMT	Symbol Digit Modalities Test
T1	After surgery and prior to chemotherapy treatment/similar point in time
T2	Mid chemotherapy treatment/3 months after T1
T3	3 months after last scheduled chemotherapy treatment/6 months post T2
TMT A	Trail Making Test (Part A)
TMT B	Trail Making Test (Part B)
TNM	Tumour Node Metastes system
UCLH	University College London Hospitals NHS Foundation Trust
West Mid	West Middlesex University Hospital NHS Trust
UK	United Kingdom
1.5 SD criteria	z scores of ≤−1.5 SD below the normative mean score for two or more NP tests
2 SD criteria	z scores of ≤−2.0 SD below the normative mean score for just one NP test

Chapter 1: Colorectal cancer, treatment and side effects

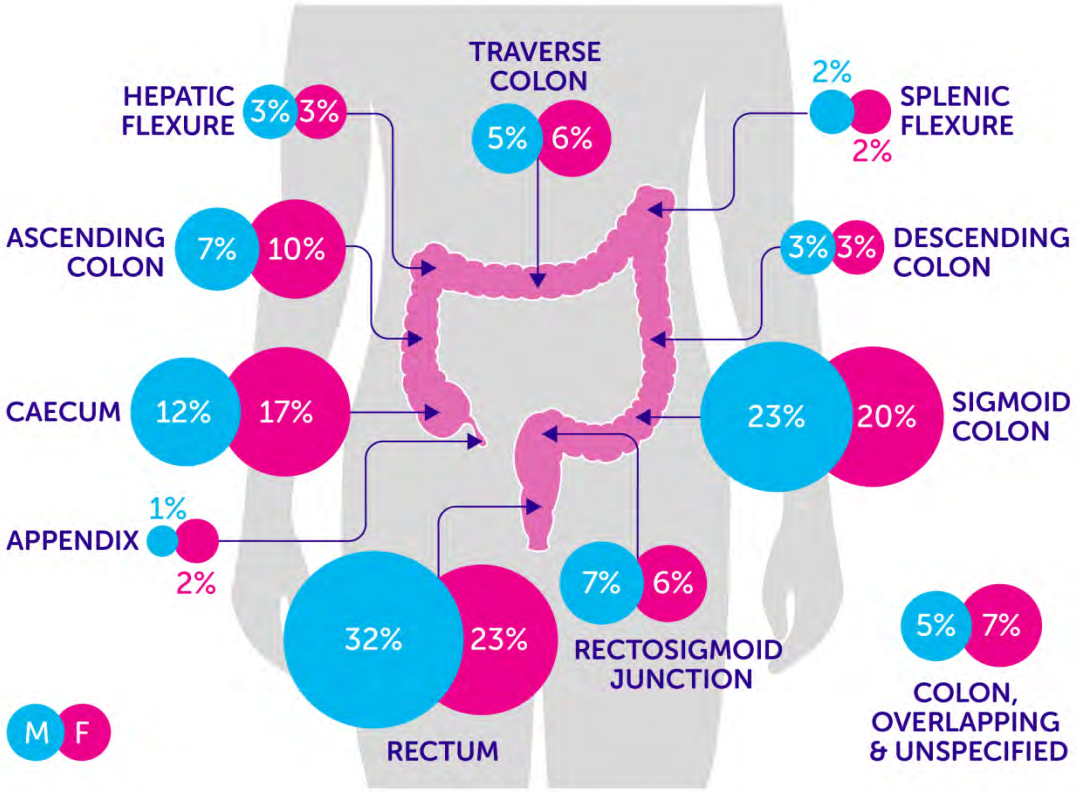
1.1 Chapter Introduction

This chapter provides relevant background information relating to colorectal cancer (CRC), available treatments and possible biological and psychological side effects. The chapter begins by providing some key statistics pertaining to the prevalence of CRC in the United Kingdom (UK), its key features and how it is detected and staged. It then highlights the available treatment options, with a focus on surgery and adjuvant chemotherapy treatment. The chapter concludes with a description of the most frequently observed side effects associated with colorectal surgery and chemotherapy.

1.2 CRC

Commonly known as bowel cancer, CRC includes both cancer of the colon (large bowel) and cancer of the rectum, accounting for 66% and 34% of CRC respectively (Cancer Research UK, 2015); with a gender distribution of 55% (22,800) diagnosed in males and 45% (18,400) in females (Cancer Research UK, 2014). Figure 1.1 shows a further breakdown of CRC locations and the percentage occurrence within gender.

Figure 1.1 Pictorial representation of CRCs percentage distribution by anatomical site and gender (Cancer Research UK, with date of source)



At approximately 5ft long, the colon is the first four sections of the large bowel, (as shown in Figure 1.2) and the fifth section is the rectum, all of which can develop cancer:

1. Ascending colon runs up the right side of the abdomen. It is connected to the small intestine by a section of bowel called the caecum;
2. Transverse colon runs across the body from right to left, under the stomach;
3. Descending colon runs down the left side of the abdomen; and
4. Sigmoid colon resembles an S-shaped bend that joins the descending colon to the rectum (Cancer Research UK, 2015).
5. Rectum

Figure 1.2 Diagram showing the parts of the colon and rectum in the bowel

As can be seen in Figure 1.2 the rectum starts in the last part of the large bowel and is where rectal cancer may develop.

There are many forms of CRC, including adenocarcinomas, gastrointestinal carcinoid tumours, gastrointestinal stromal tumours, leiomyosarcomas and primary colorectal lymphomas (Appendix A). However, 95% of all diagnosed CRCs are adenocarcinomas, a type of cancer, which often begins as small polyps or growths ("adenomas") in the inner lining of the colon or rectum and then spread to other layers (as described in Section 1.6). The other tumour types listed above are much rarer cancers, which are treated differently from adenocarcinomas of the colon or rectum and are outside the remit of this thesis. The focus of this thesis is adenocarcinomas. All further references to CRC in this thesis pertain to adenocarcinomas.

1.3 Detecting CRC

Signs and symptoms of CRC may include blood in the stool, a change in bowel habits (e.g. diarrhea, constipation, or feeling that the bowel does not empty all the way); unexplained weight loss, or feeling continually fatigued (National Cancer Institute,

2015). In such cases, a person's family doctor (GP) would normally refer them for further testing.

Symptoms can sometimes be so severe that a person goes directly to their local hospital's accident and emergency department (A&E). Approximately 24% of CRC cases are diagnosed because of patients being admitted to hospital via emergency presentations (NCIN, 2015).

However, some people may have no symptoms at all, or they may experience very subtle symptoms, which do not make them ill. This variance in symptom presentation and disease detection led to the implementation of the UK's National Health Service (NHS) bowel-screening programme. The programme's primary goal was to reduce mortality rates by detecting CRC in asymptomatic people at an early stage (Jones et al, 2009), to allow earlier treatment. Research has shown that screening reduces mortality through the removal of precancerous polyps and by identifying earlier-stage cancers (Hardcastle et al, 1996; Kronborg, et al, 1996; Mandel et al, 1993).
Screening was first implemented in England in July 2006 for 60-69 year olds and has since been rolled out across the whole of the UK (Scottish Bowel Screening Programme; Bowel Screening Wales; Northern Ireland Bowel Screening Programme, NHS Screening Programme) with the age limit extended to 74. People older than 74 may also self-refer into the programme (Morris, Whitehouse, Farrell, Nickerson et al, 2012).

A screening kit, known as the faecal occult blood test (FOBT) is sent to all people aged between 60 and 74 biennially. Individuals use the kits at home and post a series of stool samples back to the NHS for testing. If any traces of blood are found in the submitted stools the individual is asked to undergo further testing (Cancer Research UK, 2015).

Research has shown that screening with the current FOBT reduces the risk of dying from CRC by approximately 25% in patients who have used the test (Hewitson et al, 2008). By October 2008, almost 2.1 million 60-69 year olds had been invited to participate in the screening programme; however only half of those people actually did so (Cancer Research UK, 2015). Tests were returned by 49.6% of men and 54.4% of women invited (Logan, Patnick, Nickerson, Coleman et al, 2012), and uptake varied by both age and level of deprivation (von Wagner, Baio, Raine, Snowball et al, 2011).

It remains unclear from the currently available data whether the screening programme will result in a greater rate of CRC survival as we do not know whether there are differences between people that participate in screening and those that do not, or if there are already significant differences in survival between these two groups.

1.4 Prevalence

CRC is the fourth most common cancer in the UK (Cancer Research UK, 2015) and the third most common in both genders, accounting for 13% of all male cancers and 11% of all female cancers (Office for National Statistics, 2013; ISD Scotland, 2013; Welsh Cancer Intelligence and Surveillance Unit, 2013; Northern Ireland Cancer Registry, 2013). It is the third most common cause of cancer death in the UK (lung being the most common), although it should be noted that mortality rates have been falling since the 1970s (Office for National Statistics, 2014; ISD Scotland, 2014; Northern Ireland Cancer Registry, 2013). In 2012, an estimated 1.36 million CRC cases were diagnosed worldwide, with varying incidence rates between countries. Overall reported incidence rates for CRC started to decline towards the end of the 1990s (Jones, Morris, Thomas, Forman et al, 2009) but have since risen following the introduction of the national bowel screening programmes.

1.5 Risk Factors

The contributing non-modifiable and modifiable risk factors associated with developing CRC include age, inherited genetic disorders, lifestyle and environment (National Cancer Institute, 2015). A detailed account of the evidence and reasoning for these factors is outside the scope of this thesis and therefore only the key risk factors have been listed in this section.

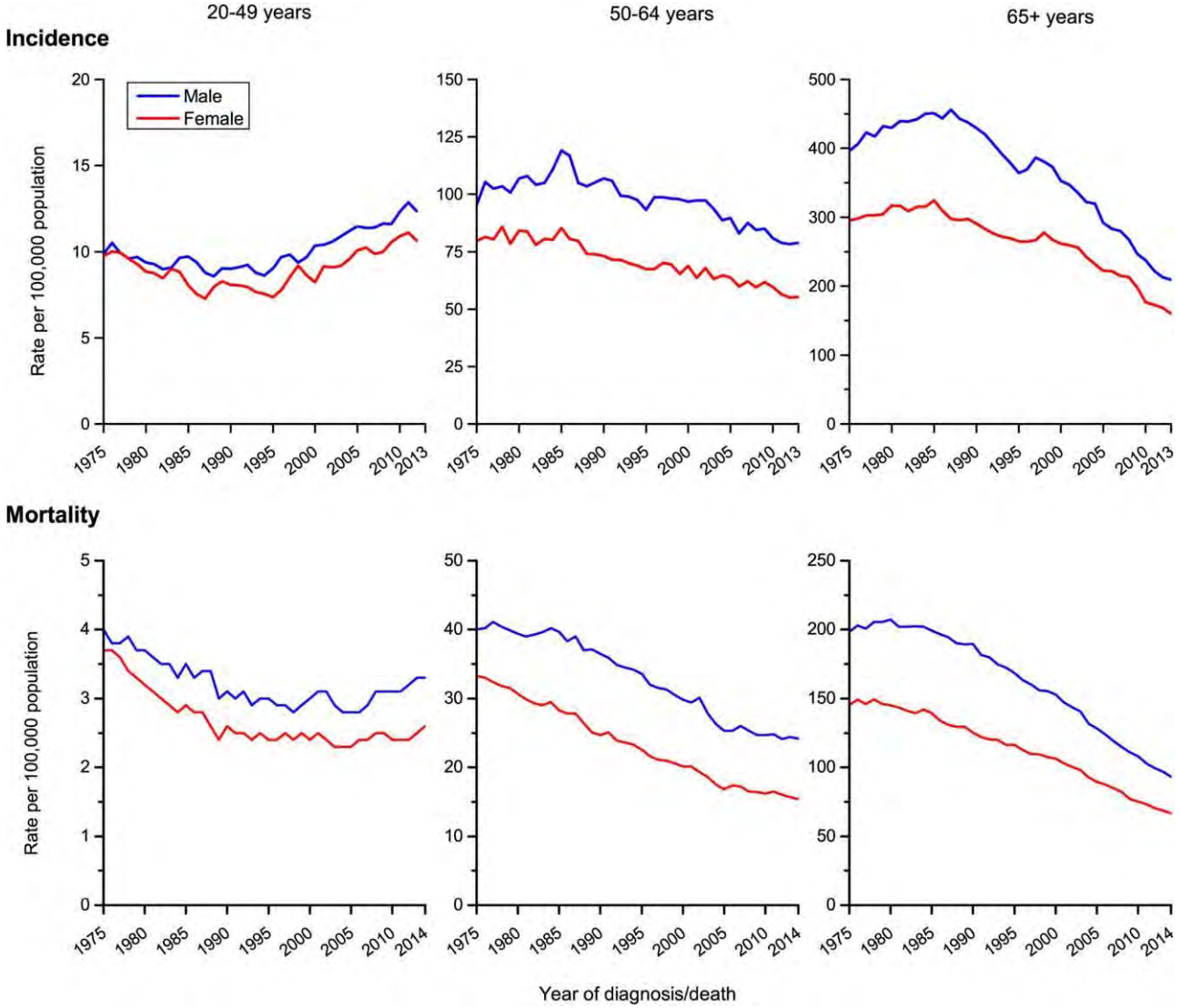
1.5.1 Non-modifiable risk factors:

Non-modifiable risk factors are those that the individual cannot control for and include age and hereditary factors.

1.5.1.1 Age

The likelihood of a CRC diagnosis increases progressively from the age of 40 and rises sharply after 50 (Ries, Harkins, Krapcho, Mariotto et al, 2006). Between 2009 and 2011, approximately 43% of CRC cases diagnosed in the UK were people aged 75 years and over and 95% were diagnosed in those 50 years and over (Cancer Research UK, 2015). However, a recent study (Siegel, Killer and Jemal, 2017) suggests that, this pattern is changing. Siegel et al (2017) reported that the incidence rates of CRC are rising in adults under 50 years old in America (Figure 1.3). The causes for this increase are still unknown, although factors that are believed to have contributed to it include increased rates of obesity, as well as changes in lifestyle patterns that have precipitated excess weight gain such as unhealthy dietary patterns and a sedentary lifestyle (Siegel, et al, 2017; Doubeni, 2014; Huxley, Ansary-Moghaddam, Clifton, Czernichow et al, 2009; Brownson, Boehmer and Luke, 2005; Ludwig, 2016; Nielsen & Popkin, 2003).

Figure 1.3 CRC Incidence and Mortality Trends by Age and Sex, United States, 1975-2014 (Siegel, Killer and Jemal, 2017).



1.5.1.2 Genetic disorders

Other non-modifiable risk factors include a family history of colon cancer and polyps (National Cancer Institute, 2015). Tubular and villous adenomas, neoplastic polyps found in the colon or rectum, are precursor lesions of CRC (Janout & Kollárová, 2001). An individual with a history of adenomas has an increased risk of developing CRC. It can take between 5 and 10 years for such adenomas to become malignant (de Jong Morreau, Nagengast, Mathus-Vliegen, et al, 2005; Davies, Miller, & Coleman, 2005), therefore early detection and removal reduces the risk of developing CRC (Grande, 2008).

People with a history of CRC or adenomatous polyps in one or more first-degree relatives are at increased risk of up to 20% (Skibber, Minsky, & Hoff, 2001), which is even stronger if the relative is younger than 60 years old (Haggar & Boushey, 2009) or if there is a history of CRC or adenomatous polyps in two or more first-degree relatives of any age (Boardman, Morlan, Rabe, Petersen et al, 2007). It is unclear why this is, but may be linked to inherited genes, shared environmental factors, or a combination of these (Haggar & Boushey, 2009).

Approximately 5-10% of CRCs are a consequence of recognised hereditary conditions (Jackson-Thompson, Ahmed, German, Lai et al, 2006) such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis CRC (HNPCC, otherwise known as Lynch Syndrome).

1.5.2 Modifiable risk factors

In contrast to non-modifiable risk factors, an individual could take steps to change the effect of a modifiable risk factor such as smoking or excessive alcohol intake.

1.5.2.1 Lifestyle

A substantial number of lifestyle factors may play an important role in the increased risk of developing CRC such as diet (Giovannucci, 2003) and lack of physical activity (Samad, Taylor, Marshall, & Chapman, 2005; Schnohr, Grønbæk, Petersen, Ole Hein, et al, 2005). Wolin and colleagues (2009) meta-analysis of 52 studies confirmed that there is an inverse association between physical actively and CRC in both men and women (i.e. the less physical activity the more CRC). Physical inactivity and excess body weight are also interrelated, such that the lack of physical activity in daily routines can also be attributed to the increased incidence of obesity in men and women, which is yet another factor associated with CRC (de Jong et al, 2005; Campbell, Cotterchio, Dicks, Parfrey et al, 2007).

Other factors that research has shown to play a role in the increased risk of developing CRC include long-term cigarette smoking (Chao, Thun, Jacobs, Henley et al, 2000; Verla-Tebit, Lilla, Hoffmeister, Brenner et al, 2006). Verla-Tebit and colleagues (2006) population based case-control study in Germany reported that when compared with non-smokers, there was an increased risk for smoking for 30 years or more (odds ratio (OR): 1.25, 95% Confidence Interval (CI): 0.90–1.75) and a significant risk increase for 40 or more pack-years of smoking (OR: 1.92, 95% CI: 1.13–3.28). The results of this study suggests that smoking for a long duration at a high cumulative dose increases the risk for CRC, particularly among women, and suggests that there is risk reduction after long-term smoking cessation (Verla-Tebit et al, 2006).

As with smoking, excessive alcohol consumption may also be associated with increased risk of developing CRC (Tsong, Koh, Yuan, Wang, et al, 2007). Tsong and colleagues

(2007) found that compared with non-drinkers, middle-aged Chinese individuals who drank seven or more alcoholic drinks per week had a 72% increased risk of CRC.

1.5.3 All risk factors

CRC can develop because of complex modifiable and non-modifiable interactions between several factors, which make establishing a clear etiology of the disease difficult. For example, the increased risk associated with overweight and obesity may reflect differences in metabolic efficiency (de Jong et al, 2005). Studies suggest that individuals who use energy more efficiently may be at a lower risk of developing CRC (Boyle & Langman, 2000). Similarly, individuals who drink large amounts of alcohol are at increased risk and they may have diets low in essential nutrients, making tissues susceptible to the formation of cancer (World Cancer Research Fund, 2007).

1.6 Diagnosis and staging of CRC

The National Institute for Health and Clinical Excellence (NICE) has published clinical guidelines for the diagnosis and management of CRC. Diagnostic investigations include a physical examination and imaging (usually a computed tomography (CT) scan), the results of which are subsequently discussed at colorectal multidisciplinary team meetings (MDTs) (consisting of oncologists, surgeons, specialist nurses, radiologists, histopathologists and the MDT coordinator) where decisions are made in relation to the staging, prognosis and management of the tumour.

Following a CRC diagnosis, the medical team will try to determine if the cancer has spread, and if so, how far. This process is known as 'staging'. Staging the cancer is determined by the size of the tumour and whether the cancer has spread to other parts of the body such as the liver or lungs (known as metastasis). It helps establish how

serious the cancer is and how best to treat it. Staging is reported to be the strongest predictor of survival for patients with CRC (Compton & Greene, 2004).

CRC survival is highly dependent upon the stage of disease at diagnosis and the earlier the stage at diagnosis, the higher the chance of survival (Haggar & Boushey, 2009). With survival rates of 90% reported for localised cases (Cancer Research UK, 2015), the sooner that CRC is diagnosed the better as there is a high probability that it can be cured when identified early (Winawer, Fletcher, Miller, Godlee et al, 1997; Winawer, Fletcher, Rex, Bond et al, 2003). In contrast to this, survival is significantly decreased for patients who have metastatic CRC (Gordon & Nivatvongs, 2007; Natarajan & Shuster, 2006). The estimated 5-year survival rates are less than 10% for patients who have metastatic disease that cannot be operated on. The tests and scans used to diagnosis CRC provide information about the clinical stage.

Although it is not always possible to stage the cancer definitively until after an operation to remove it, pre-surgery scans, provide a good indication of stage, often allowing treatment decisions to be made prior to surgery. It is important to note that the tissue removed during surgery may show a more advanced cancer (known as the 'pathologic' or 'surgical' stage), which will be different to the clinical stage. Therefore, once the specimens have been analysed in the laboratory the results are combined with the clinical stage to give a more accurate pathological stage.

The presentation of CRC is divided into three main clinical stages:

1. Early stage disease
2. Locally advanced disease with lymph node involvement
3. Metastatic disease with distant metastasis (Hassan, Advani & Alex, 2013).

There are various methods of staging CRC. In the UK, the most commonly used staging system is the Tumour Node Metastes system (TNM) which is also the most widely used system worldwide. Constantly being updated, it is now in its eighth version (since 1 January 2018) (Amin et al, 2017). Prior to January 2018, the Dukes system (detailed in section 1.6.2) was also widely used, but is now no longer referred to.

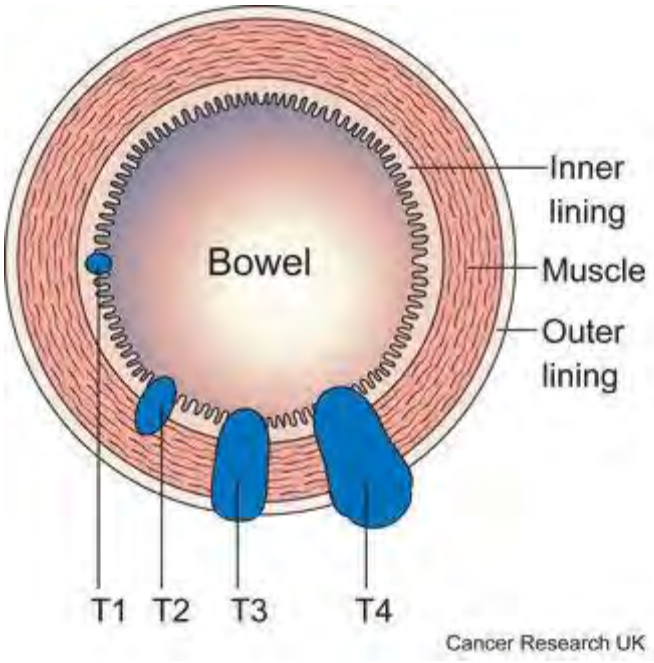
1.6.1 TNM Staging:

The TNM staging system, as defined by the American Joint Committee on Cancer (AJCC, 2017), describes the size and extent of the primary tumour (T), whether any lymph nodes contain cancer cells (N), and whether it has spread to another part of the body (M).

There are 5 stages of tumour size in CRC (see Figure 1.4):

- TX – primary tumour cannot be assessed due to lack of information
- T0 – there is no evidence of primary tumour
- T1 – the tumour is only in the inner layer of the bowel
- T2 – the tumour has grown into the muscle layer of the bowel wall
- T3 – the tumour has grown into the outer lining of the bowel wall; and
- T4 - the tumour has grown through the outer lining of the bowel wall and directly invades other nearby organs or structures and/or perforates visceral peritoneum. (The peritoneum is a membrane made up of two layers. One layer lines the cavity and the other layer lines the organs.)
    - T4a Tumour perforates visceral peritoneum
    - T4b Tumour directly invades other organs or structures.

Figure 1.4 Pictorial representation of TNM staging



There are three possible stages describing whether cancer cells are in the lymph nodes:

- NX – lymph nodes cannot be assessed due to lack of information
- N0 – there are no lymph nodes containing cancer cells
- N1 – 1 to 3 lymph nodes close to the bowel contain cancer cells
    - N1a – 1 lymph node contains cancer cells
    - N1b – 2 to 3 lymph nodes contain cancer cells
    - N1c – tumour deposits in the lymph drainage area of a primary carcinoma
- N2 – there are cancer cells in four or more nearby lymph nodes.
    - N2a – in 4 to 6 lymph nodes
    - N2 b – in 7 or more lymph nodes

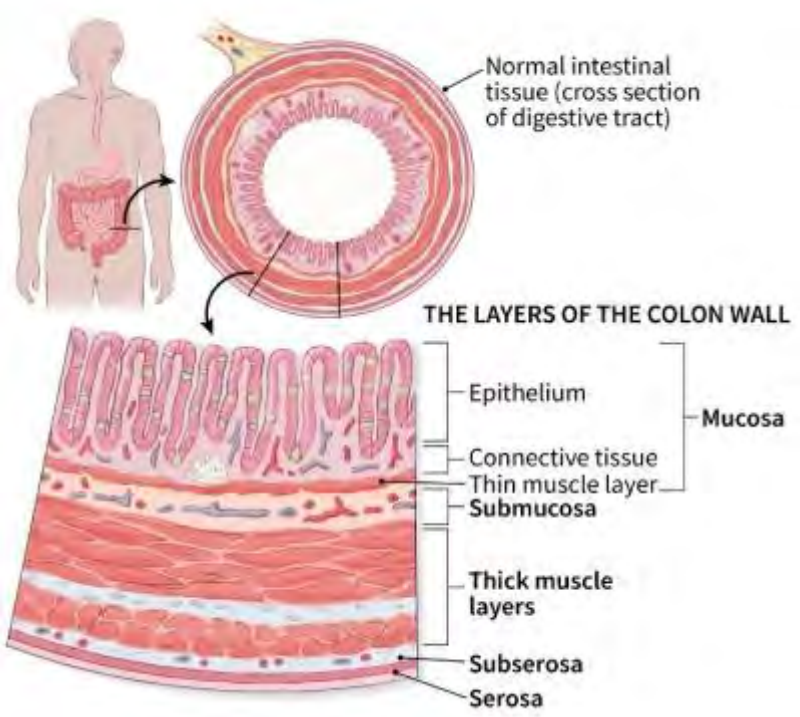
There are two stages of cancer spread (metastasis):

- M0 – the cancer has not spread to other organs
- M1 – the cancer has spread to other parts of the body.

- M1a – spread to just one organ (liver lung ovary non-regional lymph nodes)
- M1b – spread to more than one organ
- M1c – in the peritoneum with/without other organ involvement.

The T, N, and M values are taken together to determine the stage of the tumor and relate to its prognosis. They are initially recorded from the diagnostic tests (colonoscopy, CT scan and physical examination) prior to treatment and reported in the patient's medical record as documentation of the basis for treatment planning (Compton & Greene, 2004). Then once the tissue from the resected (i.e. surgically removed) colon and/or rectum has been examined (see figure 1.5), the CRC will be staged again (the pathological stage) and further treatment will be discussed at the MDT meeting.

Figure 1.5 Diagram of the layers found in the colon wall



Once patients' TNM categories have been determined after surgery (by examining the tissue removed during an operation), they are combined to assign the cancer a stage (BMJ, 2015) as set out in Table 1.1.

Table 1.1: The American Joint Committee on Cancer Staging System January 2018

Stage	T	N	M	Stage description
0	Tis	N0	M0	Earliest stage: also known as carcinoma in situ or intramucosal carcinoma (Tis). It has not grown beyond the inner layer (mucosa) of the colon or rectum.
I	T1 to 2	N0	M0	The cancer has grown through the muscularis mucosa into the submucosa (T1), and it may have grown into the muscularis propria (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II A	T3	N0	M0	The cancer has grown into the outermost layers of the colon or rectum but has not gone through them (T3). It has not reached nearby organs. It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II B	T4a	N0	M0	The cancer has grown through the wall of the colon or rectum but has not grown into other nearby tissues or organs (T4a). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0).
II C	T4b	N0	M0	The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0).
III A	T1 to 2	N1/1c	M0	The cancer has grown through the mucosa into the submucosa (T1), and it may have grown into the muscularis propria (T2). It has spread to 1 to 3 nearby lymph nodes (N1) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites (M0).
III A	T1	N2a	M0	The cancer has grown through the mucosa into the submucosa (T1). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0).
III B	T3 or T4a	N1/1c	M0	The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 1 to 3 nearby lymph nodes (N1a or N1b) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites (M0).
III B	T2 or T3	N2a	M0	The cancer has grown into the muscularis propria (T2) or into the outermost layers of the colon or rectum (T3). It has spread to 4 to 6

Stage	T	N	M	Stage description
				nearby lymph nodes (N2a). It has not spread to distant sites (M0).
III B	T1 or T2	N2b	M0	The cancer has grown through the mucosa into the submucosa (T1), and it may have grown into the muscularis propria (T2). It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites (M0).
III C	T4a	N2a	M0	The cancer has grown through the wall of the colon or rectum (including the visceral peritoneum) but has not reached nearby organs (T4a). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0).
III C	T3 or T4a	N2b	M0	The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites (M0).
III C	T4b	N1 or 2	M0	The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has spread to at least one nearby lymph node or into areas of fat near the lymph nodes (N1 or N2). It has not spread to distant sites (M0).
IV A	Any T	Any N	M1a	The cancer may or may not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to 1 distant organ (such as the liver or lung) or distant set of lymph nodes, but not too distant parts of the peritoneum (the lining of the abdominal cavity) (M1a).
IV B	Any T	Any N	M1b	The cancer might or might not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to more than 1 distant organ (such as the liver or lung) or distant set of lymph nodes, but not too distant parts of the peritoneum (the lining of the abdominal cavity) (M1b).
IV C	Any T	Any N	M1c	The cancer might or might not have grown through the wall of the colon or rectum (Any T). It might or might not have spread to nearby lymph nodes (Any N). It has spread to distant parts of the peritoneum (the lining of the abdominal cavity), and may or may not have spread to distant organs or lymph nodes (M1c).

1.6.2 Dukes system

As mentioned above, the Dukes system (A, B, C, D) (Dukes CE, 1940) was the original staging classification method but it has now been replaced by TNM. However, until the beginning of 2018, CRC teams in the UK also used the Dukes system (Cancer Research UK, 2015), which is divided into four groups as follows:

- Dukes A - the cancer is only in the innermost lining of the bowel or growing into the muscle layer (90% 5 year survival)
- Dukes B - the cancer has grown through the muscle layer of the bowel (70% 5 year survival)
- Dukes C - the cancer has spread to at least one lymph node (30% 5 year survival)
- Dukes D - widespread metastases (the cancer has spread to elsewhere in the body, such as the liver or lungs).

The TNM system is reported to have a more precise definition of the degree of primary tumour extension and it defines the number of nodes involved (Gunderson et al, 2004). TNM is considered more helpful to clinicians preoperatively than the pathologically based Dukes classification (Compton & Greene, 2004) because it incorporates both clinical and pathological staging approaches.

1.7 Treatments

Treatment of CRC is either curative or palliative. Cancers that are confined within the colon wall may be curable (i.e. a survival rate of more than 5 years) with surgery whereas cancer that has spread widely is usually incurable, with treatment plans

focusing on improving quality of life (QoL) and symptoms (known as palliative care) (National Cancer Institute, 2015).

Surgery is the primary course of treatment for most people with CRC (Cancer Research UK, 2015), with complete removal of all detectable tumours being the optimal treatment goal (Compton & Greene, 2004). However, the treatment plan may include a combination of any of the following treatments:

i. Surgery
ii. Chemotherapy
iii. Radiotherapy
iv. Biological treatments that increase the effectiveness of chemotherapy and prevent spreading of the cancer.

Radiotherapy and biological treatments are outside the remit of this thesis and are only briefly discussed in this chapter. The focus of this thesis is on curative treatments, which typically involve surgery followed by adjuvant chemotherapy treatment.

The stage, grade and size of the tumour, together with the patient's general health and fitness crudely determine the most favourable treatment course (Cancer Research UK, 2015). It should be noted that there are also biological markers (e.g. certain physiological characteristics or genes) with prognostic and predictive value that play a crucial role in the management of advanced disease and the treatment of early stage forms (De Divitiis, Nasti, Montano, Fisichella, et al, 2014; Kim, Bae, Oh, Lee et al, 2015). However, these are not discussed further here, as this topic is not directly relevant to this thesis.

1.7.1 Surgery

Eight out of ten CRC patients will have surgery (Cancer Research UK, 2015) for T1, T2 and T3 disease. Depending on the location, size and type of tumour, surgery may range from a simple local resection (i.e. cut out of the bowel lining together with a border of healthy tissue) to a more complex procedure, which may, for example, also involve sphincter-preserving surgery in case of rectal cancers. In people with early stage CRC it is possible that the entire tumour along with any associated nodes will be removed, thereby curing the patient.

Surgical treatment of a large tumour in the large bowel will involve the removal of the tumourous colon section (a "colectomy"), which may be in the right, left, or middle section of the colon (hence the terms "right hemi colectomy", "left hemi colectomy", "transverse colectomy" and "sigmoid colectomy"). Once the bowel section has been removed, the ends of the colon are re-joined, although it will sometimes be necessary to bring the end of the bowel out as an opening on the abdomen (known as a "stoma"), as shown in Figure 1.6. This will result in an 'ileostomy' when the small bowel is brought out on the abdominal wall or a 'colostomy' when the large bowel is brought out. These are usually temporary and reversible. Until reversed, a colostomy bag is fitted over the bowel opening to collect bowel motions (Cancer Research UK, 2015). However, a proportion of patients with low rectal cancers will have a permanent colostomy (Hassan et al, 2013).

Figure 1.6: Pictorial representation of a colectomy and colostomy bag

Since 1991, keyhole surgery (a "laparoscopic resection") has been used where possible (Jacobs, Verdeja & Goldstein, 1991; Franklin, Ramos, Rosenthal, & Schuessler, 1993) to remove early stage bowel tumours. This type of operation typically takes longer to perform than a traditional 'open' operation but research suggests that it may cause less pain and facilitate quicker recovery (Cancer Research UK, 2015). A recent meta-analysis found that overall complications in the laparoscopic surgery group were much lower than those in the open surgery group, although they were equally effective in terms of oncological outcomes (Ma, Yang, Qin, & Wang, 2011).

It is also important to note that there are differences in the surgical techniques used for rectal versus colon (and other common cancers) due to the increased risk of local recurrence and a poorer overall prognosis (Wolpin, Meyerhardt, Mamon, & Mayer, 2007).

1.7.2 Adjuvant chemotherapy treatment

In addition to surgery, a considerable proportion of patients will require chemotherapy and/or radiotherapy. Such treatments may be administered pre-surgery (i.e. "neo-adjuvant" therapy) with the aim of shrinking the tumour, thus making surgery more effective. Alternatively, and more commonly, these therapies can be administered post-surgery ("adjuvant" therapy) as a preventative measure with the aim of targeting residual cancerous cells. Large randomized clinical trials examining the effectiveness of adjuvant chemotherapy following curative CRC resection have consistently demonstrated an improvement in survival rates, and is the current standard of care (National Institutes of Health, 1990).

Chemotherapy is a chemical drug treatment, which destroys fast-growing dividing cancerous ("cytotoxic") cells. Unfortunately, non-cytotoxic cells are also constantly growing and dividing and are collaterally targeted by many chemotherapy treatments (e.g. bone marrow cells, hair follicle cells and the lining of the digestive system), which can lead to several adverse side effects (as detailed in section 1.8.1.2) (Cancer Research UK, 2015).

When administered, the chemotherapeutic agents are absorbed into the bloodstream and carried throughout the body. There are several methods of delivering chemotherapy including:

- an injection into the bloodstream (usually through a vein);
- through a drip (intravenous infusion) into the bloodstream; or
- orally in tablet or capsule form.

The chemotherapeutic agents circulate around the body in the bloodstream and target fast-dividing cells, destroying them or prohibiting them from spreading. The systemic nature of this therapy means that it is effective at targeting cancerous cells anywhere in the body, including potential metastases (Cancer Research UK, 2015).

Adjuvant chemotherapy is routinely recommended following curative surgical resection of T3 (node-positive) colon cancer (i.e. T3, N1+), T2 (node-negative (T2, N0) colon cancer in which high-risk features are present and T2 to T3 rectal cancer (Benson et al, 2004; Figueredo et al, 2004). Although, the optimal timeframe from surgery to the commencement of chemotherapy in CRC patients is presently unclear, it usually begins approximately 4 to 12 weeks after surgery (Biagi, Raphael, Mackillop, Kong, et al, 2011). Several meta-analyses have found that there is a significant adverse association between the time following surgery to a late start of adjuvant chemotherapy and survival. Ideally, adjuvant chemotherapy should begin within eight weeks following surgery for an optimal survival outcome (Biagi et al, 2011; Des Guetz, Nicolas, Perret, Morere, et al, 2010).

Adjuvant chemotherapy for CRC is usually administered as a treatment course over a 6-month period. The current standard duration is based on studies carried out in the 1990s using 5-fluorouracil (5FU) (O'Connell, Laurie, Kahn, Fitzgibbons Jr et al, 1998; Des Guetz, 2010). In most cases there will be between 8 and 12 cycles (depending on the regimen prescribed) where a single cycle can last from a few hours to a few days, every 2 or 3 weeks (Cancer Research UK, 2015).

The most commonly administered adjuvant chemotherapy drugs used to treat CRC (Table 1.2) include:

Table 1.2: List of adjuvant chemotherapy drugs most often used to treat CRC

Single agent or combination	Generic name
5-FU/LV	5-FU = fluorouracil
	LV= leucovorin*
Capecitabine	Capecitabine
CAPEOX	CAPE = Capecitabine
	OX = Oxaliplatin
FOLFIRI	FOL = leucovorin
	F = fluorouracil
	IRI = irinotecan
FOLFOX	FOL = leucovorin
	F = fluorouracil
	OX = Oxaliplatin

*Levoleucovorin can be used instead of leucovorin

Please refer to Appendix B for a full explanation of each of the regimens for colon cancer and the number of cycles involved.

Clinicians usually make chemotherapy treatment decisions jointly with the patient following a discussion of all available options (per NICE recommendations). These discussions usually cover the reasons why a medicine might be unsuitable for the patient, the probability of recurrence (with and without further treatment), possible side effects, and mode of delivery, considering the patient's clinical condition and preferences (NICE, 2006).

1.7.3 Radiotherapy

Radiotherapy uses high-energy x-rays to permanently damage cellular DNA, causing cancerous cells to die and healthy cells to suffer temporary damage. Radiotherapy is

often used to treat locally advanced rectal cancer and it may be used before or after surgery, mainly to shrink the cancer or slow its growth. It can be administered from the outside the body (external radiotherapy) or inside the body (internal radiotherapy) (Cancer Research UK, 2015). Radiotherapy is rarely used to treat colon cancer, whereas the benefits of pre-operative chemoradiotherapy (i.e. chemotherapy and radiotherapy together) have been established for rectal cancer (Wolpin, et al, 2007).

1.7.4 Biological Therapy

Biological therapies are drugs that can help the body to control the growth of cancer cells. Some biological therapies such as cetuximab (Erbitux) can be used to treat advanced or metastatic CRC. Cetuximab is usually administered along with chemotherapy drugs for advanced colon cancer to help patients to live longer (Cancer Research UK, 2015).

1.8 Side effects

With increased survival rates, it has become even more important to focus attention on the patient's experience of inevitable associated biological and psychological side effects related to CRC treatments. One possible side effect of chemotherapy treatment is cognitive change, the subject of this thesis. The relevant literature is discussed in detail in Chapters 2 to 5 inclusive. To understand the complete experience of patients with CRC, some of the most common physical side effects of surgery and adjuvant chemotherapy treatment are briefly reviewed in this section.

1.8.1 Biological side effects

Despite the advances in surgical and chemotherapy treatments, they are not without their risks and both can lead to a number of side effects in the short and long term.

1.8.1.1 Surgery

Side effects of colorectal surgery will depend mainly on the type of surgery and amount of bowel or rectum removed and overall health. The resected area will differ depending on where the tumour is located. For example, if the tumour is located in the rectum a low anterior resection may be required which will preserve the sphincter complex but may cause incontinence (Zingmond, Maggard, O'Connell, & Liu, 2003). If fitted, there may also be difficulties with the stoma (e.g. infections and leakages) and the patient will need to learn how to manage with it.

Although a more complicated procedure, several studies have reported the advantages of laparoscopic - surgery over open surgery including a reduction in pain, shorter hospital stay, quicker recovery of bowel function and improved cosmetic results (Kennedy, Heise, Rajamanickam, & Harms et al, 2009; Chapman, Levitt, Hewett, Woods et al, 2001; Kieran & Curet, 2004; Yong, Deane, Monson, & Darzi, 2001).

After surgery, most patients will be unable to eat or drink properly for a few days until their bowel has started to function normally. Most patients will experience loose stools and/or diarrhea for some time afterwards, and diarrhea alternating with constipation is also common particularly if a large part of the bowel has been removed (Cancer Research UK, 2015). As mentioned above, the extent and nature of symptoms such as incontinence, increased stool frequency, difficulties in evacuation, urgency and pain are related to several factors such as the nature of the surgery and type of adjuvant therapy

(Hassan & Cima, 2007).

Minor post-surgical complications include pain and tenderness in the localised area, which can be relieved with opioid analgesics. Minor wound infections, wound dehiscence and urinary tract infections may also be experienced. More serious surgical complications include an anastomotic leak (where the sutures or staples holding the two ends of the digestive tract together break or come apart such that the fluids inside the digestive tract leak into the abdomen), pneumonia, haemorrhage, kidney failure, stoma problems (Lemmens, Janssen-Heijnen, Houterman, & Verheij et al, 2007) and death.

Advances in surgical technique, anaesthesia, intensive care therapy, antibiotic treatments, thromboprophylaxis, and other supportive measures have resulted in an increase in surgical safety for CRC procedures (Longo, Virgo, Johnson, &, Oprian et al, 2000; Lykke & Nielsen, 2004). An accurate pre-surgical assessment is critical, particularly for patients suffering from comorbidities, as several specific comorbid conditions including chronic obstructive pulmonary disease (COPD) and deep vein thrombosis (DVT) have been reported to correlate to more frequent development of complications (Lemmens et al, 2007). For example, Lemmens and colleagues (2007) found that colon patients who suffered from DVT at the time of their cancer diagnosis more often had surgical complications (67% versus 30%), more minor infections (44% versus 11%), major infections (56% versus 10%), pneumonia (22% versus 2%) and thromboembolic complications (11% versus 3%).

1.8.1.2 Adjuvant chemotherapy treatment

As described above, chemotherapy drugs target all rapidly dividing cells in the body and do not discriminate between cancerous and healthy cells. The range of side effects experienced depends on the agents administered, as well as the dosage and form of administration (i.e. intravenously or orally). For example, Oxaliplatin drugs are known to cause nausea, numbness of the lips, sensitivity to cold and numbness and tingling of the hands and feet (Wolpin et al, 2007; Cancer Research UK, 2015). Side effects tend to start 2 to 3 weeks after the first chemotherapy cycle.

The use of Oxaliplatin has increased over recent years and more patients are living with its long-term side effects. Chemotherapy-induced peripheral neuropathy (CIPN) is the most common dose-limiting side effect of Oxaliplatin, and it can have a negative influence on patients' QoL (Mols, Beijers, Lemmens, van den Hurk, et al, 2013; Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014). "*Characterized by paraesthesia of the hands and feet and exacerbated by exposure to cold, it is the primary toxic effect associated with oxaliplatin*" (Wolpin, et al, 2007). Patients receiving a dose reduction because of acute neuropathy remain at risk of developing long-term CIPN (Beijers, Mols, Tjan-Heijnen, Faber, et al, 2015) and chronic neuropathy has been found to persist in 60% of patients a year or more after the cessation of chemotherapy (Mols et al, 2013; Matsumoto, Nishimura, Kanai, Mori, et al, 2008; Park, Lin, Krishnan, Goldstein et al, 2011).

The most common side effects associated with adjuvant chemotherapy for CRC are tiredness and fatigue, nausea, diarrhoea, sore mouth, hair loss or thinning, and sore eyes (Cancer Research UK, 2015, Coates et al, 1983). To help manage nausea and

vomiting antiemetic drugs are usually administered before or after chemotherapy (Hesketh, 2009). Additionally, the reduction in red blood cells can induce anaemia and subsequent breathlessness and fatigue (O'Shaughnessy, 2003; Kayl, Wefel, & Meyers, 2006). All patients react differently to treatments and some may not experience any side effects at all whilst others may suffer from some or all of them.

1.8.2 Psychological and psycho social side effects

The psychological side effects often associated with cancer include anxiety, depression and fatigue, and cognitive side effects (such as memory, attention and concentration impairment). Each of these side effects can "*cause additional suffering, weaken adherence to prescribed treatments, and threaten patients' return to health*" (Adler & Page, 2008, p. 1). Due to improvements in the prognosis and survival of patients with CRC, many individuals are now able to resume their daily routine following treatment whilst some continue their daily routine during treatment. It is important that the psychosocial impact of CRC and its treatment is understood so that it can be appropriately managed, as acknowledged by the International Psychosocial Oncology Society who have recommended further research into the psychosocial impact of cancer on the individual (Holland, Watson, & Dunn, 2011). The commonly reported psychosocial difficulties reported by CRC patients are described below.

Research suggests that one third of cancer patients suffer from some type of diagnosed mental disorder during active treatment (Singer, Das-Munshi, & Brähler, 2010). Although anxiety and depression are often discussed together and do interact (see below), they are distinct (Watson, Weber, Assenheimer, Clark et al, 1995) and particularly in relation to cancer, they may have different trajectories from diagnosis to

end of treatment and long-term follow-up (Ando, Iwamitsu, Kuranami, Okazaki et al, 2009; Den Oudsten, Van Heck, Van der Steeg, Roukema et al, 2010; Kangas, Henry, & Bryant, 2007). Taking each in turn:

1.8.2.1 Anxiety

Anxiety has been described as being "*centered on the emotion of fear and involves feelings of worry, apprehension, and dread*" (Watson et al, 1995). It can adversely affect quality of life and negatively influence compliance to treatment (Greer, Pirl, Park, Lynch, et al, 2008). Prolonged feelings of anxiety can also lead to fatigue (Bower, Ganz, Desmond, Bernaards, et al., 2006).

The prevalence of self-reported clinical levels of anxiety in the general adult population is estimated at 12.6% (Crawford, Henry, Crombie, & Taylor, 2001) compared with up to 30% in people with cancer (Roy-Byrne, Davidson, Kessler, Asmundson, et al, 2008; Stark, Kiely, Smith, Velikova, et al, 2002). Anxiety in relation to cancer often reflects a reaction to the diagnosis (Vardy & Tannock, 2007), anticipated treatment, and is often transient (Linden, Vodermaier, MacKenzie, & Greig,, 2012). Anxiety is likely to decrease after completion of primary treatment (Thomas et al, 2001).

1.8.2.2 Depression

Depression is dominated by the emotion of sadness and is associated with feelings of sorrow, hopelessness, and gloom (Watson et al, 1995), as well as fear, anger and grief (Aapro & Cull, 1999). Symptoms of depression include fatigue, sleep difficulty, and appetite loss (Artherholt & Fann, 2012). As with anxiety, depression can have an adverse effect on functional status and QoL (Carr, Goudas, Lawrence, Pirl, et al, 2002; Pirl, 2004). It can also have an adverse effect on treatment compliance, hospital stay

duration, and capability for self-care (DiMatteo, Lepper & Croghan, 2000; McDaniel, Musselman, Porter, Reed, et al, 1995). It is considered important that depression is diagnosed and treated appropriately.

There is no consensus in research regarding the incidence of clinical depression in cancer patients. There are studies, which have found no difference in the incidence of depression in cancer patients compared to the general population (approximately 6%) (Keating, Nørredam, Landrum, Huskamp, et al, 2005) whilst other studies have found that it is more than 4 times higher, with the greatest rates of depression found in those with advanced forms of cancer (40-50%) (Honda & Goodwin, 2004; Hewitt & Rowland, 2002; Fallowfield, Ratcliffe, Jenkins, & Saul, 2001; Derogatis, Morrow, Fetting, Penman, et al, 1983).

It is also important to note that there may be an interaction between anxiety and depression (van Dam, Boogerd, Schagen, Muller, et al., 1998; Castellon, Ganz, Bower, Petersen, et al., 2004). Mood changes may cause a reduction or be the consequence of a deterioration in QoL. Research has found that patients with cancer who also suffer from comorbid depression experience worse anxiety, pain, fatigue, and functioning than other cancer patients, allegedly resulting in more difficulty adhering to cancer treatments (Walker, Hansen, Martin, Symeonides, et al, 2014).

1.8.2.3 Fatigue

Research has shown that fatigue is one of the most prevalent symptoms experienced by cancer patients (Hoffman, Ryan, Figueroa-Moseley, Jean-Pierre, et al, 2007) and is often associated with chemotherapy treatment (Dikken & Sitzia, 1998). Fatigue has been reported to occur in most patients across a wide range of cancer types (Cella, Davis,

Breitbart, Curt, et al 2001; Irvine, Vincent, Graydon, Bubela, et al, 1994; Stone et al, 1999). Fifty-two percent (149 of 287) of patients with localized CRC in Vardy and colleagues study (2014) reported fatigue at (or soon after) diagnosis, compared to 26% (19 of 72) of the healthy control subjects ($p<0.0001$) (Vardy, Dhillon, Pond, Rourke, et al, 2014).

Cancer-related fatigue is characterised by feelings of tiredness, weakness, and lack of energy and has been described as a "*persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning*" (Mock, Atkinson, Barsevick, Cella, et al, 2000). In healthy individuals, symptoms of fatigue (that occur in normal everyday life) typically diminish following adequate sleep (Servaes, Verhagen, & Bleijenberg, 2002b), however cancer-related fatigue is not relieved by rest or sleep, nor does it correspond to the level of exertion in people with cancer (Glaus, Crow, & Hammond, 1996; Morrow , Shelke, Roscoe, Hickok, et al, 2005).

Cancer-related fatigue can have a profound impact on daily living (Curt, Breitbart, Cella, Groopman, et al, 2000) and several studies have reported an association between fatigue, depression, anxiety and mood disturbances (Broeckel, Jacobsen, Horton, Balducci, et al, 1998; Bower, Ganz, Desmond, Rowland, et al, 2000; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, et al, 1999; Stone, Richards, A'hern, & Hardy, 2000; Vardy et al, 2014). Fatigue has also been found to be associated with cognitive impairment in some cancer studies (Servaes, Verhagen, & Bleijenberg, 2002).

It is important to note that fatigue can occur because of the cancer itself but it may also occur as a side effect of radiotherapy and/or chemotherapy treatment (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, et al, 2007) in an estimated 34% of breast cancer

survivors (Bower et al., 2006). It remains unclear how long the fatigue persists after treatment (Hofman et al, 2007), although it was found that 35% of breast cancer patients reported fatigue between 1and 5 years after completion of their treatment, and 34% between 5 and 10 years (Bower et al, 2006).

1.8.3 Cognitive Impairment

Another commonly reported chemotherapy related treatment side effect is deterioration in cognitive function, often referred to as "chemobrain" or "chemofog," by breast cancer patients. Cognitive impairment is the focus of this thesis and will be discussed in detail in Chapters 2 to 5 inclusive.

1.9 Summary

This chapter has summarized what CRC is, and outlined the available treatments and the associated side effects of surgery and adjuvant chemotherapy. The incidence and survival rate of CRC is high, as is the prevalence of treatment-related side effects. Therefore, it is vital that the appropriate information and support is made available to all patients with CRC so that the impact of the disease and treatment process on daily tasks and QoL is minimized.

Chapter 2: Cognition, Cognitive Functioning and Cognitive Impairment in Cancer Patients

2.1 Introduction

This chapter introduces the concept of cognition and cognitive function, outlining the domains that are encompassed within such functioning. It then examines impaired cognitive functioning, using both objective and subjective assessments in patients with cancer. It also highlights some of the challenges involved in measuring any type of cognitive impairment and outlines other factors that may affect cognition.

2.2 Overview of cognitive functioning

Cognition is "*the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses*" (Oxford English Dictionary, 2016). It is a generic term that dates to the 15th century.

Cognitive function is a multidimensional concept (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005). There are distinct functions that the brain uses to execute behaviours referred to as "domains". One schema for considering domains of cognitive functioning and their corresponding components are set out in Table 2.1 (Jansen et al, 2005; Rich & Troyer, 2008). All of these cognitive domains are considered necessary for normal daily functioning (Jansen et al, 2005; Olin, 2001; Ryan, Morrow, Bromet & Parkinson, 1987).

Table 2.1: Overview of Cognitive Domains (adapted from both Jansen et al, 2005 and Rich & Troyer, 2008)

Cognitive Domain	Components	Description	Consequences of impairment
Attention	Selective attention Sustained attention Divided attention Alternating attention	*Selective attention*: The ability to examine relevant inputs, thoughts, and actions while ignoring those that distract or are irrelevant (Gazzaniga, Ivry, & Mangun, 2002; Grober, 2002; Heilman, Valenstein, & Watson, 1997). *Sustained attention:* The ability to maintain attention towards a stimulus over an extended period (Filley, 2002). *Divided attention*: the ability to focus on multiple tasks simultaneously *Alternating attention*: the ability to switch between sources of information.	Reduced awareness or ability to focus on tasks (Groth-Marnat, 2000)
Concentration	Sustained attention or vigilance	The ability to focus and sustain attention toward a stimulus for a period of time (Filley, 2002; Lezak, Howieson, Loring & Fischer, 2004.).	As above
Executive function	Initiation Planning Cognitive flexibility	Higher order cognitive abilities that are necessary for appropriate, socially responsible and effective conduct (Goodwin,	Decreased ability to categorise or compare information, prepare or organise strategies, and respond to changing stimuli. Impairment may also

Cognitive Domain	Components	Description	Consequences of impairment
	Self-monitoring Self- regulation	2012). These include a) *planning*: The ability to formulate and consider different approaches to a task and to conduct an effective approach to achieve a goal; b) *abstract thinking*: the ability to create generalised concepts from discrete instances; c) *response inhibition*: The ability to produce an uncommon response instead of an automatic response; d) *switching*: The ability to alternate between different types of information or different response categories	limit ability to solve problems, achieve goals, or be creative, adaptive, or flexible (Jansen et al, 2005).
Processing speed		The ability to rapidly process simple and complex information and respond to information (Freeman & Broshek, 2002).	Impacts the ability to perform tasks quickly and accurately. It can contribute to learning and attention issues
Language	Verbal or written expression	Includes a) *receptive language*: The ability to comprehend orally or visually presented verbal information, and b) *expressive language*: The ability to produce words or sentences	Inability to communicate (Jansen et al, 2005)

Cognitive Domain	Components	Description	Consequences of impairment
Language processing	Reception Repetition	Involves representing, comprehending and communicating symbolic information, either written or spoken (Gazzaniga et al., 2002).	As above
Motor function	Speed Strength Coordination Dexterity Apraxia	Movements and actions of the muscles, such as speed, strength and coordination.	Problems with dexterity, gait changes, weakness and tremors (Jansen et al, 2005).
Visuospatial skill	Perception Construction	The ability to process and interpret visual information regarding where things are situated in space (Spreen & Strauss, 1998)	Altered perceptions or an inability to recognize familiar objects, which could affect performance of manual tasks.
Memory	Short term memory Long term memory Recall Recognition Verbal Visual	The ability to acquire, store, retrieve and use new information (Grober, 2002).	Inability to learn, retain information or retrieve information

Different areas of the brain are activated during cognitive processing. For example, sensory input from the environment is registered in various parts of the brain located in both hemispheres. All input is then screened and processed (with the left cerebral hemisphere predominantly processing verbal information, and the right hemisphere, visuospatial information) and usually an appropriate behavioural response is produced (Vardy & Tannock, 2007).

Cognitive domains are not necessarily mutually exclusive. Some domains are so inextricably linked that impairment in one invariably affects another (Lezak et al, 2004). For example, the input of information required for information processing requires "attention" which is in turn necessary for "memory" (Jansen et al, 2005).

2.3 Cognitive function in patients with cancer

Cognitive assessment for people with cancer has increased since the early 1990's (Kayl, Collins and Wefel, 2008) and may be split into objective cognitive function and subjective cognitive function.

2.3.1 Assessing objective cognitive function

Neuropsychological tests are routinely used to measure objective cognitive function (Freeman & Broshek, 2002) in the "cancer and cognition" literature. Most comprehensive neuropsychological batteries used in such studies have included assessment of cognitive function across multiple domains, typically those detailed in Table 2.1. Several neuropsychological measures are often included in a test battery that the cancer patient is asked to work through, usually lasting several hours (Freeman & Broshek, 2002). Most neuropsychologists recommend a comprehensive battery of neuropsychological measures as the gold standard for assessing cognitive function, but

vary in opinion as to which tests, and how many, should be incorporated into a battery (Vardy, Rourke & Tannock, 2007). More than 40 neuropsychological tests have been used in "cancer and cognition" research to date (Jansen et al, 2005; Dwek, Rixon, Hurt, Simon & Newman, 2017). As these tests have different psychometric properties and may involve different aspects of the cognitive domain, it is difficult to compare findings across studies. In addition, often a test will tap into more than one domain as illustrated in Chapter 3, Section 3.6, and Table 3.3. This further complicates the task of identifying which specific domains are responsible for the performance on a particular test.

There are hundreds of neuropsychological tests available for use. Test selection is very important and will vary with the hypotheses being evaluated. Measures chosen for the neuropsychological assessment of patients with cancer should be psychometrically sound with established reliability and validity and appropriate normative studies (Kayl et al, 2008). (The importance of normative data is discussed below). They should also include assessment of the full range of psychological functions (Jansen et al, 2005). The neuropsychological (NP) tests used in this thesis were chosen in accordance with the International Cognition and Cancer Task Force's (ICCTF) recommendations (Wefel, Vardy, Ahles & Schagen, 2011) and the purpose and goals of this study and are detailed in Chapter 7. The tests are also discussed within six domains (attention, concentration, motor function, executive function, verbal and visual memory) as set out in Chapter 7.

2.3.1.1 Objective cognitive impairment (OCI)

To evaluate whether an individual or group of individuals score(s) on a particular NP test suggest impaired performance it is first necessary to establish what constitutes a normal score. There are various methods for doing this.

Normative data:

One method is by reference to data already collected from a group of healthy individuals with similar demographic characteristics to the sample under investigation (Mitrushina, Boone, Razani & D'Elia, 2005) at the analysis stage. Such data is known as normative data and is often used to compare cognitive performance in the "cancer and cognition" literature (Mitrushina et al, 2005).

Normative data establishes a baseline distribution for a score, against which the patient score can be compared. Published normative data from healthy controls usually contain large sample sizes, which are likely to provide good estimates of the population parameter under investigation (e.g. attention) (Wefel, Saleeba, Buzdar & Meyers, 2010). It is important when using normative data to consider potential sample differences (e.g. socio demographic factors such as age and education) that relate to the parameter being investigated and may differ significantly between the sample population in the study and the control population (Wefel et al, 2010). Age, gender, intelligence and education are all factors that could influence cognitive function (Ferguson & Ahles, 2003). As further discussed in Section 2.4, it is important to note that other factors such as (including but not limited to) fatigue, anxiety and depression may also affect cognitive function (Ferguson & Ahles, 2003; Minisini, Atalay, Bottomley, Puglisi, et al, 2004), and therefore are often assessed in "cancer and cognition" studies in order to determine their impact (if any) on cognitive function (Vardy & Tannock, 2007).

Control/comparison groups

Whilst normative data is often considered the "gold standard" for comparing cognitive performance in the "cancer and cognition" literature (Mitrushina et al, 2005), data may also be collected from a "control group". There are different types of control group. One

type is a healthy control group. Similar to normative data, the data collected from a healthy group of individuals with homogeneous demographic characteristics, which match the subject/sample in question, is used as the frame of reference. Alternatively, (or in addition to the healthy controls), a group of individuals who have the same cancer diagnosis but receive different treatments may be used. This may enable researchers to establish, the relative effects of a specific treatment. The ICCTF is of the opinion that the relative neurological effects of a treatment such as chemotherapy can be established if appropriate assessment time points and comparison groups (such as patients who receive the same ensemble of treatments (e.g. surgery) with or without chemotherapy treatment) are used in a study (Wefel et al, 2011).

Ideally several control groups will be used (i.e. both local controls and published normative data) in the same period as the patient group (Wefel et al, 2011). Both groups would undergo the same cognitive assessments in the same timeframe as the group of interest. The ICCTF believes that this approach can help to establish whether cognitive impairment is present, and whether apparent changes in cognitive function are due to practice effect (i.e. a change over time attributed to familiarity with the assessment rather than a true improvement) or are secondary to the cancer itself, the treatment, or both (Wefel et al, 2011).

Choosing a control group against which to assess whether patients with cancer suffer any OCI during and/or after treatment is not straightforward. Different types of control group can lead to different results. For example, Argyriou and colleagues, (2011) observed that most impairment occurred "*if the chemotherapy patients' cognitive performance is compared with normative data*" but that "*there is less impairment if a*

control group is used for comparison and little to no impairment if baseline data from the patients themselves are used".

Categorising OCI

Another difficulty in evaluating impairments in cognitive function is determining what constitutes impairment: "What is the appropriate cut off point for categorising impairment?" Once a control group has (or groups have) been chosen, an impairment criterion needs to be established in order to assess the relative performance of the participant in comparison to the normal/comparative population(s). The definition of OCI is complex because NP test batteries include numerous tests which are each individually scored (Vardy et al, 2007).

There is a wide range of impairment criteria used in the "cancer and cognition" literature to define cognitive impairment. A definition of OCI is usually based on cut off scores for the individual NP tests (Jansen et al, 2005). Various cut-off criteria have been used to define OCI including 1, 1.5 and 2 standard deviations (SD) below the normative group mean score (or mean score of an appropriate control group) on one or more NP tests (Lezak, Howieson & Loring, 2012) using standardised T or Z scores. Others have calculated global deficit scores and defined OCI as having a global deficit score (Vardy et al, 2015). In the "cancer and cognition" literature published to date there is no standard or consistency in the definition of cognitive impairment used in studies (Vardy et al, 2007). This subject (including the criteria chosen for this study) is discussed further in Chapter 7.

2.3.2 Assessing subjective cognitive function

Subjective cognitive function is the perceived, self-reported view of one's own mental function (Biegler, Alejandro Chaoul & Cohen, 2009). In contrast to objectively measured cognitive function, subjective cognitive function is measured using self-report questionnaires, diaries and/or interviews/focus groups.

2.3.2.1 Subjective cognitive impairment (SCI)

SCI refers to an individual's perceived cognitive difficulties experienced in daily life, such as problems with concentration, memory, learning and language (Pullens, De Vries, & Roukema, 2010). As with NP measures, there are a variety of self-report measures available for assessing subjective cognitive functioning (Pullens et al, 2010). Such measures assess the impact of cognitive impairment on the individuals' everyday life (Hutchinson, Hosking, Kichenadasse, Mattiske & Wilson, 2012), providing an understanding of treatment outcomes from the patients' perspective (Kayl et al, 2008). As mentioned above, they range from diary entries to interviews and/or questionnaires. Similar, to the research in relation to OCI, studies to date have used a variety of measures to assess SCI in patients with cancer (Table 2.2). For example, Pullens, De Vries & Roukema's (2010) systematic review found that 10 different standardised self-report questionnaires and nine non-validated questionnaires and/or semi-structured interviews were used across 27 studies to measure SCI.

Table 2.2: An example of the range of subjective cognitive measures used in a the "cancer and cognition" studies reviewed in Chapter 3

Number of studies (First author)	Measure used
3 Studies: Hermelink et al, 2007; Mehnert et al, 2007; Weis et al, 2008	Fragebogen erlebter Defizite der Aufmerksamkeit (questionnaire of experienced attention deficits) (FEDA)
3 Studies: Donovan et al, 2005; Ahles et al, 2008; Ahles et al, 2010	Multiple Ability Self-Report Questionnaire (MASQ)
2 Studies: Bender et al, 2006; Bender et al, 2008	Patient's Assessment of Own Functioning (PAOF)
5 Studies: Castellon et al, 2004; Jenkins et al, 2006; Quesnel et al, 2009; Jenkins et al, 2004; Schilder et al, 2009	Cognitive Failure Questionnaire (CFQ)
3 Studies: Jansen et al, 2008; Cimprich et al 2005; Cimprich 1999	Attentional Function Index (AFI)
2 Studies: Hurria et al, 2006; Von AhD et al, 2009	Squire Memory Self-Rating Questionnaire (SSRQ)
15 Studies: Schagen et al, 1999; Schagen et al, 2002; van Dam et al, 1998; Hermelink et al, 2007; Mehnert et al, 2007; Quesnel et al, 2009; Weis et al, 2009; Ahn et al, 2006; Galalae et al 2005; Schilder et al, 2009; Debess et al, 2010; Jansen et al, 2011; Hedayati et al, 2012; Cruzado et al, 2014; Hermelink et al, 2015	European Organization for Research and Treatment of Cancer quality of life core questionnaire (EORTC QLQ-C30)
2 Studies: Ahn et al, 2006; Galalae et al 2005	EORTC Breast Cancer Specific (EORTC QLQ-BR23)
1 Study: Weis et al, 2009.	Multidimensional Fatigue Inventory (MFI-20)

Number of studies (First author)	Measure used
4 Studies: Downie et al 2006; Vardy et al 2006; Biglia et al 2012; Lange et al, 2014	The Functional Assessment of Cancer Therapy—Cognitive Function Instrument) (FACT-Cog)
10 Studies: Schagen et al, 1999; Schagen et al, 2002; van Dam et al, 1998; Downie et al, 2006; Berglund et al 1991; Mehlsen et al, 2009; Servaes et al, 2002; Shilling & Jenkins 2007: Schilder et al, 2009; Kopplemans et al, 2012	Interviews/ self-constructed questionnaires

As can be seen in Table 2.2 the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Aaronson et al, 1993; Kayl et al, 2008) was most often used prior to 2010. The EORTC QLQ-C30 is a cancer specific quality of life questionnaire that assesses subjective cognitive functioning based on one question concerning memory and another concerning concentration problems occurring during the previous week. More recently, Wagner and colleagues (2009) developed another questionnaire, the Functional Assessment of Cancer Therapy—Cognitive Function Instrument (FACT-Cog) which was based on qualitative input obtained from cancer patients (who reported cognitive concerns) and from oncologists and nurses (Wagner, Sweet, Butt, Lai & Cella 2009). It assesses SCI using language found to be relevant to cancer patients experiencing cognitive problems. Both questionnaires are cancer specific and consequently focus on issues that are important to patients with cancer. Generic instruments are intended to be applicable to a wide range of health problems (Fitzpatrick et al, 1992). Whereas disease specific questionnaires such as the FACT Cog are more sensitive to small differences that might be significant to patients who have cancer and to any changes that may occur over time during the treatment for the specific disease (Cella et al, 1993). The FACT-Cog assesses the nature and severity of cognitive deficits and the impact of such deficits on the patients' quality of life. The FACT-Cog has 37 items whereas the EORTC QLQ-C30 has two items concerned with cognition.

2.4 OCI "versus" SCI

The type of data gathered by NP assessments and self-reports is not the same. Self-report questionnaires require participants to have insight into their own functioning, including the ability to identify their own disease-related deficits and preserved skills

(Roessler-Górecka, Iwański & Seniów 2013) whereas objective NP assessments are performance-based tests to assess cognitive functioning (Harvey, 2012). Therefore, they are conceptually different measurement tools.

There is an argument that NP tests are not designed to measure functioning in everyday situations. In addition, NP tests are administered at one point in time therefore they may not tap into the same domains as self-report measures which typically ask about experiences over a period of time (Wagner et al, 2009).

As will be discussed in Chapter 3, the incidence of both OCI and SCI varies widely across studies. Each does reportedly occur in a subset of patients with cancer. However, even when both objective and subjective cognitive impairment are found to be present, the two are not necessarily related (Hutchinson et al, 2012). For example, in a breast cancer study examining self-reported cognitive problems in women receiving adjuvant treatment, it was found that 71% of patients reported memory problems four weeks after the final chemotherapy session whilst only 30% showed objective decline at that time (Shilling & Jenkins, 2007).

There have been some studies, which have found a significant relationship between objective and subjective measures. For example, Mehnert and colleagues (2007) found a significant correlation between poorer performance on objective measures of working memory, selective attention, visuo-spatial working memory and visual delayed recall and more self-reported cognitive changes in cancer patients treated with chemotherapy. Reid-Arndt and colleagues (2010) also found a significant correlation between self-reported cognitive functioning and immediate memory and response inhibition.

Whilst various explanations have been proposed for such discrepancies, further research is required to fully understand why this difference between self-reported cognitive complaints and objectively measured cognitive functioning occurs. It has been suggested that it is important therefore that future studies include both objective and subjective measures (O'Farrell, MacKenzie, & Collins, 2013) and examine the impact of all cognitive problems on daily functioning and quality of life (Ahles & Saykin, 2001). This thesis will examine the relationship between cognitive impairment and health related quality of life (HRQoL) (Chapters 5 and 9).

2.5 Factors commonly associated with cognitive function

When assessing cognition it is important to consider the range of potential factors that may have the ability to influence cognitive outcomes. These factors could confound the results found when assessing cognitive impairment (objective and subjective) in patients with cancer, and lead to inaccurate results.

Figure 2.1: Potential contributing factors for chemotherapy related cognitive impairment:

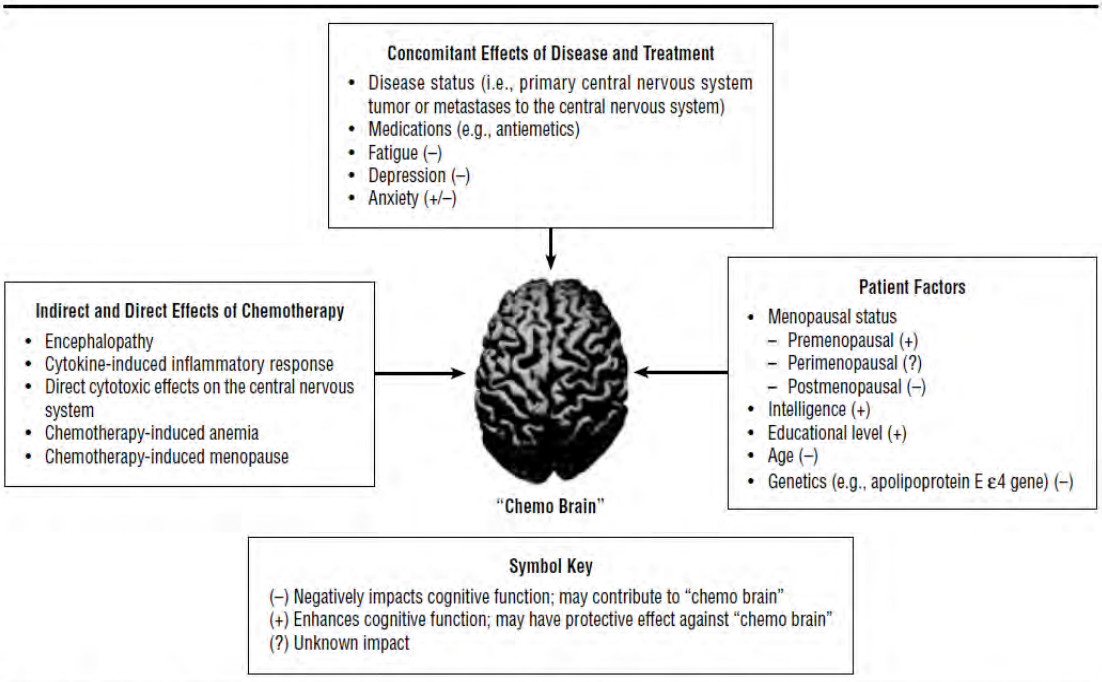


Figure 1. Potential Contributing Factors for Chemotherapy-Induced Impairments

Note. Photo from "The Human Brain: Chapter 5: The Cerebral Hemispheres," by T.H. Williams, N. Gluhbegovic, & J.Y. Jew, 2005. Retrieved September 29, 2005, from http://www.vh.org/adult/provider/anatomy/BrainAnatomy/Ch5Text/Section01.html. Copyright 2005 by T.H. Williams, N. Gluhbegovic, J.Y. Jew, and the University of Iowa. Reprinted with permission.

2.5.1 Indirect and direct effects of chemotherapy

2.5.1.1 Direct effects of chemotherapy on the central nervous system

There are several interacting pathogenetic mechanisms involved in treating cancer with chemotherapy, which may affect the cognitive ability of cancer survivors (Argyriou, Assimakopoulos, Iconomou, Giannakopoulou & Kalofonos, 2011).

As mentioned in Chapter 1, chemotherapy drugs are used to prevent the cancer cells from multiplying and spreading to other tissues. However, they can also have toxic effects on normal cells (Skeel and Khleuf, 2007). Although chemotherapy drugs do not usually cross the blood-brain barrier (i.e. the physical barrier whereby cells at three key interfaces form barriers between the blood and the central nervous system (CNS)),

there are some that do via direct or indirect mechanisms, potentially contributing to CNS toxicity (Simó, Rifà-Ros, Rodriguez-Fornells & Bruna 2013). For example, Meyers and Perry (2008) found that platinum-based agents such as Oxaliplatin have been associated with CNS neurological toxicity. As mentioned in Chapter 1, Oxaliplatin is often used to treat CRC. Data from animal studies suggest that higher levels of chemotherapy may cross the blood-brain barrier than previously thought and even small doses of chemotherapy can cause cell death in structures vital for cognition (Dietrich, Han, Yang, Mayer-Prösche & Noble, 2006).

Recent structural imaging studies have found an association between chemotherapy treatment and a volume reduction of both grey and white matter and altered white matter integrity (Inagaki et al, 2007; McDonald, Conroy, Ahles, West, & Saykin, 2010; Deprez et al, 2011, 2012). This decrease may persist in a subgroup of patients (Saykin, Ahles & McDonald, 2003; Inagaki et al, 2007; McDonald et al, 2010; de Ruiter et al, 2012; Koppelmans et al, 2012). Reduced white matter integrity and impaired hippocampal neurogenesis are thought to represent major cell-biological mechanisms underlying the typical cognitive complaints reported by cancer survivors, including deficits in attention, memory and processing speed (Monje & Dietrich, 2012).

2.5.1.2 Anaemia

Anaemia (a deficiency in red blood cells) has been associated with an increased risk of OCI in several chronic illnesses, including renal disease (Stivelman, 2000) and vascular dementia (Milward et al, 1999).

Cancer patients often experience symptoms of anaemia (Nowrousian, 2002; Ludwig et al, 2004) and it is frequently associated with an advanced stage of the disease,

worsening during chemotherapy or radiotherapy treatment (Nowrousian, 2002). The prevalence of anaemia varies depending on the type of cancer (Knight, Wade & Balducci, 2004; Groopman & Itri, 1999) with approximately 40% of patients with early-stage colon tumors (Knight et al, 2004) and 50% of patients with solid tumours presenting with anaemia at diagnosis (Bohlius, Weingart, Trelle, & Engert, 2006). In addition, the incidence of chemotherapy-induced anaemia depends on the intensity of the treatment, which may increase with cumulative cycles (Jansen et al, 2005). It has been reported that prior to chemotherapy treatment, 44% of patients with breast cancer had anaemia, which increased to 60% after 6 cycles of chemotherapy (Tas et al, 2002). However, 71% of patients with colon cancer had anaemia before initiation of chemotherapy and Tas and colleagues (2002) reported that there was no difference observed in post treatment haemoglobin values compared with pre-treatment values in this patient group.

Recent studies have found that epoetin alfa treatment (used to increase haemoglobin levels and thereby reduce anaemia) may maintain or improve objectively measured cognitive functions in patients with cancer through both direct and indirect mechanisms (Ferrario et al, 2004). These findings suggest that declines in haemoglobin levels during chemotherapy treatment are associated with adverse changes in cognitive functioning (Jacobsen, 2004). Consequently, it is arguable that chemotherapy-induced anaemia may also cause cognitive impairment (Cunningham, 2003).

There are numerous symptoms associated with anaemia, the primary one being fatigue, which can impair a patient's ability to carry out normal daily activities (Cella, 1997). However, fatigue is a multifactorial syndrome that is not only caused by anaemia, therefore attempting to establish the relative contribution of anaemia to fatigue is a very complex undertaking. Even when anaemia improves, not all the symptoms of

fatigue might be relieved because fatigue can be present independently of anaemia (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003; Tchen et al, 2003; Mock, 2004).

2.5.1.3 Chemotherapy induced menopause/hormonal changes

Hormonal changes either dependent on or independent of cancer therapy could be a contributory factor to cognitive impairment (Kaiser, Bledowski & Dietrich, 2014). While more pronounced cognitive deterioration has been reported for combined chemotherapeutic and anti-hormonal treatment when compared with chemotherapy alone (Bender et al, 2006), other studies have found that hormonal changes do not contribute to OCI (Hermelink et al, 2008).

Hormonal changes secondary to chemotherapy-induced menopause may indirectly adversely affect cognitive function because of the decreased levels in neuro-protective oestrogen hormones. However, a study of 110 patients with breast cancer failed to reveal a significant association between either hormone level or menopausal symptoms, and OCI (as measured by the High-Sensitivity Cognitive Screen) following adjuvant chemotherapy (Tchen et al, 2003). There was a higher incidence of moderate or severe OCI in the patient's receiving chemotherapy than in the healthy controls (16% v 4%) and they experienced more menopausal symptoms (median FACT-ES scores, 58 v 64; $p < .0001$).

Patients treated with hormonal therapies for prostate or breast cancer may experience cognitive impairment because of reduced testosterone and oestrogen levels (Ahles & Saykin, 2007). Oestrogen deficiency in chemotherapy-induced menopause occurs faster than in normal menopause and it is associated with impairments in learning and memory, particularly verbal memory (Cutter, Norbury, & Murphy, 2003). It is uncertain

whether this accelerated decrease in oestrogen causes greater cognitive impairments (Shilling, Jenkins, Fallowfield, & Howell, 2001). The antioxidant and neuro protective effects of testosterone and oestrogens, and the importance of oestrogens in maintaining telomere length are highlighted in several trials (Vardy et al, 2007; Walker, Drew, Antoon, Kalueff & Beckman, 2012) which suggest that reduced concentrations of these hormones secondarily to hormonal therapy can cause chemotherapy related cognitive impairment (CRCI) even when administered without chemotherapy.

2.5.2 Concomitant effects of cancer and its treatment

Since many patients diagnosed with cancer suffer with anxiety, depression and/or fatigue (see Chapter 1) it is important to consider their effect when assessing both OCI and SCI.

2.5.2.1 Anxiety

Although anxiety has not consistently been a proven risk factor for OCI (Vearncombe et al, 2009; Cimprich, Ronis, & Trask, 2005; Mandleblatt et al, 2014), high levels of anxiety have been shown to be associated with poorer performance on cognitive tests as a result of decreased attentional control (Eysenck & Calvo, 1992). SCI appears to be more strongly associated with anxiety symptoms than OCI (van Dam et al, 1998; Jenkins et al, 2006; Pullens, De Vries, Van Warmerdam, Van De Wal & Roukema, 2013), with anxiety being one of the most common psychiatric disorders among women with breast cancer (Maass, Roorda, Berendsen, Verhaak & de Bock, 2015).

As mentioned in Chapter 1, anxiety can develop as a reaction to being diagnosed with a life-threatening disease (Vardy and Tannock, 2007). It may also be related to actual

treatment. Breast cancer studies have reported increased levels of anxiety in patients undergoing chemotherapy treatment compared to other treatments (Schreier and Williams, 2007). There is also evidence of a relationship between SCI and anxiety at the end of chemotherapy treatment and for up to two years after completion of systemic therapy (Pullens et al, 2010; Schagen et al, 1999; van Dam et al, 1998; Hermelink et al, 2007; Schilder et al, 2009). Anxiety could continue to be a significant problem for many women years after the diagnosis of breast cancer (Hodgkinson, Butow, Fuchs et al, 2007). Hodgkinson and colleagues (2007) found a prevalence of 9.4% in women evaluated between two and ten years after cancer diagnosis, which was considerably higher than age-adjusted community prevalence rates (5.9%) in Australia (Hodgkinson et al, 2007). These anxiety rates were found to be equivalent to those reported by women within the first 3 months of diagnosis (8.6%) and by women with advanced stage disease (6%) (Kissane, Grabsch, Love et al, 2004). Both studies used the Hospital Anxiety and Depression Scale (HADS) to measure anxiety.

2.5.2.2 Depression

There is not usually a significant correlation found between OCI and depression (van Dam et al, 1998; Schagen et al, 1999; Brezden et al, 2000; Ahles, Saykin, Furstenberg , et al, 2002; Schagen et al, 2002; Tchen et al, 2003; Castellon et al, 2004; Bender et al, 2006; Jenkins et al, 2006; Mar Fan et al, 2005; Wefel et al, 2004; Wieneke & Dienst, 1995; Cimprich et al, 2005; Cull et al, 1996; Eberhardt, Dilger, Musial et al, 2006). However, as with the findings regarding anxiety, numerous studies in the "cancer and cognition" literature have shown a relationship between depression and SCI (van Dam et al, 1998; Cimprich, 1999; Castellon et al, 2004; Cimprich et al, 2005; Cull et al, 1996; Bender et al, 2006; Jenkins et al, 2006; Vearncombe et al, 2009). Jenkins and colleagues (2006)

found that 55% of breast cancer patients who were about to start adjuvant chemotherapy treatment reported psychological distress (on the General Health Questionnaire) (Goldberg & Williams, 1988), compared with 62% about to start endocrine therapy and/or radiotherapy, and 16% in healthy controls. At 6 months, the incidence was 51%, 24% and 18% respectively (Jenkins et al, 2006).

2.5.2.3 Fatigue

As discussed in Chapter 1, Section 1.8.2.3, fatigue is the most commonly reported symptom associated with chemotherapy treatment (Ashbury, Findlay, Reynolds & McKerracher, 1998; Downie et al, 2006;), affecting 75% to 95% of cancer patients (Vardy & Tannock, 2007). Fatigue is often significantly associated with SCI but not with OCI (van Dam et al, 1998; Schagen et al, 1999; Servaes, Verhagen, & Bleijenberg, 2002; Tchen et al, 2003; Castellon et al, 2004; Bender et al, 2006; Mar Fan et al, 2005; Shilling, Jenkins, Morris, Deutsch & Bloomfield et al, 2005; Jenkins et al, 2006; Kreukels et al, 2006, Vardy et al, 2015).

2.5.3 Patient factors

2.5.3.1 Genetics

Research has indicated that various genetic and other confounding factors are also implicated in the genesis of CRCI (Saykin, Ahles, McDonald, 2003). However, this is outside the remit of this thesis.

2.5.3.2 Age, education and intelligence

Older age, level of education and intelligence are often associated with poorer cognitive function (both objective and subjective) in the general population (Craik, 1994).

Age:

The negative effects of older age on objective cognitive functions are well documented (Deary, Corley, Gow et al, 2009), including cognitive decline in the domains of processing speed, attention and executive function. Thus, it is possible that chemotherapy exacerbates the effects of old age on cognitive function for cancer patients. Ono and colleagues meta- analysis (2015) suggested that cognitive decline associated with chemotherapy for breast cancer might interact with age, whereby older patients may have a higher risk of developing and/or experiencing persistent OCI after chemotherapy.

Lange and colleagues (2014) assessed 123 women with breast cancer over the age of 65 after surgery, but before the start of adjuvant treatment. Compared with normative data based on age and education, 41% of the patients had OCI (mainly impaired visual episodic memory) pre-treatment, which is significantly higher than what would be expected when looking at healthy population norms. It is also a higher percentage than the 20% to 30% of breast cancer patients aged 45 to 55 years who exhibited pre-treatment OCI in Ahles and colleagues study (2012). Lange contends that their findings support the hypothesis that elderly patients may be more sensitive to the impact of cancer on cognition. This is consistent with the link between biological processes underlying cancer, ageing, neuro-degeneration and a cognitive decline as proposed by Ahles and colleagues (2012). Larger, longitudinal studies are necessary to investigate whether or not cancer therapies accelerate cognitive ageing (Ahles et al, 2012) and to properly determine the duration of OCI after chemotherapy (Vardy & Tannock, 2007).

In relation to SCI, Hurria and colleagues (2006) found that more than 60% of elderly breast cancer patients perceived pre-existing memory problems and were more likely

to report further memory deterioration after chemotherapy. It is also worthwhile noting that aging is often associated with increasing comorbidities (e.g. cardiovascular disease) and functional decline, that have themselves been associated with cognitive impairment (Joly et al, 2015).

IQ and Education:
IQ and the level of education in study patients have also been found to significantly moderate the magnitude of post-chemotherapy cognitive impairment in cross sectional studies (Joly et al, 2015). Chemotherapy patients with fewer years spent in education tended to show greater OCI than those with higher levels of education. Having more years in education is associated with higher cognitive functioning (Cimprich, So, Ronis & Trask, 2005). Mandelblatt and colleagues (2014) found that breast cancer patients aged between 60 and 94 had similar NP scores to the controls. However, patients with more advanced disease stage had lower executive function than early stage cancer, with significantly higher impairment among older, non-white, less-educated women and those with greater comorbidity.

2.6 Quality of life

In recent years, there has been an increase in the attention directed towards the impact of cancer and its treatment on quality of life (QoL) (Arriba, Fader, Frasure & Von Gruenigen, 2010). QoL is a multidimensional person-centred concept, encompassing an assessment of one's perceived health status and well-being in different life domains and includes both physical and mental health components (Bowling, 1991; Campbell Converse, & Rodgers, 1976; Cella and Tulsky, 1993) as well as overall satisfaction with life. In the context of an illness, this concept may be narrowed to health related QoL

(HRQoL) involving domains, which are specifically related to health and/or disease, including physical, social, emotional, cognitive, sexual and functional outcomes (Kirshner & Guyatt, 1985; Cella et al, 1993).

Since the 1990's there has been quite a lot of research examing QoL in patients diagnosed with CRC (Schag, Garz, Wing, Sim & Lee, 1994; Sprangers, Taal, Aaronson & Te Velde, 1995; Allal, Bieris, Pelloni, et al., 2000). Ramsey and colleagues (2000) examined QoL in survivors of CRC and found that the impact of CRC (for all stages) on HRQoL was greatest in the first 2 to 3 years after diagnosis. Pain, functional well-being, and social well-being were affected most substantially across all stages of CRC and times from diagnosis. Although those patients who were diagnosed with stage 4 disease and lived longer than 3 years experienced relatively high HRQoL. Ramsey and colleagues (2000) noted that HRQoL for patients with CRC is likely affected by both the burden of the disease itself and the treatment regimens that are administered (which as discussed earlier are accompanied by various side effects).

As mentioned, one possible side effect that has been associated with chemotherapy treatment for solid tumors is cognitive impairment. Cognitive status, whether alone or in combination with other factors can significantly influence an individual's perception of QoL (Abrahamson, Clark, Perkins, & Arling, 2012). Deficits in various cognitive domains such as memory, attention and executive function, for example, may negatively affect an individual's life in various ways (Pan, et al, 2015) and a number of QoL domains (Mitchell, Kemp, Benito-León, Reuber, 2010). For example, impaired verbal abilities may lead to communication difficulties thus hindering a person's ability to maintain social roles (Kiely, 2014). Attention deficits may affect routine daily activities such as eating, bathing and personal hygiene (Bronnick, et al, 2006); deficits in

attention, memory and executive function may be linked with the mechanisms of the chronicity of pain (Attal, et al, 2014); an awareness of cognitive impairment may cause depression (Jorm, 2001). An adverse effect on a patient's HRQoL due to impaired cognitive function (whether objective or subjective) may have implications for daily functioning which could prevent a return to work or normal social life (Wefel et al, 2011), and affect interpersonal relationships and leisure activities (Mitchell, et al, 2010). The clinical relevance of cognitive changes in patients with solid tumours is therefore significant, particularly in light of the increasing number of long-term cancer survivors in the population. In some patients, fear of this possible side effect may influence treatment decisions. For example, those offered adjuvant chemotherapy treatment as a preventative measure (rather than a cure) might choose not to undergo the treatment if they believe that it may affect their ability to return to work.

It is interesting that although there is evidence from other populations (e.g., traumatic brain injury, multiple sclerosis) that cognitive functioning is an individual variable that can affect functioning in various QoL domains (e.g. social functioning) (Girard et al., 1996; Hanks, Rapport, Millis, & Deshpande, 1999; Rao, Leo, Bernardin, & Unverzagt, 1991), the link between functional outcomes and cognitive deficits among cancer survivors has yet to be clearly analysed and developed (Reid Arndt, et al 2009). The magnitude and course of CRCI and its precise impact on HRQoL is still uncertain. However, with the increase in survival times, HRQoL has become a meaningful patient-reported outcome measure for individuals with cancer (Arndt, 2004). Improving HRQoL, along with preventing avoidable ill health, is an increasingly important aspect of health promotion (World Health Organisation, 1998). The relationship between OCI and HRQoL is more closely examined in Chapter 5.

2.7 Summary

This chapter introduced the concept of cognition, cognitive functioning, and its measurement. It outlined the domains of cognitive functioning that are essential to an individual's ability to function independently. It also highlighted the complexities associated with the measurement (both objective and subjective) and interpretation of NP assessments in relation to patients with cancer. The current evidence regarding CRCI is discussed in more depth in the following three chapters.

Chapter 3: Chemotherapy Related Objective Cognitive Impairment

3.1 Introduction

This chapter provides a review of the literature concerning the relationship between chemotherapy treatment for adult patients diagnosed with solid tumours (such as breast, colon and testicular) and OCI.

3.2 Background

Since the early 1980s, there has been increasing interest in the psycho-oncological research community regarding the cognitive impact of systemic chemotherapy (Silberfarb, Philibert, and Levine, 1980; Oxman & Silberfarb, 1980). As mentioned in Chapter 1, a commonly patient-reported post-chemotherapy treatment side effect is deterioration in cognitive function, colloquially referred to as "chemobrain" or "chemofog" (Olin, 2001; Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Phillips & Bernhard, 2003; Tannock, Ahles, Ganz & van Dam, 2004).

3.3 Prevalence

One of the first studies to report on the association between chemotherapy and the development of cognitive deficits was authored by Silberfarb and colleagues in 1980. A short battery of NP tests was administered to 50 cancer patients and it was reported that chemotherapy was "*the major variable associated with cognitive impairment*". However, systematic NP research examining the relationship did not begin in earnest until the mid-1990s to early 2000s (Brezden, Phillips, Abdolell, Bunston, & Tannock,

2000; Ahles, Saykin, Furstenberg, Cole et al, 2002; van Dam, Boogerd, Schagen, Muller et al, 1998; Wienke & Dienst, 1995). This coincided with the establishment of adjuvant chemotherapy as the new standard of care for treatment of most breast tumours (Abrams, 2001).

The first of such papers, in 1995 found that 75% (21 of 28) of breast cancer patients in the study who had completed chemotherapy showed moderate impairment on one or more NP measure when compared with published norms from healthy individuals (Wienneke & Dienst, 1995). The researchers noted that performance of the chemotherapy group as a whole was significantly below estimated premorbid function in areas of verbal and visual memory, mental flexibility and speed of processing, attention and concentration, visuo-spatial ability, and motor function.

That study was followed by van Dam and colleagues' seminal paper published in 1998. They assessed the prevalence of OCI in high-risk breast cancer patients randomised to high (*n*=34) or standard (*n*=36) dose adjuvant chemotherapy treatment followed by hormonal treatment compared with a control group of breast cancer patients who did not undergo adjuvant chemotherapy treatment (*n*=34). Cognitive impairment on the NP assessments was found in 32% of the patients having high dose chemotherapy, 17% of those on standard dose and only 9% of the controls. The researchers interpreted these results as evidence of neurotoxicity caused by systemic chemotherapy and an implied dose relationship between adjuvant chemotherapy treatment and OCI. Table 3.1 summarises the "cancer and cognition" studies published between 1995 and 2018, which examined CRCI in patients with solid tumours highlighting the incidence of cognitive impairment found.

As Table 3.1 indicates 18 cross sectional studies following van Dam's study (1998) supported a link between chemotherapy and OCI (Schagen et al, 1999; Brezden et al, 2000; Ahles et al., 2002; Schagen et al, 2002; Tchen et al., 2003; Castellon et al., 2004; Poppelreuter et al, 2004; Wefel et al., 2004a;Downie et al, 2006; Scherwath et al, 2006; Mehnert et al, 2007; Ahles et al, 2008; Bender et al, 2008; Schagen et al, 2008; Schilder et al, 2009; Reid Arndt et al, 2009; Von Ah et al, 2009; Kopplemans et al, 2012). However, 4 studies published during the same time period (i.e. 1999 to 2017) found no such relationship (Freeman et al, 2002; Donovan et al, 2005, Pedersen et al, 2009; Prokasheva et al, 2011).

Of the NP studies to date that have found a relationship between chemotherapy and OCI, it occurs in at least one cognitive domain in 8% (Scherwath et al, 2006) to 75% (Wienke & Dienst, 1995) of patients with cancer treated with chemotherapy, according to the definition of OCI used by each researcher (Table 3.1). (The issue of the definition of OCI employed by researchers is discussed in Section 3.4.4).

Although these early studies have been pivotal in drawing attention to the issue of CRCI, the studies that found OCI have not been consistent in their findings (Hodgson, 2008). The lack of consensus regarding prevalence of OCI in the "cancer-cognition" literature is most likely due to the heterogeneity of patients, methods and measurement in the studies. As indicated in Table 3.1, there is wide variation in study design, patient populations (type of cancer, disease severity, and management), and instruments used to assess cognition, criteria for defining OCI and/or method of analysis (Shilling, Jenkins, & Trapala, 2006) used by each researcher. These issues are discussed in detail in Section 3.4.

Table 3.1: Table of characteristics of CRCI studies since 1998 in patients with solid tumours

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
Silberfarb 1980	Cross sectional	50	Mixed cancer population	Hetero-geneous	TMT B, Digit Symbol, CCST	SDS Brief MAACL	18%	-	CT patients worse than non-CT patients
Oxman 1980	Longitudinal	11	Mixed cancer population	T1: Pre CT, T2: 24 hour after CT T3: 1 month after CT	WAIS; HRNB	-	-	No differences on any cognitive subtests at any time	-
Kaasa 1988	Longitudinal	51 44	NSCL (Non operable)RT NSCL (Non operable)CT	T1: Pre CT/RT T2: 5/11 weeks post CT/RT respectively	BVRT, VLT & TMT A & B	-	-	Both groups improved or showed no change after treatment. CT group showed tendency towards OCI but not statistically significant.	-
Cimprich 1992	Cross sectional	32	BC pre CT	3 days post-surgery	DS, Alphabet Backward, SDMT & Letter Cancellation	AFI; VAMS (depression)	Decreased capacity to direct attention; > 25% severely impaired	-	Depression not significantly correlated with NP tests of directed attention. Significant positive correlation between VAMS scores & overall mean scores on AFI. No significant relationship

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
									between scores on NP tests & overall mean on AFI
Wienneke & Dienst 1995	Cross sectional	28	BC post CT	~6 months post CT (5-12 months post)	9 domains: *Attention/concentration*: DS, Digit Symbol *Processing speed*: PASAT TMT A & B *Memory*: CVLT, CFT *Abstract/Conceptualisation*: Categories, Short Booklet, Similarities (WAIS-R) TMT A&B *Language:* COWA *Visuospatial:* Rey CFT, Block Design, Digit Symbol *Motor*: GP (2.5–3 hours)	BDI Clinical interview applying DSM-III-R criteria	75% moderate impairment in ≥1 tests		OCI not related to depression or type of CT or time since treatment
Meyers 1995	Cross sectional	21 25	SCLC pre CT SCLC post CT/RT (pre PCI)	Pre CT Post CT	6 domains: *Intellectua*l: DS, Digit Symbol, Arithmetic, Similarities Block design *Visual perceptual*: TMT A *Executive Function*: TMT B, WCST, *Language*: COWA *Memory*: Verbal selective reminding, BVRT *Motor dexterity*: Grip strength, GP	-	70–80% memory impaired pre CT Up to 38% have deficits in executive function approx. 1/3 have impaired motor coordination	-	No difference in OCI before or after treatment
Cimprich 1998	Longitudinal	74	BC	T1: 12 days pre surgery	DS forward & backward, SDMT & NCPC	-	When compared with published	Approx. 27% perceived effective	Older age & more extensive surgery increase likelihood

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
				T2: 15 days post-surgery			norms, mean test scores at T1 fell within normal range for healthy adults	cognitive functioning	of loss of attention due, in part, to greater risk of attentional fatigue
van Dam 1998	Cross sectional	34 36 34	BC post high dose CT BC post standard CT (FEC) 17 BC no CT	2 years post CT/ diagnosis	Domains not specified RAVLT, CFT, DS, Digit symbol, TMT A & B, D2 Test, Stroop, Word Fluency from Dutch Aphasia Society Test, FFTT, FVRT, FBCT, FVST. (2 hours)	Semi structured interview HSCL-25 EORTC-QLQ-C30	32%: BC high dose CT; 17%: BC standard dose CT; 9%: no CT.	SCI in 12%-38%: CT high dose SCI in 11%-31%: CT standard dose SCI in 6%: No CT (score ≥2/4 per domain)	No significant relationship between OCI & SCI. Significant relationship between subjective cognitive problems reported at interview & cognitive functioning scale of EORTC QLQ-C30
Schagen 1999	Cross sectional	39 34	BC post CT (CMF) BC no CT	>6 months post CT ~ 2 years	Domains not specified RAVLT, FFTT, FVRT, FBCT, FVST, Stroop, TMT A & B, D2 test, CFT, Word fluency from SAN, Digit Symbol, DS, Visual reproduction of WMS (2 hours)	Semi-structured interview EORTC-QLQ-C30 HSCL-25	28%: BC CT 12%: no CT Affected domains: attention, mental flexibility, speed of information processing, visual memory, & motor function.	SCI in 8%-31%: BC CT SCI in 0%-6%(score ≥2/4 per domain) Significantly more concentration problems 31% & memory problems 21% in BC CT	OCI unaffected by anxiety, depression, fatigue, & time since treatment & not related to SCI. Overall OCI score correlated with self-reported problems from interview. SCI appeared to be related to anxiety & depression

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
								CT patients scored significantly lower than no CT	
Brezden 2000	Cross sectional	31 40 36	BC on CT BC post CT HC	On CT 2 years	6 domains: memory, language, visual motor, spatial, attention & concentration, self-regulation & planning HSCS (25 min)	POMS	BC on CT: 48% BC post CT: 50% HC:11%	-	-
Cimprich 2001	Longitudinal	47 48	BC (55 to 79 years) Controls with no BC	T1:Pre surgery; T2: 2 weeks post-surgery; T3: 3 months post-surgery For non BC: post MMG & 3 months later	DS forward & backward; SDMT; NCPC	SDS; POMS (depression subscale)	T1: BC group scored significantly lower than HC on measures of attention. No significant change in attentional performance between T1 & T2. There was improvement at T3	-	T1: mean scores of attentions tests for both groups fell w/in normal ranges for healthy adults
Ahles 2002	Cross sectional	71 57	BC or lymphoma post CT BC or lymphoma no CT	10 years post CT	8 domains: *Verbal ability:* WAIS-III vocab, WRAT-3 reading, BNT, COWA*;* *Spatial ability:* WAIS-III Block Design,	SSRQ CES-D STAI FSI	CT: 39% No CT:14% Affected domains: verbal memory	Survivors treated with CT reported more SCI	-

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
					Verbal learning: CVLT; *Verbal memory:* WMS-R; *Visual memory:* WMS-R; *Psychomotor function:* WAIS-III Digit Symbol, TMT A & B; *Motor function:* Finger tapping*;* *At Attention:* CPT *Attention reaction time:* CPT (2h)		& psychomotor function most affected		
Castellon 2002	Cross sectional	36 17	BC CT BC no CT	2-5 years post diagnosis	6 domains: *Memory, attention/ concentration; processing efficiency, executive function, sensorimotor function, language.* Tests: TMT A&B, Category Test, GP, HVLT, Faces I & II, PASAT, RBANS, Stroop word & colour, COWAT, Sensory perceptual exam (2h).	CFQ	-	-	Visuospatial score significantly correlated with CFQ
Freeman 2002	Cross sectional	8 9	BC on CT BC post CT	on CT: at least 4 cycles 6–12 months post CT	TMT A&B; Category Test; GP; HVLT; Faces I & II; PASAT; RBANS; Sensory Perceptual Exam; Stroop; COWAT (2h)	CES-D; FACT B, Symptom Checklist 90-R, SSA Self-rate EF, PF &CF (scale of 1-10)	No impairment CT worse than post CT	Found a trend for a significant negative relationship between depression and self rated cognitive functioning	The relationship between self-report measures and cognitive performance showed a significant inverse relationship between depression (on

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
									CES-D) and the interference (Stroop divided attention). No other significant correlations between self-report measures and NP measures.
O'Shaugh-nessy 2002	Longitudinal (pilot study)	51 49	BC on CT on epoetin alpha BC on CT on placebo	Pre-CT, pre cycle 4 & 6 months post CT	EXIT 25; CLOX (20 min)	POMS; LASA (QoL); FACT A	No difference in groups at 6 months	-	Pilot study not all data analysed
Schagen 2002	Cross sectional follow up to 1999 study	22 23 31 27	BC post high dose CT BC post standard dose CT (FEC) BC post Standard dose CT (CMF) BC no CT	~4 years post treatment	7 domains: *verbal function, memory ,attention/concentration, speed of information processing, motor functioning, visuospatical functioning & mental flexibility:* RAVLT, CFT copy & recall, DS, Digit Symbol, TMT A & B; D2 Test, Stroop; Word Fluency, FFTT, FVRT, FBCT, FVST (2h)	Semi-structured interview EORTC-QLQ-C30; HSCL-25	CT post high dose: 14% CT standard; 9% CT post standard:13% No CT:11%	-	Overall OCI score correlated with self- reported problems from interview. Improvement in performance observed in all CT groups, but control group there was a slight deterioration
Servaes 2002	Cross sectional	150	BC <50 years at diagnosis (heterogeneous treatments)	Mean 28 months post treatment	CRT Digit Symbol	CIS; Self-reported memory & concentration	BC survivors worse - slower reaction time	-	Fatigue is correlated strongly with daily self-reported cognitive

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
		78	Age matched HC			SIP-8 (Mobility & Ambulation subscales)			functioning, but not with NP functioning
Kibiger 2003	Cross sectional	61	Mixed cancer population (BC, CRC, Lung, lymphoma etc)	Homogeneous	Oral TMT-B & modified Stroop	ZSDS; DRS BPI (3 items)	4.9% (n= 3) impaired on TMT. No-one impaired on Stroop; 5 impaired on Stroop word card 7 impaired on Stroop colour word card	-	-
Tchen 2003	Cross sectional	100 100	BC on CT HC	2-6 weeks post CT	HSCS TMT A & B; CPT	FACT F; FACT G; FACT ES	16% 4%	-	BC experienced much more fatigue than HC
Castellon 2004	Cross sectional	36 17 19	BC post CT BC no CT HC	2-5 years post diagnosis & surgery 2-5 years	8 domains: *Verbal Fluency*: COWAT; Verbal learning: CVLT *Verbal memory*: WMS; *Visual memory:* WMS-R Visual Repro I & II, RCF - recall; *Visuospatial Function:* Block design, RCF -Copy *Psychomotor Speed*: Digit Symbol, TMT A & B *Reaction Time*: Cal CAP *Executive Attention*: PASAT, Stroop (2h)	CFQ STAI; BDI-2 MOS SF-36 (Fatigue subscale)	BC CT performed significantly worse than BC no CT Neither group was significantly different from HC's Domains most impacted: visual memory, visuo-spatial function & verbal learning	-	Self-report measures significantly associated with anxiety, depression & fatigue but not related to OCI

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
Icononomou 2004	Longitudinal	102	Lung (n=22), BC (n=26), CRC (n=25) genito-urinary (n=12) other (n=17)	T1: Pre CT T2: Post CT	MMSE	EORTC QLQ-C30; HADS	15% with MMSE <24 at T1 & T2. No significant changes during CT in mean MMSE scores or in proportion of patients who scored < 24.	-	Significant correlation between OCI & SCI (CI of EORTC QLQ & MMSE)
Jacobsen 2004	Longitudinal	77	Mixed solid tumours	T1: Pre CT T2: Pre Cycle 4	DS; Digit Symbol; TMT, HVLT, COWA,	FSI.	Significant changes over time in TMT A&B & Digit Symbol & Visual Reproduction – improved	-	-
Poppelreuter 2004	Cross sectional	119	Mixed cancer population	Heterogeneous -several weeks to 19 years. post diagnosis	LMI & II; Digit span; TMT; TAP; MWT – B (45 mins)	FEDA; HADS	29 patients (24%) showed test performances below the 10th percentile in at least 2 different domains of cognitive functioning 72 (61%) displayed	18.5 - 38.7% (<10th percentile)	Attentional functioning was worse than memory. No significant correlation between OCI & SCI. Individual objective NP scores correlated with FEDA subscales

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
							deficits in at least 1 test.		
Wefel 2004a	Cross sectional	84	BC	Pre CT	*Attention:* WAIS-R/III DS, WAIS-R Digit Symbol; WAIS-R Arithmetic; WAIS-III LN; WMS-III MC; TMTA; *Memory*: HVLT; VSRT, NVSRT; ROCFT; *Language:* COWA; BNT; MAE Sequential Commands; *Executive function*: TMTB; Category Test; WAIS-III Similarities; *Visuo spatial:* WAIS-R BD; ROCFT Copy; JLO *Motor:* GRIP; GP (40-120 mins)	BDI; BDI-2; BAI; STAIS; MMPI	35% impaired overall cognitive function. Verbal learning (18%) &memory function (25%) were impaired significantly more frequently relative to normative expectations	-	-
Wefel 2004b	Prospective Longitudinal	18	BC	T1: Pre CT T2: 6 months T3: 18 months	7 domains *Attention*: WAIS-R DS & arithmetic *Processing Speed*: WAIS-R Digit symbol, TMTA *Learning*: VSRT & NVSRT long term storage *Memory:* VSRT & NVSRT delayed recall *Executive:* TMTB; CT; WAIS-R Similarities; *Visuo spatial:* WAIS-R Block Design *Motor skill*: GP	MMPI; FACT B	T1: 33% 61% decline in ≥1 tests between T1 & T2 T3: 50% of those who experienced decline improved & 50% remained stable	**-**	**-**
Cimprich 2005	Cross sectional	184	BC	**18 days pre surgery**	DS; TMT; TS & TW	AFI; SDS; POMS-SF	Mean scores of attention generally fell w/in normal	Perceived cognitive functioning: 25% effective,	No significant correlation between OCI & SCI; Symptom &

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
							range for healthy adults Age & education significant predictors of OCI. Older age associated with poorer performance on measures	50% moderate, 25% lower effectiveness	mood distress were significant predictors of SCI
Donovan 2005	Cross sectional	**60** **83**	BC post CT & RT (6 months) BC no CT, just RT	~1 year	5 domains: *Episodic memory*: CVLT, WMS-III - visual repro; *Attention*: DS, Spatial Span, TMT A & B; *Complex cognition*: Digit Symbol; *Motor*: Finger Oscillation Test; *Language*: COWA	MASQ	No difference between groups.	No significant difference between groups Sample as a whole reported SCI occurring frequently	-
Mar Fan 2005	Longitudinal (1 & 2 year follow up of Tchen Study)	104 102	BC post CT HC	T1: after 3 cycles of CT (CT n=104) (HC n=102) T2: 1 year post T1 (CT n=91) (HC n=81) T3: 2 years post T2 (CT n=83) (HC n=81)	6 domains (*memory, language, attention/ concentration, visual motor, spatial & self-regulation):* HSCS, TMT A & B, CCP	FACT F; FACT G; FACT ES	Moderate/ severe CI decreased in CT patients from 16% to 4.4% & 3.8% & in HC from 5 % to 3.6% & 0%	-	No significant difference in overall QoL between BCs & HCs by T2 On-going association between fatigue, menopausal symptoms, & overall QoL throughout study
Shilling 2005	Longitudinal (preliminary analysis of	50 43	BC pre CT HC baseline	T1: pre-treatment baseline	4 domains: *Visual memory:* Complex Figure;	CFQ; FACT F	Decline in 34% CT vs. 19% HC	SCI related to QoL & GHQ12 scores	-

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
	Jenkins article)			T2: 4 weeks post CT (6 months in HCs)	*Executive Function*: Stroop; *Working memory*: Spatial span, DS, Letter/number sequencing; *Processing Speed*: Letter cancellation task	FACT B & ES & F (patients only); GHQ-12			
Bender 2006	Longitudinal	19 15 12	BC had CT only BC - CT & Tam DCIS (just surgery)	T1: after surgery pre CT T2: 1 week after CT T3: 1 year after T2	6 domains: *Attention*: DS, TMTB *Concentration*: DVT; *Verbal learning & memory:* RAVLT, Rivermead Behavioural Memory Test; *Visual Learning & memory*: RCFT *Psychomotor Efficiency*: GP TMTA; *Visuospatial Ability*: RCFT (90 mins)	PAOF BDI-II POMS	Worse memory in CT groups: CT& Tam deterioration in visual & verbal memory; CT alone - worse verbal working memory	CT &Tam reported more memory complaints	No relationship between OCI & SCI
Downie 2006	Cross sectional	21	BC post CT	2-6 weeks post CT	5 domains: *verbal memory, language, attention & concentration, visual motor/spatial ability & self-regulation & planning:* HSCS	Semi structured interview FACT G FACT F FACT ES	Scores on HSCS suggested 61 % difficulties with language & 48% memory Language was most severely affected domain, then memory	78% & 95% reported language & memory problems respectively 90% reported at least mild difficulties with attention &	Fatigue common in all. No correlation between HSCS & subjective reports

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
								concentratio n	
Hurria 2006a	Prospective Longitudinal	28	BC aged >65 years	T1: Pre CT T2: 6 months post CT	7 domains: *Attention:* TMT A; *Verbal memory:* HVLT-R; *Visual memory*: RCFT; *Verbal function*: WRAT-R reading subtest, BNT, COWAT: *Spatial function:* WAIS-III Block design, RCFT; *Psychomotor function*: WAIS-III Digit symbol, TMT A& B; *Executive function*: TMT B, Stroop colour & word, COWAT (45 mins)	FACT B ADLs IADLs KPS MMSE GDS	11% at T1 25% decline between T1 & T2 Most affected domains - Visual memory, spatial function, psychomotor function, & attention.		
Hurria 2006b	Prospective Longitudinal	45	BC aged >65 years	T1: Pre CT T2: 6 months post CT	-	SSRQ	-	Patients who perceived poorer memory than average at T1 were more likely to report further memory deterioration at T2 (63%) than those who perceived that their memory was average or better than	-

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
								average at T1 (27%)	
Jenkins 2006	Longitudinal	85 43 49	BC who will have CT BC not for CT HC	T1:Pre CT T2: 6 months/post CT T3: 18 months/ 12 months post CT	5 domains: *Verbal memory:* WMS; AVLT *Visual memory*: Complex figure; *Executive function*: Stroop; *Working memory:* DS; Spatial span; Letter/number sequencing *Processing speed*: Letter cancellation task	BCFQ FACT-F FACT B, F (patients only) FACT ES GHQ -12	CT: Decline in 20% at T2, 18% at T3 no CT: 26% T2 & 14% T3 HC: 18% T2 & 11% T3 i.e. no real difference between groups most affected domains = Concentra-tion & memory Improve-ment found in 22% CT, 16% no CT & 16% HC	BCFQ not reported CT reported significantly more SCI post treatment compared to T1	Individual objective test scores correlated with BCFQ scores QoL & SCI significantly correlated. No differences in SCI between BC & HC. Qol scores not significantly lower in participants with reliable decline on OCI measures at T2 & T3
Schagen 2006	Prospective longitudinal	28 39	BC high dose CT BC standard dose CT	T1: Pre CT T2:12 months post T1 (i.e. 6	6 domains: *focused-sustained attention; working -verbal -visual memory; processing speed; executive function;*	-	Greater deterioration in high dose CT than controls over time	-	-

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
		57 60	BC no CT HC	months post CT)	*verbal/motor function* 10 tests not specified				
Scherwath 2006	Cross sectional	24 23 29	BC post high dose CT BC post standard dose CT BC no CT	5 years post CT	TMT A&B; TAP; Test d2; WMS-R; VLMT (Form A); ROCFT; RWT; LPS(<2 h)	-	8%: post high dose CT 13% -post standard dose CT but not significantly different 3%: No CT	-	-
Vardy 2006	Longitudinal	31 77 51	94% BC w/in 2 years of CT < 65 & 2 CRC w/in 2 years of CT < 65 HC BC no CT (just for FACT-Cog)	3 assessments, 7 – 90 days apart T1: after 3 cycles & w/in 2 years of CT T2: ~ 17 days later T3: ~ 17 days later	Eng Speakers (n=20)- HSCS, All participants: CogHealth (18 mins)& PC based Headminder	FACT Cog Structured interviews	Cancer group on HSCS: 30% (6/20) had mod-severe CI at T1; 5% at T2 & 6% at T3 T1: 17/31 (55%)scores > 1 SD below mean for norm data in ≥1 domain Headminder T1: 8/31 (26%)scores >1 SD below mean for norm data in ≥2 domains CogHealth	On FACTCOG, 9 of 19 patients (47%) rated their cognition as >1 SD below per CT BC control group	No correlation between NP test & FACT-Cog. Poor correlation between patients' perception of their SCI & OCI

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
Hermelink 2007	Longitudinal	109	BC	T1: PreOp CT T2: before last CT (approx. 5 months post T1)	WMS-R Logical Memory I & II DS Digit Symbol TMT A & B D2 Test RWT	FEDA EORTC- QLQ-C30 HADS	1/3 showed compromise pre CT; 27% had OCI at the end of CT; 28% improved.	Significant increase in SCI at T2 compared to T1	No correlation between OCI & SCI, anxiety & depression. SCI significantly correlated with anxiety & depression.
Mehnert 2007	Cross sectional	24 23 29	BC high dose CT BC standard dose CT Early stage cancer no CT	5 years post CT	TMT A&B; TAP; D2 Test; VLMT; WMS-R; ROCFT; RWT; LPS; HAWIE-R	EORTC-QLQ-C30 FEDA MFI-20 (German version)	Global OCI: 13% standard-dose; 8% high-dose & 3% in no CT group (<5th percentile on ≥4 tests of 18)	0-37% (FEDA score ≥3 (scale 0-4) on each subscale)	82% reported fatigue. Standard dose CT: DS, visuo-spatial working memory significantly correlated to SCI
Shilling & Jenkins 2007	Longitudinal	93 49	BC CT BC no CT	T1: Pre CT T2: 1 month post CT T3: 6 months post CT (18 months for non-CT)	see Jenkins 2006 above for full list	Structured interviews at T2 & T3 only GHQ -12 FACT B	See Jenkins et al 2006	71% poor memory at T2; 60 % at T3. 64 % poor concentration T2; 42% at T3	SCI was unrelated to OCI; but was associated with psychological distress and QoL.
Ahles 2008	Cross sectional	110 22 45	Invasive BC non-invasive BC matched HC	Post-surgery pre CT, RT or HT	8 domains: *Verbal ability:* WRAT-3, Vocabulary (WASI), Verbal Fluency Test (D-KEFS);	MASQ STAI, CES-D FSI	Scores within normal range. Lower overall cognitive performance in invasive BC	No group differences on MASQ total score or any subscale	No significant correlations between any of NP domains & self-report measures of

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
					Verbal memory: CVLT-II, Logical Memory I & II (WMS-III); *Visual Memory:* Faces I & II (WMS-III); *Working memory:* PASAT; *Processing Speed:* TMT, Color word interference test; GP, Digit Symbol; *Sorting*: Sorting Test; *Distractibility:* CPT; *Reaction Time:* CPT; Block Design: WASI		(22%) compared to non-invasive BC (0%) & HC (4%) Most affected domains were verbal ability & memory domains (verbal, visual & working)		depression, anxiety or fatigue. No significant correlation between OCI & SCI
Bender 2008	Cross sectional	30 50 48	BC CT CT with tamoxifen DCIS - No CT/Tamox-ifen	2 years post treatment	5 domains: *Attention*: DVT, TMTA, DS *Learning & memory*: RVLT, ROCF, RBMTS, FWS, TMT; *Psychomotor speed*: GP, DSST; *Mental flexibility*: TMTB; *Visuospatia*l: ROCF	PAOF POMS BDI-II	-	CT patients reported significantly more memory problems (25%) than HC (6%).	SCI correlated significantly with anxiety, depression, fatigue & menopause symptoms but not with OCI
Jansen 2008 prelim to 2011	Longitudinal	32	BC CT < 65	T1: Pre CT T2: week after cycle 4 T3: 1 week post CT; T4: 6 months post CT	RBANS Stroop GP	AFI CES-D STAI LFS	13% pre CT. Most affected domains = visuospatial skills & total cognitive scores 37% post CT. Most affected domains =	Significant decrease over time in SCI (attention)	No significant correlations between SCI & OCI. Significant correlation between SCI & depression

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
							visuospatial skill, motor function, imm memory & language. Significant improvement in executive function		
Schagen 2008	Cross sectional	70 57 55	Testicular (S+CT) Testicular (S+RT) Testicular (S only)	6 months post treatment	See Schagen et al 2006	Structured interview re memory; EORTC QLQ HSCL-25 MFI-20	S +CT: 14.30% S+RT: 17.50% S only: 5.50%	32% 32% 27%	No significant correlation between overall OCI & SCI. SCI related to anxiety & depression & fatigue
Stewart 2008	Longitudinal	61 51	BC CT BC HT	T1: pre CT post-surgery T2: w/in 2 months post CT	8 domains: *Executive function*: PASAT, TMT B, WCST; *Language function*: BNT, COWA; *Motor:* GP; *Processing speed*:Digit Symbol (WAIS-III), Symbol Search (WAIS-III), TMTA; *Verbal learning & memory*: CVLT, Logic memory II (WMS-II); *Visual learning & memory:* RVLT, Family Pictures II (WMS-II); *Visuospatial function*: Block design (WAIS-III);	POMS The Quick Test	31% (19/61)CT v 12% (6/51) non CT Working memory most affected domain	n/a	CT participants who declined were less educated & higher baseline depression scores

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
					Working memory: Arithmetic (WAIS-III), CCCs, DS & Letter Number sequencing (WAIS-III), Spatial span (WMS-II).				
Whitney 2008	Longitudinal	14	NSCL	T1: pre-treatment T2: 1 month post CT T3: 7 months post CT	4 domains: *Executive Function*: WCST-CR; COWA *Visuo-spatial function*: Block Desgin; *Memory*: HVLT-R, RCFT Immed; *Attention*: CPT	AMNART PHQ BFI FACT-L	T1: 71% showed OCI T2:62% experienced OCI on ≥ 1 of 6 tests but these effects dissipated by T3. Conceptual flexibility most affected domain		No significant correlations between OCI & age, mood fatigue or QoL at any time point
Collins 2009	Longitudinal	53 40	BC CT (50-65 years) BC HT (50-65 years)	T1: Pre CT T2: 1 month post CT T3: 1 year post T2	8 domains: *Executive Function:* PASAT, TMTB, WCST; *Language function*: Boston naming test, COWA *Motor:* GP; *Processing Speed*: Digit symbol, Symbol search, TMTA; *Verbal Learning & Memory*: CVLT, Logical memory II, WMS-III; *Visual Learning & Memory:* RVLT, Family pics II;	POMS	OCI at T2: BC CT: 34% BC HT:13% OCI at T3: BC CT: 11% BC HT: 10%		CT patients who were also on HT at T3 tended to perform more poorly on NP tests than those not on HT - particularly on processing speed & verbal memory

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					Visuospatial Function: Block design; *Working memory*: CCCs; Arithmetic, DS, Letter-number sequence & spatial span (all WAIS-III).				
Jim 2009	Cross sectional	97 90 187	BC Surgery &CT/ CT&RT BC Surgery & RT HC	Approx. 6 months post completion of treatment	*Episodic Memory: Verbal:* CVLT *Nonverbal:* Visual Reproduction subtest of WMS-III; *Attention:* DS, Spatial Span, TMT A and Ruff 2 & 7 Test *Complex Cognition*: Digit Symbol (of WAIS-III), TMT B and COWA	MAQ FSI CES-D	When compared with HCs, BC CT performed significantly worse on tests assessing episodic memory and complex cognition. Effect sizes small.	No group differences were observed with regard to cognitive symptoms.	No significant relationship between OCI & depression or fatigue
Mehlsen 2009	Longitudinal	34 12 12	BC CT < 65 cardiac patients < 65 HC < 65	BC: pre CT & 4/6 weeks post CT Cardiac: 4 days post hospitalisation & 3 months HC: interval of 12 -16 weeks	*Processing speed*: WAIS-III Coding & Symbol search, TMT A & B *Working memory*: WAIS -III Arithmetic, DS & Letter number sequencing; *Visuospatial ability:* RCTF-C *Visual memory*: RCTF-IR, RCTF -DR, RCTF - recognition *Verbal memory*: RAVL, WMS-III LM-IR & LM-DR *Verbal fluency*: WF-animals, WF-F, WF-N *Response inhibition*: Stroop	BDI-II POMS PSS PSI Social Support ques of TSLS Questions re concentration attention & memory	Decline on > 2 NP measures: BC 29%, Cardiac: 25% HC: 17 % Improvement on ≥3 NP measures in BC: 24% Cardiac: 33% HC: 25%	BC CT group reported decreases in attention, memory, & concentration, whereas other 2 groups reported no changes or improvement in cognitive function	CT not associated with CI. No associations found between SCI & decline in NP scores

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Pedersen 2009	Cross sectional	36 36	Testicular CT Testicular non CT	2 - 7 years post treatment	*Processing speed*: WAIS-III CD & SS, TMT A & B *Working memory*: WAIS-III A, DS, LN *Visuospatial construction*: RCFT Copy *Visual learning & memory*: RCFT Recall & recognition *Verbal learning & memory*: WMS-III Imm & delayed recall, RAVLT *Verbal fluency*: Animals, F & N words *Response inhibition*: SCWT interference score (90 mins)	BDI-II POMS (dep-ression) PSS SSQT	CT: 5.6% Non CT: 8.3 %	-	Psychological measures not associated with no. of NP tests scored in impaired range. No difference in proportion of OCI patients in CT group compared to no CT group (X = 0.22, p = .64).
Schilder 2009	Cross sectional	80 48	BC CT post-menopausal HC	2 years post CT	8 domains: *Verbal memory*: RAVLT (Dutch short version) WMS -R memory subtest, Visual Association test *Working memory*: WAIS-III LN *Attention/concentration:* Stroop Card 1 & 2, TMTA *Mental flexibility*: Stroop card 3, TMT B *Information processing speed:* Fepsy reaction times *Manual motor speed*: Fepsy finger tapping *Verbal fluency* (D A T) Category fluency	CFQ Interviews re cognitive complaints EORTC-QLQ-C30 HSCL MFI FACT B & ES	Approx. 25% (28% of CT & Tam & 24% CT & exemestane) v 6% HC. Most affected domains = verbal fluency & information processing speed	25% reported memory complaints	Significantly more patients than HCs reported complaints with daily memory 25% v 6% SCI significant correlations with anxiety, depression, fatigue & menopausal symptoms but not OCI

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Quesnel 2009	Longitdudina	41 40 45	BC CT <70 BC RT <70 HC<70 - JUST T1	T1: Pre CT T2: After 1st CT T3: 3 months post CT	*Verbal memory*: RAVLT *Visual memory*: CFT *Attention & concentration*: DS, VMS, Ruff 2&7 *Executive Function*: TMT *Speed of information processing*: SDMT *Verbal fluency*: VFT (60-90 mins)	CFQ HADS MFI ISI EORTC-QLQ-C30 Menopause specific QoL questionnaire WAIS-III PC - just at T1	CT impaired on verbal fluency		CT reported more cognitive difficulties than non-CT at T2 which returned to baseline level at T3
Reid Arndt 2009	Cross sectional	46	BC CT	1 month post CT	5 domains: *Immediate memory*: WMS-III logical mem I WMS-III visual reproduction I *Delayed memory*: logical mem II WMS-III visual reproduction II Rey AVLT Delayed Recall *Attention:* TMT A, WAIS-III DS *Executive Functioning*: TMT B , Stroop *Verbal Fluency*: COWAT, Category Fluency	Hesitation scale POMS-SF WRAT-3 FACT B; CIQ Social role functioning question	OCI in executive functioning (27.1%) & verbal fluency (41.3%)	-	OCI had no significant impact on QoL. Evidence of deficits in executive functioning adversely affecting engagement in social activities & roles. Fatigue associated with poorer QoL
Von Ah 2009	Cross sectional	52 52	BC CT HC	1.2 - 15.8 years post completion of primary cancer therapy	RAVLT DS SDMT COWA	SRS CES-D	BC: 17% impaired on AVLT Sum Recall;	Approx. 14% of BC group self-reported clinically significant levels of	No relationship between self-report of memory & actual measured

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							17% on AVLT Delayed Recall; 25% impaired on one or both of these indices In executive cognitive function - 12% were clinically significant impaired on COWA 64% had no scores at or below the 7th percentile of HC cut-off; 21% had 1 test below cut-off; 15% had ≥2 indices below cut-off	memory impairment	memory performance
Vearncombe 2009	Longitudinal	138 21	BC CT BC no chemo	T1 -Pre CT T2- 1 month post CT	*Verbal learning & memory:* AVLT *Visual memory*: WMS -III Visual reproduction imm delayed & recognition *Working memory*: WAIS-III Backward DS *Processing speed*: SDMT oral version	HADS FACT B FACIT - Fatigue	16.9% on multiple tests. Affected domains = verbal learning & memory, abstract	-	Higher levels of fatigue, depression & lower functional wellbeing at T1 significantly associated with change in NP measures

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					Attention: TEA Visual elevator & telephone search *Executive function*: WAIS-III Matrix reasoning, Stroop, DKEFS Card sorting task, COWA *Motor co-ordination*: Purdue Pegboard (2.5 h)		reasoning & motor co-ordination.		
Weis 2009	Longitudinal	90	BC CT	T1: 9 months post CT start of rehab (n=96) T2: ~26 days later (n=96) T3: 6 months after T2 (n=90)	TAP RBMT WMS-R LGT-3	FEDA HADS MFI-21 EORTC-QLQ-C30	21% at T3 Most deficits in sustained attention & verbal semantic memory	36%at T3(1.5 SD below mean of norms)	10 patients had both OCI & SCI; 22 only SCI & 9 only OCI
Ahles 2010	Longitudinal	60 72 45	BC CT BC no CT HCs	T1: Pre CT T2: 1 month post CT T3: 6 months post CT T4: 18 months post CT	*7 domains:* *Verbal ability*: WASI, D-KEFS *Verbal memory*: CVLTest-II,20 Logical Memory I & II (WMS-III) *Visual memory*: Faces I & II (WMS-III) *Processing speed*: Digit Symbol-Coding (WAIS-III), TMT, Color word interference test, GP *Sorting*: Sorting Test (D-KEFS) *Distractibility*: CPT	MASQ STAI CES-D FSI	Older patients with lower pre-treatment cognitive reserve on CT performed worse on processing speed compared to non-CT & HCs. CT also has effect on verbal ability	CT group as a whole reported more SCI than other groups	-

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					Reaction time: CPT		which resolved over time		
Debess 2010	Longitudinal	120 208	BC CT < 60 HC	T1: Pre CT T2: 6 months later	ISPOCD battery VLT CST Stroop LDCT	Danish GPS POMS EORTC- QLQ-C30 Questions about memory etc	4.1% decline on ≥2 tests No significant difference between groups at T2		No significant correlations between objective tests & subjective ratings of cog function
Reid Arndt 2010	Longitudinal	46	BC CT	T1:1 month post CT (n=46) T2: 6 months post CT (n=39) T3: 1 year post CT (n=33)	5 domains: same as 2009 paper	Hesitation scale POMS-SF BDI-II FACT B CIQ Social role functioning question	< 20% across tests evidenced deficits in delayed memory, processing speed response inhibition & verbal fluency at each time point.	-	RCI suggested statistically reliable improvements in each domain for modest portion of participants
Tagar 2010	Longitudinal	30 31	BC CT BC No CT	T1:Post surgery pre CT T2: 6 months post T1 T3: 6 months post T2	5 domains: *Motor*: GP, Finger Tapper *Language*: COWAT, BNT *Attention/concentration/working memory*: TMT, WAIS-III DS, digit symbol, number/letter Arithmetic *Visuospatial*: RCFT	Participants rated perceived memory BDI II ZAS	No OCI T1: CT group had lower verbal memory scores than no-CT group	SCI in CT group went up over time: T1 = 27%, T2 = 43%, T3 = 46%	Memory problems: CT: T1, 30% T2, 39% T3, 38% Non CT: T1 = 32% T2 = 35% T3 = 31%.

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									No correlation between OCI & SCI
Wefel 2010	Longitudinal	42	BC CT	T1: pre CT (N=42) T2: during CT (2.9 months after T1) (N=37) T3: shortly after CT (7 months after T1)(N=33) T4: > 13 months post CT (N=28)	4 domains : *Attention:* WAIS-R DS *Processing speed*: WAIS-R Digit symbol, TMT A *Learning & memory*: HVLT *Verbal memory*: Buschke Selective Reminding Test *Visual memory*: BVRT *Executive Function*: MAE COWA, TMTB	FACT B BDI STAI	21% 9 of 42) pre CT; 65% (24 of 37) at T2 61% (17 of 28) at T3. Within this group of patients, 71% (12 of 17) evidenced continuous decline from the acute interval, and 29% (5 of 17) evidenced new delayed OCI Learning & memory, executive function & processing speed most affected	-	Learning & memory declined most frequently at T4, with less frequent declines in executive function & processing speed. Cognitive decline was not associated with mood or other measured clinical or demographic characteristics, but late decline may be associated with baseline level of performance.

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Jansen 2011 (linked to 2008)	Longitudinal QoL study	327/ 562	CRC	N/A	See previous study	EORTC QLQ-C30	see previous study	CT associated with lower long term QoL	CT associated with lower long term QoL
Prokasheva 2011	Cross sectional	20 20	BC CT BC no CT	>18 months post CT (i.e. 2-5 years post diagnosis)	Doors & People	Hebrew version of Dutch Cog Problems in daily life checklist	40% in both grps had mild OCI 7.5 % moderate impairment in episodic memory. CT group significantly different to non-CT on verbal recall	69% memory complaints (reported problems on 2 items for the domain) no overall score provided	SCI unrelated to NP performance Memory deficits were observed in BC patients who receive either CT or Tam alone compared to age-adjusted norms
Skaali 2011	Longitudinal	122	Testicular	T1: After surgery pre CT T2: 8 -23 months post CT/T1: 31 no CT, 38 had 1 CT cycle & 53 had 2 or more CT cycles	5 domains: *Attention, concentration & working memory*: SWM & CRT *Learning & memory*: HVLT R, PAL *Speed of information processing*: TMT A, CWI 1&2 *Executive Function*: CWI 3&4, IED *Motor function*: GP	Semi structured interviews IES; SCIN EPQ-18; CAGE Questionnaire (assessed hazardous alcohol-use by four items); Fatigue question	Both CT groups: 29% at follow up - problems identified in memory or concentration	20% had an increase in SCI from T1 to T2 - larger %'s in CT groups: 29% in I-CT group; 25% in multi CT group; 3% in no CT No significant	No significant association between increase in SCI & a decline in OCI from T1 to T2. An increase of SCI from T1 to T2 was significantly associated with higher follow-up level of psychological distress, fatigue, lower level of

First Author	Study Design	Sample Size	Patient Groups & Controls	Time of Assessments	NP Measures & Domains Assessed	Subjective Measures	% OCI	% SCI	Significant Relationships
								difference between 1 CT & multi CT group	education & worsening Raynaud like symptoms.
Wefel 2011	Cross sectional	69	Testicular pre CT	Pre CT post-surgery	6 domains: *Attention*: WAIS-R DS *Psychomotor speed*: WAIS-R Digit symbol, TMT A *Language*: COWA *Learning & memory*: HVLT T1-3 *Executive function*: TMT B *Motor*: GP	CES-D STAIS	46% Most affected domains = learning & memory, executive function, upper extremity fine motor dexterity	-	10% reported clinically significant symptoms of depression; 7% anxiety. Association between psychomotor speed & depression & anxiety
Biglia 2012	Longitudinal	40	BC CT < 65	T0: pre CT T1: I month post T0 T2: 3 months post T1 T3: 6 months post CT	MMSE, Attentive matrices, DS forward, TMT A & B, Phonemic word fluency, Short story imm recall, Short story delayed recall, RAVLT - imm & delayed Raven's progressive matrices	HADS Mini MAC EORTC QLQ-C30 MADRS Karnosfky Performance status FACT-Cog	T3- decrease in global cognitive functioning & visual selective attention. Verbal skills, oral learning & short term memory showed a non-significant worsening trend. Global cognitive functioning	Women did not believe they had important cognitive problems: FACT-cog total score was 3.18, i.e close to 4 which indicates 'absence of the problem'.	SCI unrelated to OCI. SCI associated with depression, anxiety, reported sadness & some items of the EORTC QLQ C30

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							pre CT was good		
Hedayati 2012	Longitudinal	18 45 14 69	BC CT BC HT BC no adjuvant treatment HC	T1: Pre diagnosis T2:Post surgery pre CT T3: 6 months after start of CT T4: 3 months post T3	Headminder web-based neuropsychological battery Cognitive Stability Index (30 mins) - has 10 subtests for 4 domains: *Attention, memory, response speed & processing speed*	Swedish BDI EORTC QLQ-C30	Scores for response speed & memory declined immediately after CT completed. These scores tended to improve at 3 months follow-up	-	After beginning hormone treatment, women's memory scores tend to be lower than HCs suggesting a possible age-dependency or disease- & host-related factors
Kopplemans 2012	Cross sectional	196 1509	BC CT HC	21 years post CT	MMSE - used to screen 6 domains: *Processing speed*: LDTS, Stroop colour word test *Learning & memory*: 15-WLT, *Visuospatial ability*: DOT *Verbal fluency (executive function)*: WFT *Psychomotor speed & dexterity:* PPB	Interview on clinical & socio demographic factors including question re medical history; CES-D Subjective memory complaints measured with 3 yes/no questions	CT group significantly worse on immediate & delayed verbal memory, processing speed, executive function & psychomotor speed	Proportion of BC who reported problems with re-membering did not differ between groups. BC CT were more likely to report an increase in word-finding problems & forgetting pursuits.	BC CT experienced fewer symptoms of depression but had significantly more memory complaints SCI was not related to OCI
Andries 2013	Longitudinal	57	CRC	T0: pre-CT	MMSE	Emotional distress: PDI,	Significant improvement	Improvement in	

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				T1: end of CT T2: 6 months post T1	*Visuo-spatial memory*:, (Clock Drawing Test, CDT, Rey Complex Figure, copy and recall), *Information processing speed:* TMT-A, TMT-B *Verbal memory* (Rey Auditory Verbal Learning Test, call and recall),	Anxiety: STAI-Y1 and Y2), Depression: GDS for > 65 years old; BDI <65 years old	in T2 scores vs T0, especially in tests measuring verbal memory and information processing speed	emotional performance, anxiety and depression a short time after CT	
Cruzado 2014	Longitudinal	81	CRC	T1: pre-CT (n=81) T2: pre last-CT (n=73) T3: 6 months post last CT (n=54	*Attention & visual-motor ability:* TMTA *Executive function*: Digit symbol, Inter Stroop, TMT B *Verbal memory*: Imm-Mem, Imm-Mem-Q Delayed-Mem, Delayed-Mem-Q *Verbal learning*: LMWT Spanish adaptation	EROTC QLQ - C30 HADS BF13	37 % pre CT, mainly in processing speed & pscyhomotor executive function. 54% improved at T3, whereas 18% showed worsening on at least 1 test T3 - main domain affected = verbal memory with an acute decline in 56%	Not significant	No correlation between objective tests & QoL, anxiety, depression, fatigue or haemoglobin level
Lange 2014	Cross sectional	123	BC > 65 years	Pre CT	4 domains:	FACT-Cog BDI	41% overall OCI;	Healthy subjects had	Cognitive complaints were

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					Episodic memory: Verbal - G&B procedure; Visual - RCF *Working memory*: WAIS-III Arithmetic, DS & LN *Information processing speed*: TMTA *Executive function*: TMT B, Verbal fluency: category (animal) & Letter P	FACIT - Fatigue; FACT B GDS IADL ADL	29 % on 1 test, 12% on ≥2 tests 21% impaired visual episodic memory 16% impaired executive functions	significantly more complaints on FACT-Cog PCI & PCA than patients	correlated with verbal episodic memory impairment. 6% had anxiety; 10% depression & 29% severe fatigue
Mandelblatt 2014	Cross sectional	164 182	BC > 60 years HC	Post op & pre systemic therapy	*Attention, working memory & processing speed*: DS, TMT A, DST, Driving scenes. *Language*: Boston naming test, Category fluency *Executive Function*: TMT B, COWAT, Figure drawing *Learning & memory*: Logical memory I & II, List A & B immediate recall, List A short recall delay, long delay *Visuo spatial*: Figure drawing copy (55 mins)	Structured survey	14 %: BC 15% HC Trend: BC with more advanced disease stage toward lower executive function than HC. BC with high comorbidity levels had higher rates of OCI than those with low comorbidity levels (25.7% v 4.4%).	No self-reported differences in cognition between BC & HC	BC reported significantly higher levels of anxiety, depression, fatigue & QoL than HC. Surgery, anxiety, depression, fatigue, & current physical or emotional function were not associated with OCI in any group.

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Hermelink 2015	Cross sectional	166 60	BC <65 years Negative mammogram (controls)	Pre CT	*Attention*: TAP, TMTA & computerised equivs *Memory & Learning*: DS, VLMT & computerised equivalents *Executive function*: TMT B, RWT & computerised equivalents (1h)	PTSD diagnostics FEDA EORTC-QLQ-CF PHQ-D	BC scored worse than controls on 2 of 20 cognitive indices Risk of overall OCI was not increased in BC group. Both groups scored statistically significantly below or, more rarely above the pop norms on > 1/3 cognitive indices		SCI associated with Go/Nogo omission errors & more pronounced in BCs. The effect of having cancer on Go/Nogo errors was mediated by PTSD symptoms
Hess 2015	Longitudinal	231	Ovarian CT	T1: Pre CT T2: Pre 4th cycle T3:after 6 cycles T4: 6 months post CT	Headminder Clinical Research Tool (a computerised cognitive function test) (3 domains) *processing speed, motor reaction time & attention*	FACT O FACT Ntx HADS; PAF	17% at T4. Attention was most affected domain	-	No significant relationship between cognitive function & QoL
Vardy 2015	Longitudinal	173 116 73	CRC CT CRC No CT	T1: pre CT T2: 6 months (n =137, 90,	4 domains: *Attention & working memory*: DS, spatial span & LN	FACT F FACT G GHQ	T1: 43% CRC CT & no CT 5% HC	SCI was more common at T2 in CT participants (32%) than	No association between overall cognitive function & fatigue, QoL, anxiety/depressi

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		72	Metastatic CRC HC	52 & 72 respec) T3: 12 months (n =118, 87, 41 & 70 respec) T4: 24 months (n = 99 & 72 CRC CT & No CT)	*Processing speed:* Digit symbol, TMT A & B *Verbal learning & memory*: HVLT *Visual learning & memory*: BVMT CANTAB: Attention & complex reaction time, Attention & simple reaction time, Discriminability - memory, Verbal learning & memory, Spatial working memory, Discriminability learning		T2: 39% CRC CT & no CT ; 6% HC T3: 46% CRC CT & no CT 13% HC T4: 36% CRC CT & no CT Most affected domains = Processing speed, verbal learning/ memory & attention/ working memories Consistent results obtained using CANTAB; patients with localized CRC had significantly more OCI than HCs at	in no CT group (16%; P = .007) or in HC's (12.5%). No significant differences between groups at T3	on or any blood test Objective cognitive function was only weakly associated with SCI in executive function & processing speed. More participants who had CT had SCI at T2 (32%) 'v' non CT (16%) with no significant difference at T3

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							each assessment; No significant difference between CT patients & no CT patients.		
Klemp 2017	Longitudinal	20	BC	T1: pre CT (n=20) T2: after cycle 3 of CT (n=20) T3: 2-3 weeks post CT (n=20) T4: 8 years later (n=16)	HSCS @ T1, T3 & T4	CDS (26 item); The Cognitive Problems Scale from the BCPT; 4 interview questions related to self-reported changes in cognitive functioning at T3 & T4 FACT Cog @T4 MOS SF36 BDI BFI	No significant changes in HSCS total scores	Significant decline over time for BCPT. Significant change between T2 & T3 as well as T1 & T3. Significant increase in depressive & fatigue symptoms between T1 & T3. Fatigue decreased from T3 to T4 – with a return to near baseline at T4	SF-36 PCS scores significantly improved over time. Higher QOL was correlated with better subjective cognitive function (r = 0.705, p = 0.002) at T4 Depression and fatigue were associated with participants' scores on the BCPT at T3 and T4.

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Lange 2018	Longitudinal	58 61 62	All > 65 years BC CT BC no CT HC	T1: pre T2: post	4 Domains: *Episodic memory, working memory, processing speed, executive function*: Grober and Buschke procedure, RCT, WAIS-III arithmetic, DS & letter number sequencing, TMT A&B, verbal fluency test.	-	T1: 46% BC CT 38% BC no CT	-	31% without initial OCI developed impairment; 15% normal aging; 12% non-pathological decline & 6% accelerated decline
Morin & Midlarsky 2018	Longitudinal	403	Mixed cancer	T1: 2 years before diagnosis T2: cancer diagnosed after T1 T3: 2 years after diagnosis T4: 4 years after diagnosis	*Attention, Working Memory & Verbal Memory*: 10 unrelated nouns read out – participants had to recall immediately and then after 30 minute delay		CT participants were significantly more likely to be in high recall class. I.E No association between CT and lower cognitive functioning over time		
Ramalho 2018	Longitudinal	418	Breast	T1: pre treatment T2: 1 year follow up	MoCA	HADS	T1 – T2 - 34 patients presented incident CI (8.1%)	-	Statistically significant association between CT & OCI but only among women with no anxiety at T1
Sales 2018	Longitudinal	85 49	CRC CT	T1: pre treatment	3 Domains: *Memory*: HVLT, BVRT *Attention:* DS forward, TMT A, Digit symbol	PHQ ECQ CCI	No difference found in global NP score,	-	-

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		26	No CT	T2: 1 year follow up	*Executive Function*: DS backward, TMT B, Stroop C, Phonemic verbal fluency		attention or memory between the 2 groups during the follow up period. Significant difference found for executive function at T1 – worse for CT group		

Key: **BC**: Breast cancer; **CRC**: Colorectal cancer; **SCLC:** Small cell lung cancer; **NSCL**: Non-small cell lung cancer: **HC**: healthy controls; **CT:** Chemotherapy treatment; **RT**: Radiotherapy treatment; **HT**: Hormone treatment; **Tam**: Tamoxofin. **OR**: Odds ratio;

AVLT: Auditory Verbal Learning Test; **BNT**: Boston Naming Test; **BVMT-R**: Brief Visuospatial Memory Test Revised; **BVRT:** Benton Visual Retention Test; **Cal CAP**: California Computerized Assessment Package; **CANTAB**: Cambridge Neuropsychological Test Automated Battery; **CCCs:** Consonant Trigrams; **CCP/CPT**: Conner's Continuous Performance Test; **CCST**: Cognitive Capacity Screening Test; **CFT:** Complex Figure Test; **CLOX**: Clock drawing task; **COWA**: Controlled Oral Word Association Test;**CRT:** Headminder Clinical Research Tool; **CST:** Concept Shifting Test**; CVLT:** The California Verbal Learning Test**; CW:** Color-Word Interference Test; **DKEFS:** Delis-Kaplan Executive Function Scale; **DS**: Digit Span of the Wechsler adult intelligence scale; **Digit Symbol**: Digit symbol of the Wechsler adult intelligence scale; **DSST**: Digit Symbol Substitution Test; **D2:** D2 Test; **DVT:** Digit Vigilance Test**; EXIT 25:** Executive Interview (25 item); **FFTT**: Fepsy Finger Tapping Task; FVRT: Fepsy Visual Reaction test; **FBCT:** Fepsy Binary Choice test; **FVST:** Fepsy Visual Searching test; **FWS:** Four-Word Short-Term Memory Test; **Gordon CPT**: Gordon Continuous Performance Test; **GP:** Grooved Pegboard; **GRIP:** Grip Strength; **HAWIE-R:** Hamburg-Wechsler-Intelligenztest fu¨r Erwachsene, Revision 1991 (Wechsler Adult Intelligence. Scale-Revised, German version); **HRNB**: Halstead-Reitan Neuropsychological Test Battery; **HSCS:** High Sensitivity Cognitive Screen; **HVLT-R**: The Hopkins Verbal Learning Test; **IED:** Intra-Extra Dimensional Set Shifting; **ISPOCD battery**: International Study of Postoperative Cognitive Dysfunction; **JLO:** Judgment of Line Orientation; **LDCT:** Letter-Digit Coding Test; **LGT3:**Lern- und Geda¨chtnistest (Learning and Memory-Test); **LM1 & II:** Logical Memory I & II; **LPS:** Leistungspru¨fsystem (Achievement measure system); **MAE:** Multilingual Aphasia Examination; **MMSE:** Mini- Mental State Examination; **MOCA:** Montreal cognitive assessment; **MWT-B**: Multiple-Choice-Vocabulary-Test; **NCPC:** Necker Cube Pattern Control test; **NVSRT**: Nonverbal Selective Reminding Test; **PAL**:Paired Associates Learning; **PASAT**: Paced Auditory Serial-Addition Task; **RAVL/RAVLT**: Rey Auditory Verbal Learning Test; **RBANS:** Repeatable Battery for the Assessment of Neuropsychological Status; **RBMTS:** Rivermead Behavioral Memory Test; **Rey CFT/ RCFT/ ROCFT**: Rey-Osterrieth Complex Figure test; **RWT**: Regensburg Word Fluency Test; **S.A.N Test**: Word fluency subtest from the S.A.N. test; **Stroop:** Stroop Test; **SCWT:** Stroop Color and Word Test; **SDMT**: Symbol Digit Modalities Test; **SWM:** Spatial Working Memory; **TAP**: Test battery for attentional performance; **TEA VE:** Visual Elevator & **TEA TS**: Telephone Search; **TMT A&B**: Trial Making Test Part A & Part B; **TS:** Three Shapes; **TW**: Three Words; **VFT:** Verbal Fluency Test; **VLT/VLMT**: Verbal Learning Test ; **VMS**: Visual Memory Span (Subtests of the WMS-R); **VSRT**: Verbal Selective Reminding Test; **WAIS–III**: Wechsler Adult Intelligence Scale –III; **WAIS-III LN**: WAIS-III letter number sequencing; **WAIS-R**: Wechsler Adult Intelligence Scale Revised; **WAIS-R BD**: Wechsler Adult Intelligence Scale Revised - Block Design; **WCST**: Wisconsin Card Sorting

Test; **WCST CR:** Wisconsin Card Sorting Test – number of correct responses; **WF-animals:** category fluency—animals**; WF-F/ WF-N:** phonological fluency—words beginning with F and N**; WMS-R:** Wechsler memory scale-revised; **WMS III LM:** Wechsler Memory Scale third edition subtest Logical Memory; **WRAT – 3:** The Wide Range Achievement Test, Third Edition;

Brief MAACL: Brief Multiple Affect Adjective Check List; **ADLs:** activities of daily living; **AFI:** Attentional Functional Index; **AMNART** (Whitney 2008); **BAI:** Beck Anxiety Inventory; **BCFQ:** Broadbent cognitive failures questionnaire; **BCPT**: The Breast Cancer Prevention Trial; **BDI:** Beck Depression Inventory; **BDI-II:** Becks Depression Inventory-Second Edition; **BF13:** Item 3 of Brief Fatigue Inventory; **BPI:** Brief Pain Inventory; **CCI/ Comorbid medical conditions:** Charlson comorbidity index; **CDS:** Cognitive Difficulties Scale; **CES-D**: Centre for Epidemiological Studies Depression Inventory**; CFQ:** The cognitive failures questionnaire; **Checklist 90-R**: the Symptom Checklist 90-Revised; **CIS**: Checklist Individual Strength; **CIQ:** Community Integration Questionnaire; **DRS:** Dementia Rating Scale; **DSM III R:** Diagnostic and Statistical Manual of Mental Disorders-III—Revised; **ECQ:** Everyday Cognition Questionnaire; **EPQ -18:** The Eysenck Personality Questionnaire (18 items); **FEDA:** self-perceived cognitive deficits; **FSI:** The Fatigue Symptom Inventory; **GDS:** Geriatric Depression Scale; **GHQ-12:** General Health Questionnaire 12; **GPS**: General Perceived Self-Efficacy; **HADS:** Hospital and Depression Scale; **HSCL-25**: The Hopkins symptom checklist – 25; **IADLs** instrumental activities of daily living; **IES:** The Impact of Event Scale; **ISI:** Insomnia Severity Index; **KPS:** Karnofsky performance status**; LFS:** Lee Fatigue Scale**; MADRS:** Montgomery Asberg Depression Rating Scale**; MAQ:** The Mental Abilities Questionnaire**; MASQ:** Multiple ability self-report questionnaire; **MFI-20:** Multidimensional fatigue inventory; **Mini MAC:** Mini-Mental Adjustment to Cancer; **MMPI:** Minnesota Multiphasic Personality Inventory; **MMSE:** Mini-Mental State Examination; **MOS SF-36**: (Fatigue subscale): Medical Outcomes Study, general health survey, short form; **PAF**: patients perceptions of cognition; **PAOF:** Patient's Assessment of Own Functioning; **PDI:** Psychological Distress Inventory; **PHQ:** Patient Health Questionnaire; **POMS:** Profile of Mood States; **POMS-SF**: Profile of Mood States –Short Form**; PSI:** Physical Symptoms Inventory; **PSS**: Perceived Stress Scale; **PTSD:** Post traumatic stress disorder; **SCIN**: Scale for Chemotherapy-Induced Neurotoxicity; **SDS:** Symptom Distress Scale; **SIP-8 (**Mobility & Ambulation subscales): Sickness Impact Profile ; **STAI-Y:** Spielberger State-Trait Anxiety Inventory**; SRS:** Squire Self-Report Scale; **SSA**: Social Support Appraisal scale; **SSRQ:** Squire Memory Scale; **SSQT:** Social Support Questionnaire of Transactions; **STAI:** State Trait Anxiety Inventory; **STAI-Y1 and Y2**: State and Trait Anxiety Inventory Premorbid; **TSLS:** Transactions Satisfaction with Life Scale; **VAMS:** Visual Analog Mood Scale; VIQ: American version of the Nelson Adult Reading Test; **WRAT-3:** The wide range achievement test-3; **ZSDS**: Zung Self-Rating Depression Scale **EORTC QLQ-C30**: European Organization for Research and Treatment of Cancer Quality of Life questionnaire; **FACT A:** Functional Assessment of Chronic Illness Therapy **FACT B:** Functional Assessment of Chronic Illness Therapy –Breast; **FACT C:** Functional Assessment of Chronic Illness Therapy – Colorectal; **FACT Cog**: Functional Assessment of Cancer Therapy - cognitive function; **FACT ES**: Functional Assessment of Chronic Illness Therapy - Endocrine; **FACT F:** Functional Assessment of Chronic Illness Therapy - Fatigue subscale; **FACT G:** Functional Assessment of Chronic Illness Therapy - General; **FACT L**: Functional Assessment of Chronic Illness Therapy – Lung; **FACT O**: Functional Assessment of Chronic Illness Therapy – Ovarian; **FACT – ntx**: neuropathy scale; **FACIT**: Fatigue: Functional Assessment of Chronic Illness Therapy –fatigue; **LASA (QoL):** linear analog scale assessment of quality of life.

3.4 Methodological issues associated with OCI studies

3.4.1 Study design: Cross sectional "vs" longitudinal

The early studies in this area (such as Wienneke & Dienst 1995, and van Dam et al, 1998) were retrospective and cross sectional in design, which meant that it was not possible to know whether OCI was already present prior to chemotherapy treatment or was attributable to the treatment itself (Cimprich et al., 2010; Schilder et al., 2010; Wefel et al., 2004a). Without pre-chemotherapy treatment evaluations of cognitive function, it was possible that the early studies both underestimated and/or overestimated the prevalence of OCI (Hodgson, 2008). Underestimations might have occurred as a result of failing to capture subtle losses in higher functioning individuals whose scores had declined but still fell within normal limits (Wefel et al., 2004a). In Wefel and colleagues, (2004b) pre-chemotherapy study there were no overall mean differences in cognitive function between patients and normative data (obtained from the general population). Within-subject analyses, however, revealed that 61% of the participants were found to have had cognitive declines in learning, attention, and processing speed. If there had not been a pre-chemotherapy treatment assessment, 46% would not have had detectable OCI because their post-chemotherapy treatment assessment scores were within the normal range. This finding is extremely important, as OCI is often subtle (Janelsins, Kesler, Ahles, & Morrow, 2014) and it demonstrates the limitation of restricting the analysis to a comparison to normative data.

Overestimation might have occurred because such studies were unable to detect changes from baseline (Olin, 2001; Ahles et al., 2002; Wefel et al., 2004). Later studies have found that up to 41% of patients with solid tumours have shown pre-

chemotherapy treatment OCI (see Section 3.5.2) which was probably misattributed to a relationship with chemotherapy in earlier cross sectional studies (Hodgson 2008).

These issues led researchers to conduct more prospective longitudinal studies in the early 2000s, which included baseline measurements prior to chemotherapy combined with multiple assessments over time to determine how an individual's objective cognitive performance changed over the course of chemotherapy treatment. Increasingly, longitudinal studies began to appear which presented stronger evidence of the role of chemotherapy treatment in CRCI (Ahles et al., 2010; Bender et al., 2006; Hurria et al, 2006; Jansen et al, 2011; Minisini et al., 2008; Quesnel et al., 2009; Schagen et al, 2006; Shilling et al, 2005; Stewart et al., 2008; Vearncombe et al., 2009; Wefel et al, 2004b; Wefel et al., 2010). However, these studies were not without their methodological limitations as will be discussed below.

3.4.2 Time of assessment

There is great variation in the time at which OCI is assessed in the literature. Early cross-sectional studies (i.e. pre-2005) ranged from 6 months (Wienke & Dienst, 1998; Schagen et al, 1999, Freeman et al, 2002) to 2 years after chemotherapy treatment (van Dam et al, 1998; Brezden et al, 2000; Castellon et al, 2002).

Multiple assessment points are used increasingly by researchers, but the timing of the assessment(s) vary widely across studies (Table 3.1). Not all longitudinal studies include a pre-chemotherapy treatment baseline assessment. The timings of the first assessments range from pre-surgery (Cimprich et al, 1998; Cimprich et al, 2001; Vardy et al, 2006; Hermelink et al, 2007) to immediately after surgery but prior to chemotherapy (Bender et al, 2006), to first assessments conducted during

chemotherapy treatment (Brezden et al, 2000; Mar Fan et al, 2005) and sometimes the first assessment is not until after the end of chemotherapy treatment (Reid Arndt et al, 2010). The interval between assessments also varies, from months to years. Generally, a shorter interval between assessments enables the onset of cognitive change to be identified more accurately. This variability in the timing of baseline and subsequent measures makes it difficult to compare results across studies, which led the ICCTF to make recommendations for subsequent longitudinal studies to begin with a pre-treatment assessment (Wefel et al, 2011).

3.4.3 Controls/comparison groups

As discussed in Chapter 2, Section 2.3.1.1 various control/comparison groups have been used by researchers for the purposes of establishing impairment. The type of control group used is an important methodological consideration when exploring the course and duration of OCI. There is debate in the psycho-oncology field regarding the most appropriate comparison groups: norms for individual tests, and/or matched healthy controls given the same battery of tests, administered under identical conditions as the patient group, and/or another patient group who experience similar levels of distress (Ahles et al, 2008).

As can be seen in Table 3.1, numerous longitudinal studies (i.e. 21 out of 45 (i.e. 46.67 %) of those listed) (Oxman et al, 1980; Cimprich et al, 1998; Iconomou et al, 2004; Jacobsen et al, 2004; Wefel et al, 2004b; Hurria et al, 2006a; Hurria et al, 2006b; Hermelink et al, 2007; Jansen et al, 2008; Whitney et al, 2008; Weis et al, 2009; Reid Ardnt et al, 2010; Wefel et al, 2010; Skaali et al, 2011; Biglia et al, 2012; Andries et al, 2013; Cruzado et al, 2014; Hess et al, 2015; Klemp, 2017; Morin & Midlarsky, 2018;

Ramalho et al 2018) did not use a control and/or comparison group. One reason could be that in longitudinal studies there is an assumption that each participant serves as his or her own control for disease and host effects.

In studies that have used a control group, 9 (11.7%) of those listed in Table 3.1 used just healthy controls (usually matched for age and education) (Cimprich et al, 2001; Servaes et al, 2002; Tchen et al, 2003/ Mar Fan et al, 2005; Shilling et al, 2005; Schilder et al, 2009; Von Ah et al, 2009; Debess et al, 2010; Kopplemans et al, 2012 and Mandelblatt et al, 2014). However, Hodgson and colleagues (2008), argue that a reliance on healthy controls alone does not account for cancer-related factors other than chemotherapy that might contribute to cognitive changes. Healthy controls may therefore preclude the consideration of the effects on cognition of the cancer itself.

Of the included studies, 34 (i.e. approximately 44%) used a cancer control group, most likely in an effort to account for the cancer and host factors (e.g. van Dam et al, 1998; Schagen et al, 2002; Ahles et al, 2002; Castellon et al, 2002; Donovan et al, 2005; Bender et al., 2006, Scherwath et al, 2006; Mehnert et al, 2007; Shilling et al, 2007; Bender et al, 2008, Schagen et al 2008; Stewart et al, 2008; Collins et al, 2009; Pedersen et al, 2009; Verncombe et al, 2009; Tagar et al, 2010; Prokasheva et al, 2011; Sales et al, 2018). Furthermore, by using a cancer control group in the longitudinal studies researchers have been able to ensure consistency between the groups in test-retest intervals (Wefel et al, 2010). However, some of these studies appear to ignore the fact that such comparison groups would often be receiving alternative treatments which may potentially have had an effect on cognition (such as hormonal therapies, and/or radiotherapy). The ability to compare patients to normative samples as well as to locally tested comparison groups is considered ideal (Ahles et al 2008; Wefel et al,

2011). Eleven studies used both healthy controls and a cancer control group (Castellon et al, 2004; Jenkins et al, 2006; Schagen et al, 2006; Vardy et al, 2006; Ahles et al, 2008; Jim et al, 2009; Quesnel et al, 2009; Ahles et al, 2010; Hedayati et al, 2012; Vardy et al, 2015; Lange et al, 2018).

Several studies used cancer control groups specifically because they were interested in comparing the effect of alternative treatments (Donovan et al, 2005; Bender et al, 2006; Schagen et al, 2008; Stewart et al, 2008; Collins et al, 2009; Quesnel et al, 2009) which is the approach taken in this thesis.

Differences in control groups probably contribute to the differences in reported rates of OCI across the studies (Wefel et al, 2010) and prevent direct comparisons. However, as outlined in Chapter 9, the use of a control group is critical in longitudinal study designs to control for practice effects of repeated testing, as recommended by the ICCTF (Wefel et al, 2011).

3.4.4 Definition of OCI

As discussed in Chapter 2, Section 2.3.1, various methods exist which can determine what constitutes below normal performance on NP tests. Individual test or domain scores may be used, and different cut-off points selected per test and/or test battery. There is no established "gold standard" for defining OCI or a universally accepted classification system for lower than expected cognitive performance (Ahles et al, 2008) in the "cancer and cognition" literature.

Researchers have used various cut-off points to determine whether there is OCI (Dwek et al, 2016). Some studies converted the NP test scores (raw scores) into standardised

scores using published normative data adjusted for age, education, and gender, defining impairment based on standard deviations below the mean. This procedure enables comparisons to be drawn across different tests with different units of measurement (number of correct words, time taken, etc.) and different distributions (e.g. normal, skewed etc) and is discussed in detail in Chapter 8. The number of standard deviations considered as indicative of impairment has also varied across the studies, as has the number of tests required (Vardy, Rourke & Tannock, 2007). For example 1, 1.5 and 2 standard deviations (SD) below the normative group mean score on between 1 to 4 NP assessments have been used as cut offs indicative of impairment (Lezak et al, 2012). Other studies have used an actuarial approach that weights the number and severity of below average scores in a NP battery, ignoring scores in the average range or better (Wefel et al, 2011).

The extent of OCI found to exist in a study often depends on the definition used by the researchers. For example, Vardy and colleagues (2015) found that diagnosis of CRC itself prior to the start of chemotherapy treatment led to substantial OCI when compared with healthy controls. Depending on the criteria used, they found that the rates of OCI in patients with localised CRC ranged from 36% to 52% between pre-chemotherapy treatment to 24 months later, compared with 6% to 19% in healthy controls.

3.4.5 Sample characteristics

The majority of studies in patients with solid tumours have been conducted on female breast cancer patients (Janelsins et al, 2014) (see Table 3.1). Consequently, little was

known about OCI in men or in patients with other types of cancer until relatively recently.

Additionally, most studies have included heterogeneous samples, ranging from the inclusion of participants with different types of cancer (e.g. Silberfarb, 1980; Kibiger et al, 2003; Iconomou et al, 2004; Jacobsen et al, 2004; Poppelreuter et al, 2004; Morin & Midlarsky, 2018) to participants with different stages of cancer, and participants who were treated with different chemotherapy regimens (e.g. Iconomou et al, 2004) with potentially different side effects (as mentioned in Chapter 1). For example, Iconomou and colleagues (2004) did not analyse differences in the 102 cancer patients who took part in their study, although they acknowledged that the great heterogeneity of cancer diagnoses and the wide variety of chemotherapy regimens may have been responsible for the lack of side effects found.

Differences in chemotherapy dosage may also contribute to differences in OCI. Weinke & Dienst (1995) reported that the cognitive impairment found in their cross-sectional breast cancer study was not related to depression, type of chemotherapy or time since treatment, but was positively related to the length of chemotherapy treatment, suggesting a dose response relationship. This was later confirmed by van Dam and colleagues (1998) who found that a large proportion of the breast cancer patients receiving high dose chemotherapy (32%) were assessed as having OCI when compared with those on standard dose treatment (17%). This was further supported by Schagen and colleagues, (2006). However opposite findings were reported by Mehnert and colleagues (2007) and by Schwerth and colleagues (2006) who found that a greater proportion of those patients on standard dose chemotherapy treatment were assessed

as having OCI (13% compared with 8% in both studies) although there were no significant group differences were observed.

In some studies, the participants were also receiving additional treatments such as hormone therapy or radiation therapy (Jansen et al, 2008). Without a systematic examination, such variations in treatment regimens and cancer stage make it difficult to isolate the effects of chemotherapy on cognition.

3.4.6 Sample size

As can be seen in Table 3.1, participant numbers have ranged from 11 (Oxman et al, 1980) to 196 breast cancer patients (Kopplemans et al, 2012), to 231 ovarian cancer patients (Hess et al, 2015), 182 testicular patients (Schagen et al, 2008), 362 CRC patients (Vardy et al, 2015) and 119 participants from a mixed cancer population (Poppelreuter et al, 2004). Researchers frequently acknowledge that the small to moderate sample sizes are a limitation (Brezden et al, 2000; Schagen et al, 2002; Castellon et al, 2004; Wefel et al, 2004b; Bender et al, 2006; Hurria et al, 2006; Scherwath et al, 2006; Mehnert et al, 2007; Jansen et al, 2008; Mehlsen et al, 2009; Schilder et al, 2009; Reid-Arndt et al, 2009; Reid-Arndt et al, 2010; Tagar et al, 2010; Prokasheva et al, 2011; Biglia et al, 2012; Cruzado et al, 2014). It is possible that smaller samples have lacked the power to detect associations (Hermelink et al., 2007; Wefel et al., 2004b).

3.5 Trajectory and affected cognitive domains

3.5.1 Onset

Early neuropsychological studies in cancer patients with solid tumours examined cognition following systemic treatment at a single point in time without a pre-treatment assessment (Janelsins et al, 2011). The timing of the assessment varied widely from 6 months (Wieneke & Dienst, 1995; Schagen et al, 1999), through 2 years (van Dam et al, 1998; Brezden et al, 2000), 10 years (Ahles et al, 2002) and up to 20 years (Kopplemans et al, 2012) post-chemotherapy treatment. Although these particular cross sectional studies did find some evidence of OCI at the time of assessment it is not possible to determine when the onset of such impairments began.

One of the first prospective studies examining CRCI in breast cancer patients (*n*=18) was carried out by Wefel and colleagues (2004b), with measures taken prior to chemotherapy treatment (T1), 3 weeks post-chemotherapy (i.e. approximately 6 months after the first assessment)(T2), and 18 months after T2(T3). They found that 6 (33%) breast cancer patients demonstrated OCI on at least 2 NP tests prior to starting chemotherapy treatment. As mentioned in Section 3.4.1, this suggests that it is possible that early cross-sectional studies overestimated CRCI.

3.5.2 Pre-chemotherapy

Following Wefel and colleagues' study (2004b) pre-chemotherapy cognitive compromise has been found in several longitudinal studies (Hurria et al, 2006a; Hermelink et al, 2007; Jansen et al, 2008; Hermelink et al, 2015; Vardy et al, 2015; Lange et al, 2018). Studies with this design have reported OCI in 36% to 52% of CRC patients (Vardy et al, 2015) and between 17% and 33% in breast and testicular tumours

(Wefel et al, 2004; Vearncombe et al 2009; Wefel et al, 2011). It has been suggested that the tumours and previous surgeries can cause cognitive impairment in patients with lower cognitive reserve (Ahles et al, 2010). (Cognitive reserve is defined as an innate and developed cognitive capacity that can limit a person's vulnerability to brain insults (Hardy et al, 2018)). Yao and colleagues (2016) found evidence of executive function impairment in patients with breast cancer prior to surgery relative to healthy controls.

In 2007 Hermelink and colleagues assessed cognitive function after diagnosis but prior to surgery, and then again prior to the final chemotherapy treatment. They observed impaired cognitive function in one third of the participants prior to any treatment whatsoever, during a time known to be particularly stressful. They assert that this was a possible indication of OCI at this time being related to stress-response symptoms, which may interfere with performance during NP testing. This raises the possibility that earlier cross sectional studies attributed OCI to treatment, when in fact it may have already existed prior to treatment. It is arguable that any such OCI found prior to the commencement of systemic treatment in a subset of cancer patients may have been due to the effects of stress, fatigue or the toxic by-products of the cancer itself (Anderson-Hanley et al, 2003).

Although it is unclear whether lower-than-expected pre-treatment cognitive function is attributable to an adverse effect of the cancer itself or to other unidentified factors, the results of these studies underscore the importance of designing future studies with a pre-treatment baseline evaluation (Cruzado et al, 2009; Vardy et al, 2007; Wefel et al, 2011).

3.5.3 Course

In the studies that report OCI there is conflicting data regarding its course. When OCI is measured over time in longitudinal studies, there is great variation in the when or how often cognitive function is measured; making it difficult to assess the course of OCI or compare results across studies (see Table 3.2). For example, in the first longitudinal study Wefel and colleagues (2004b) measured OCI prior to chemotherapy treatment, approximately 6 months later and then 1 year post chemotherapy treatment. Whereas Mar Fan and colleagues (2005) assessed OCI after 3 cycles of chemotherapy (i.e. mid-chemotherapy treatment), 1 year later and 2 years after that; and Weiss and colleagues (2009) did not assess OCI for the first time until 9 months post-chemotherapy treatment, then approximately 26 days later and again 6 months after the second assessment.

Nevertheless, in the first longitudinal study Wefel and colleagues (2004b) found that OCI was present prior to chemotherapy treatment in 33% of the participants (4 women exhibited impairment on 2 tests and 2 exhibited impairment on more than 2 tests). By the time of the second assessment, 61% (i.e. approx. 11) of the 18 participants in the study experienced a decline in one or more aspects of objective cognitive functioning, and by 18 months, 50% of breast cancer patients who experienced cognitive decline at the second assessment showed improvement whereas 50% remained stable. These findings suggest that for a subset of patients' OCI experienced during systemic treatment is transient and can return to per treatment levels with time.

Table 3.2: Table of longitudinal studies (post 2000) that have explored the course of OCI in patients with solid tumours

Author & year	Time of assessment	Course	Improvement?
Wefel 2004b	T1: Pre-CT T2: 6 months T3: 18 months 18 BC	T2: 61% exhibited a decline in 1 or more domains T3: 50% of those that experienced declines improved & 50% remained stable	In some patients
Mar Fan 2005	T1: after 3 cycles of CT (CT n=104) (HC n=102) T2: 1 year post T1 (CT n=91) (HC n=81) T3: 2 years post T2 (CT n=83) (HC n=81)	Over the 2 years of follow-up, the proportion of patients with moderate-severe cognitive impairment improved from 16% to 4%. All the patients with moderate-severe impairment at T1 who underwent subsequent assessment improved to a level of mild impairment or better. Of patients and controls who scored as having mild impairment or better at T1, 3 patients (3.8%) and no HCs were noted to have moderate-severe impairment at T3.	Yes
Bender 2006	T1: post-surgery pre-CT T2: 1 week after CT T3: 1 year after T2 19 BC had CT only 15 BC - CT & tamoxifen 12 DCIS (just surgery)	Women who received CT plus tamoxifen exhibited deterioration on measures of visual memory and verbal working memory and reported more memory complaints. Women who received CT alone also exhibited deteriorations in verbal working memory. Conversely, cognitive function scores improved in women who received no therapy, indicating practice effects.	No
Hurria 2006	T1: Pre-CT T2: 6 months post-CT	Seven patients (25%) experienced a decline in cognitive function, defined as a 1-SD decline from pre- to post testing in two or more neuropsychological domains. I.e. from before CT to 6 months after CT	Not over the time tested

<table>
<tr><th>Author & year</th><th>Time of assessment</th><th>Course</th><th>Improvement?</th></tr>
<tr><td>Jenkins 2006</td><td>T1: Pre-CT
T2: 6 months
T3: 18 months</td><td>The results from this study suggest that only a small proportion of women receiving adjuvant treatments for breast cancer experience objective measurable change in their concentration & memory. It is reassuring that the majority are either unaffected or even improve over time.

Decline in 20% on CT at 6 months & 18% at 18 months compared with
26% & 14% no CT (at 6 & 18 months respectively) and
18% & 11% HC's at (6 & 18 months respectively)</td><td>Yes</td></tr>
<tr><td>Schagen 2006</td><td>T1: Pre-CT
T2: 12 months post-T1 (i.e. 6 months post-CT)

28 BC high dose CT
39 BC standard dose CT
57 BC no CT
60 HCs</td><td><table><tr><th>Group</th><th>n</th><th>No. impaired at T1 (%)</th><th>No. impaired at T2 (%)</th><th>No. having cog deterioration from T1 to T2 (%)</th></tr><tr><td>Standard CT</td><td>39</td><td>5 (12.8)</td><td>4 (10.3)</td><td>5 (12.8)</td></tr><tr><td>High dose CT</td><td>28</td><td>6 (21.4)</td><td>6 (21.4)</td><td>7 (25.0)</td></tr><tr><td>No CT</td><td>57</td><td>17 (29.8)</td><td>13 (22.8)</td><td>10 (17.5)</td></tr><tr><td>HC</td><td>60</td><td>6 (10.0)</td><td>4 (6.7)</td><td>4 (6.7)</td></tr></table></td><td>No</td></tr>
<tr><td>Vardy 2006</td><td>T1, T2 & T3 approx. 17 days apart from each other. Patients had had 3 cycles of CT & were w/in 2 years of CT</td><td>A large practice effect was seen for the HSCS, with moderate– severe cognitive impairment decreasing from 30 to 5% between the first and second assessment</td><td>Yes – when using the HSCS- practice effects or genuine improvement?</td></tr>
<tr><td>Hermelink 2007</td><td>T1: pre neo-adjuvant CT</td><td>Towards the completion of CT, approximately 25% of patients showed a decline, whereas another 25% demonstrated improvement of cognitive function</td><td>28% improved, 27% declined</td></tr>
</table>

Author & year	Time of assessment	Course	Improvement?
	T2: pre-final neo-adjuvant CT		
Jansen 2008/2011	T1: Pre-CT; T2: week after cycle 4; T3: 1 week post-CT; T4: 6 months post-CT	After completion of CT, only mean visuospatial skill ($p<0.001$) and total cognitive scores ($p<0.002$) decreased over time. In contrast, mean executive function ($p<0.014$) scores improved over time. 10 women (33%) had a decrease of ≥ 1 SD on ≥ 2 tests after completion of CT. Decreased scores of at ≥ 1 SD were found most often for visuospatial skills (40%), motor function (13%), immediate memory (13%), language (13%), delayed memory (13%), and attention (7%). In contrast, 5 women (17%) had an increase in ≥ 1 SD for ≥ 2 tests after CT.	Yes improved for some, worsened for others
Stewart 2008	T1: pre CT T2: end of CT (2 groups: BC CT & BC no CT)	A threefold greater risk of cognitive decline in CT patients compared with the hormonal patients (31% and 12%, respectively), even after statistically accounting for age, education, intelligence, fatigue, psychological distress, and regression to the mean between T1 & T2. There was no difference in the frequency of reliable cognitive improvement (5% in CT group; 6% in hormonal group; p = 0:82).	Short period – decline between T1 & T2
Collins 2009	T1: Pre-CT; T2: 1 month post-CT T3: 1 year post-T2	T1 to T2: a significantly higher rate of cognitive decline in CT group than HT group: 34 vs. 13%; No difference in rate of cognitive improvement 8% in each group. At T3, there was no significant difference between the CT group and HT group with respect to frequency of reliable cognitive decline: 11 vs 10%; or improvement: 11 vs 5%.	Yes - Results indicate that cognitive perturbations noted in the short term are no longer evident at 1 year following completion of therapy.

Author & year	Time of assessment	Course	Improvement?
Mehlsen 2009	T1: Pre CT and 4 days after hospitalisation for BC & Cardiac respectively T2: 4-6 weeks post CT 25 weeks after T1 for Cardiac group 12-16 weeks post-T1 for HC	Among the cancer patients, 29% showed decline on > 2 cognitive measures v 25% and 17% in cardiac patients and HCs, respectively. Improvement on 3 or more cognitive measures was found in: 24% of cancer patients, 33% of cardiac patients, and 25% of HCs	Yes in some
Quesnel 2009	T1: Pre-CT T2: After 1st CT T3: 3 months post-CT 41 BC CT 40 BC no CT 45 HC	T1: the average performance of all BC patients was inferior on two measures of attention when compared with HCs. T2 & T3 all BC patients showed decreased verbal memory, as compared with T1. There was also a negative impact on verbal fluency BC CT group that was maintained at T3.	Verbal fluency affected and still impaired at T3. But average performance of **all** BC patients appeared unchanged or improved on many NP tests.
Vearncombe 2009	T1: Pre-CT T2: 1 month post-CT 136 BC CT 21 BC no CT	16.9% BC CT declined on a number of measures but there was improvement in visual memory and executive function consistent with practise effects	Yes, in some domains – but practice effects or real improvement?
Weis 2009	90 BC all post CT T1: end of hospital rehab T2: approx. 1 month post T1	At T3, 19 of the 90 tested patients (21%) were found to have clinically relevant cognitive deficits according to author criterion. (49 patients showed no signs of impairment)	Prevalence of OCI significantly decreased as time elapsed after the end of

Author & year	Time of assessment	Course	Improvement?
	T3: approx. 6 months post T2		treatment, although 21% still displayed indications of clinically relevant long-term cognitive deficits
Ahles 2010	T1: Pre-CT T2: 1 month post-CT T3: 6 months post-CT T4: 18 months post-CT 60 BC CT 72 BC no CT 45 HCs	The data suggest that CT has an acute effect on verbal ability, which resolved over time. CT group failed to improve at T2 but improved at T3 & T4.	Verbal ability improved over time
Debess 2010	T1: Pre-CT T2: 1 month post-CT (approx. 6 months post-T1) 120 BC CT 208 controls	CT group: 14.9% showed a decline on cognitive shifting test (P = 0.002) 12.2% showed a trend of improvement on delayed memory (P = 0.023).	Yes in memory No in cognitive shifting
Reid Arndt 2010	T1: 6 months post-CT (n=39 BC CT) T2: 12 months post-CT (n=33 BC CT)	< 20 % of participants across tests evidenced deficits in delayed memory, processing speed, response inhibition, and verbal fluency at each time point.	Reliable change index analyses suggested statistically reliable

Author & year	Time of assessment	Course	Improvement?
			improvements in each cognitive domain for a modest portion of participants
Wefel 2010	T1: pre-CT T2: during CT (2.9 months after T1) T3: shortly after CT (7 months after T1) T4: > 13 months post CT 42 BC	Before CT, 21% (9 of 42) evidenced cognitive dysfunction. T2 to T3, 65% (24 of 37) demonstrated cognitive decline. At T4, 61% (17 of 28) evidenced cognitive decline after cessation of treatment. Within this group of patients, 71% (12 of 17) evidenced continuous decline from T2 to T3, and 29% (5 of 17) evidenced new delayed cognitive decline	In some but more decline in a proportion of participants
Biglia 2012	T0: pre-CT T3: immediately post-CT 40 BC	T0 to T3 - mean scores showed a significant worsening in the global cognitive functioning and in the visual selective attention while processing speed significantly improved during time, probably due to practice effect. (Used the MMSE). Note 42% of the women did not show any change	Yes in processing speed only But worsened in global cognitive functioning
Hedayati 2012	T1: Pre-diagnosis T2: Post-surgery pre CT T3: 6 months after start of CT T4: 3 months post-T3	Memory scores for women with BC were significantly lower than those for HCs over time, even after controlling for age and education. Memory & response speed scores were lower after CT than before ($P< 0.01$ for both). Whilst scores for response speed and memory declined immediately after CT was completed. These scores tended to improve at T4.	Yes

Author & year	Time of assessment	Course	Improvement?
	18 BC CT 45 BC HT 14 BC no adjuvant treatment 69 HCs	Processing speed and attention improved significantly over time in all groups, a result consistent with a practice effect	
Cruzado 2014	T1: pre-CT (n=81) T2: pre last-CT (n=73) T3: 6 months post last CT (n=54) CRC	At T1: 30 patients (37 %) had OCI. At T2: 27 patients (37 %) experienced OCI. At T3: 21 of 54 patients (39 %) were classified as showing OCI. A total of 31 % of patients experienced a statistically significant impairment in TMTA and 39 % in TMTB (binomial test, P=0.000) in each of the three assessment periods. A total of 28 patients (52 %) showed a decline from T1 to T2; Improvement in some tests was observed in 15 patients (28 %) in this period. A total of 29 patients (54 %) showed clinical improvement T2 to T3, whereas 18 (33 %) of them showed worsening in at least one test	Yes some do – others get worse There is a deficit in psychomotor processing speed and executive functions before CT which is maintained throughout the process.
Vardy 2015	T1: pre-CT T2: 6 months T3: 12 months T4: 24 months 173 CRC CT 116 CRC No CT 73 metastatic 72 HCs	Adjusting for practice effect, rates of OCI were 39%, 46%, and 36% at 6, 12, and 24 months, respectively, in the localized CRC group, compared with 6% and 13% in HCs at T2 and T3, respectively (all $P < .001$) There was OCI in 48% to 52% of patients with localized CRC at all time points, compared with 13% to 19% of HCs (all $P < .001$) After adjusting for practice effect, 20% of patients with localized CRC had significant decline in cognitive function from T1 to T3 compared with 4% of HCs ($P = .001$)	

Author & year	Time of assessment	Course	Improvement?
		24% of patients with CRC had deterioration greater than expected from T1 to T3, compared with 7% of HCs. There was a non-significant trend for more cognitive decline in patients with localized CRC who received CT than in those that did not (32% *v* 23%, respectively)	

Key: BC: breast cancer; CRC: colorectal cancer; HC: healthy controls; CT: chemotherapy treatment; DCIS: ductal carcinoma in situ; NP: neuropsychological; OCI: Objective cognitive impairment; HSCS: High Sensitivity Cognitive Screen

As can be seen in Table 3.2, similar findings suggesting that OCI improves and/or resolves over time in a proportion of patient participants have also been reported in 15 longitudinal studies since 2005 (Mar Fan et al, 2005; Jenkins et al, 2006; Vardy et al, 2006; Jansen et al, 2008; Collins et al, 2009; Mehlsen et al, 2009; Quesnel et al ,2009; Vearncombe et al, 2009; Weiss et al, 2009; Ahles et al, 2010, Debess et al, 2010, Reid-Arndt et al, 2010; Wefel et al 2010; Hedayati et al, 2012; Cruzado et al, 2014). Jansen and colleagues (2011) reported substantial improvement in all domains affected by chemotherapy treatment 6 months after completion of treatment. However, impairment may only resolve over time in some domains. For example, in Ahles and colleagues (2010) study the negative impact of chemotherapy treatment on verbal ability resolved over time but not in relation to processing speed. Cruzado and colleagues (2014) reported similar findings in their study involving patients with CRC, where 54 % of the patients experienced an improvement within 6 months following the end of chemotherapy treatment, although 18 patients were found to have worse results in at least one of the nine tests undertaken.

It should also be noted that improvements have reportedly ranged from just prior to the end of chemotherapy treatment (Hermelink et al, 2007) to 1- 3 months post-chemotherapy treatment (Debess et al, 2010), to 8 months after the last chemotherapy treatment (Collins et al, 2009, Jenkins et al, 2006). OCI at longer term follow-up may not be as pronounced as during or just after treatment. For example, Ono and colleagues (2015) argued that breast cancer patients may have recovered from short-term cognitive impairment associated with chemotherapy and/or developed compensatory cognitive strategies after experiencing a series of chemotherapy doses.

Studies involving other solid tumours have also reported that OCI improves in a subset of patients treated with chemotherapy over time. For example, Whitney and colleagues (2008) found that by 7 months after the end of chemotherapy treatment, most of the cognitive decline experienced (before and just after treatment) actually dissipated in a subset of lung cancer patients that had exhibited decline at 1-month post chemotherapy treatment. (Immediately prior to chemotherapy treatment (i.e. T1) 71% of the participants demonstrated OCI. At 1-month post treatment (T2) 62% demonstrated cognitive decline in at least 1 of 6 NP tests. All patients who completed the 7-month follow up assessment showed improvements on measures for which they showed decline at T2). However, as can be seen in Table 3.2, there are also studies which have found that the trajectory of OCI can worsen rather than improve (Bender et al, 2006; Hurria et al, 2006; Schagen et al, 2006; Stewart et al, 2008; Wefel et al, 2010; Biglia et al, 2012).

3.5.4 Duration

Early cross sectional studies indicate that significant cognitive impairments persist for 1 year or longer in a sizeable subgroup of breast cancer patients (ranging from 13% to 39%), (Ahles et al, 2002; Castellon et al, 2004; Schagen et al, 1999; Scherwath et al, 2006; van Dam et al, 1998). Several other cross sectional studies have reported symptoms lasting from 3 months to 20 years post-chemotherapy treatment (Schagen et al, 1999; Ahles et al, 2002; Wefel et al, 2004b; Koppelmans et al, 2012). Whereas a number of longitudinal studies have reported symptoms lasting from shortly after chemotherapy treatment up to 2 years post-chemotherapy treatment in a subset of patients (Quesnel et al, 2009; Wefel et al, 2010; Cruzado et al, 2014; Vardy et al, 2014),

as presented in Table 3.2. Given the variability in time and frequency of assessments, measures and definitions of OCI used, research designs and samples across the studies it is not possible to state the precise duration of OCI.

A review of the literature to date suggests that the duration of OCI is unknown (Cruzado et al, 2014). As described in Section 3.5.3, some researchers have even suggested that it is transitory (Ahles et al, 2002; Schagen et al, 2002; Vearncombe et al, 2009) whereas others have reported that it could last indefinitely for some patients (Ahles et al, 2012)

3.6 NP tests used to determine which cognitive domains are most affected

The ICCTF (Wefel et al, 2011) reports that memory, processing speed, and executive function seem to be most vulnerable to adverse effects of chemotherapy. Whereas Anderson-Hanley and colleagues (2003) earlier meta-analysis (which examined 30 studies) suggested that the domains of verbal memory and executive function are particularly affected. Jansen and colleagues (2005) review of 16 studies, found that only visual memory was significantly impaired across all comparison types. Therefore, it would appear that all cognitive domains (outlined in Chapter 2) have reportedly been implicated in at least one "cancer and cognition" study listed in Table 3.1 (Ahles et al, 2010; Collins et al, 2013; Jansen et al, 2011; Kyale et al, 2010; Quesnel et al, 2009; Tager et al, 2010; Vearncombe et al, 2009).

As can be seen in Table 3.1, many researchers utilise different batteries of NP tests: Of the 77 studies listed in Table 3.1, 41 (53%) reportedly included assessments on memory, 32 (41.6%) on attention and 24 (31%) on executive function. However, as can

also be seen in Table 3.1, not all researchers specified which domains were assessed. In a review of 43 breast cancer studies published between 1960 and 2011, Cheung, Tan and Chan (2012) found that memory was the most frequently assessed domain. They also reported that 79% of the studies assessed executive function while 56% assessed language and 51% assessed perception.

It is important to note that there is a considerable degree of inconsistency in the mapping of NP tests onto cognitive domains across studies (Dwek et al, 2016; Bernstein et al, 2017), and each test measures more than one domain. An example of a few tests that measure different domains can be seen in Table 3.3 (Freeman & Broshek, 2002).

Table 3.3: Some examples of neurocognitive measures that assess more than one cognitive domain (Adapted from the table in Freeman & Broshek, 2002)

Test*	Attention/ Concentration	Memory	Processing Efficiency	Executive Functioning	Sensorimotor Function	Language
Trails A	X		X		X	
Trails B	X	X	X	X	X	
Category Test	X	X		X		
Grooved Pegboard					X	
HVLT Immediate	X	X	X			X
HVLT Delay		X				X
HVLT Recognition	X	X				X
COWAT	X		X			X

*Each measure appears under more than one domain of skill because no designed test measures only one function discretely.
Abbreviations: COWAT = Controlled Oral Word Association Test; HVLT = Hopkins Verbal Learning Test

In addition, researchers do not always measure the same domains and if they do, they frequently use different tests to assess the same domains. Therefore, it is arguable that this inconsistency pertaining to the most vulnerable cognitive domains is attributable to the researchers' assignment of a given test to a particular cognitive domain, as well as to the multifactorial nature of the NP tests themselves. Furthermore, in some studies a NP test has been used to measure more than one domain of cognitive function and other studies simply report global difficulties rather than domain-specific ones (e.g., Schagen et al, 1999; Scherwath et al, 2006; Wieneke & Dienst, 1995).

3.7 Summary

As has been demonstrated above, the nature and severity of OCI reported in a study depends very much on the design (Anderson-Hanley et al, 2003; Falleti et al, 2005; Jansen et al, 2005). It is generally acknowledged that the large number of methodological issues have caused significant difficulty when interpreting the available data regarding the incidence of OCI.

Chapter 4: Chemotherapy Related Subjective Cognitive Impairment

4.1 Introduction

This chapter provides a review of the literature concerning the relationship between chemotherapy treatment for adult cancer patients diagnosed with solid tumours (such as breast, colon and testicular) and subjective cognitive impairment (SCI). It then goes on to discuss the relationship between OCI and SCI and the consequences of both in terms of quality of life.

4.2 Background

As discussed in Chapter 2, patient self-reports (including quantifiable questionnaires, interviews, focus groups and diary entries) provide another approach to assessing cognitive function and impairment. This chapter concentrates on the studies that have measured SCI via scorable self-reported questionnaires and/or interview or focus groups.

SCI is often assessed alongside OCI in the "cancer and cognition" studies that examine and evaluate cognitive changes. As can be seen in in Chapter 3, Table 3.1, more than half of the included studies utilised subjective assessments in addition to the NP measures. Bray, Dhillon and Vardy's (2018) systematic review evaluating self-reported cognitive function and its associations with NP tests and patient-reported outcomes in adult cancer patients who received chemotherapy treatment for a solid cancer (in studies reported between 1936 and December 2017) found that 50% of the 101 included studies used NP testing alongside the subjective questionnaires.

4.3 Prevalence

Studies in patients with breast cancer suggest that up to 70% of women receiving chemotherapy self-report some degree of SCI (Boykoff, Moieni and Subramanian, 2009).

In van Dam and colleagues (1998) seminal paper they reported that 12%-38% of breast cancer patients on high-dose chemotherapy reported SCI, 11%-31% in the standard chemotherapy dose group and 6% in the patients who only had surgery (as measured by the two items in the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) and interviews). However, as with the studies that examine OCI, there is a large variation in the amount of SCI reported across studies. For example, in a later breast cancer study, Shilling and colleagues (2007) found that 71% and 61% of participants reported problems with memory at one month and six months respectively after chemotherapy treatment, 64% reported problems with concentration one month after chemotherapy and 42% six months after the end of chemotherapy treatment.

Various studies describe different percentages of prevalence of SCI, resulting in a lack of clarity (Pullens, De Vries, & Roukema, 2010). Eleven studies included in Pullens and colleagues (2010) review described prevalence of SCI as ranging from 21% to 90%. As with OCI, this variation in percentages is most likely to be a reflection of the different definitions and measures used in the literature to date.

It should also be noted that often SCI is not of primary interest in the "cancer and cognition" literature. Bray and colleagues (2018) found that fewer than 20% of the

studies included in their review defined self-reported cognitive symptoms as the primary outcome, and mostly this was a secondary outcome or was not specified.

4.4 Methodological issues

All of the issues discussed in Chapter 3, Sections 3.4.1 (Study design), 3.4.2 (Time of assessment), 3.4.3 (Controls/comparison groups) and 3.4.5 (Sample characteristics) are equally applicable in the evaluation of SCI, particularly where SCI is measured alongside OCI. These issues are briefly described in relation to SCI in this section.

4.4.1 Study design: Cross sectional "vs" longitudinal

There is significant variation between studies in relation to design (whether interview type studies or questionnaire studies). As with OCI studies, some are cross sectional (e.g. Cimprich, 1999; Schagen et al, 1999; Von Ah et al, 2009) whilst others are longitudinal (e.g. Jenkins et al, 2006; Jansen et al, 2008; Quesnel et al, 2009). In Bray and colleagues (2018) systematic review they found that out of 101 included studies 48 (47%) were cross sectional and 38 (38%) were longitudinal, with varying sample sizes ranging from 9 to a population study of 1889 participants (Amidi et al, 2015; Dumas et al, 2013), with approximately 50% of the studies having less than 100 participants (Bray, Dhillon & Vardy, 2018).

Similarly only three of the twenty qualitative interview/focus group studies detailed in Table 4.1 are longitudinal (Kanaskie & Loeb, 2015; Mitchell 2007; Mitchell & Turton, 2011). Consequently, the majority of such studies to date have precluded any examination of the cancer/chemotherapy journey specifically in relation to cognitive changes experienced by these patients over time. Whilst all three of the longitudinal

studies aimed to capture participants' experiences and perceptions of cognitive impairment over time, one study interviewed 7 breast cancer patients who had already completed chemotherapy treatment within the past 12 months (Kanaskie & Leob, 2015). One study interviewed participants up to 10 times during their chemotherapy treatment (Mitchell, 2007) and the other study interviewed participants halfway through chemotherapy treatment, and then on completion of chemotherapy treatment (Mitchell & Turton, 2011).

4.4.2 Definition of SCI

As discussed in Chapter 2, SCI refers to perceived cognitive difficulties experienced by an individual in their everyday life, such as problems with concentration, memory, learning and language (Pullens et al, 2010; Hutchinson et al, 2012). However, as in the OCI studies, researchers have used different definitions of SCI, making it difficult to interpret the data.

In Pullens and colleagues (2010) systematic review, it was found that only 7 out of the 27 included studies described the definition of SCI (Schagen et al, 1999; Schagen et al, 2002; Von AhD et al, 2009; Bender et al, 2008; Cimprich et al, 2005; Cimprich et al, 1999, Schilder et al, 2009). Some studies reported a theoretical definition, whereas others reported cut-off points or percentiles that patients at least needed to rate in order for them to be considered as having SCI. For example, several studies (Schagen et al, 1999; Schagen et al, 2002; Schilder et al, 2009) interviewed breast cancer patients about cognitive problems (memory, attention, thinking and language) encountered in daily life and asked them to indicate on a 5-point Likert scale the extent to which problems in each of these domains occurred in their daily activities. Scores ranged from

0 (not at all) to 4 (extremely). Only patients who rated their cognitive problem as at least 2 (moderate) in a distinct domain were considered as having a complaint about their cognitive functioning in the related domain.

4.4.3 Measures

Researchers use various measures to evaluate SCI. Bray and colleagues (2018) systematic review found considerable diversity in the selection of self-reported cognitive measures used. An earlier systematic review examining (amongst other effects) the prevalence and course of SCI in breast cancer patients (Pullens et al, 2010) found that in the 27 studies included in the review 10 different self-report questionnaires were used to measure SCI. Additionally, some included studies used the subscales from questionnaires such as health status questionnaires, whilst nine authors used "self-made" and non-validated questionnaires and/or semi-structured interviews to examine SCI (Schagen et al, 1999; Schagen et al, 2002; van Dam et al, 1998; Downie et al, 2006; Berglund et al, 1991; Mehlsen et al, 2009; Servaes et al, 2002; Shilling & Jenkins, 2007; Schilder et al, 2009).

As discussed in Chapter 2 (Section 2.3.2.1) and highlighted in Chapter 3, Table 3.1, researchers who have examined SCI alongside OCI have used the Questionnaire for Self-Perceived Deficits in Attention (FEDA) (Mehnert et al, 2007; Schilder et al, 2010; Downie et al, 2006), the CFQ (Castellon et al, 2002; Castellon et al, 2004; Shilling et al, 2005; Jenkins et al, 2006; Schilder et al, 2009; Quesnel et al, 2009), the cancer-specific Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) (Wagner et al, 2009) and the two "cognitive failure" items in the EORTC QLQ-C30, (van Dam et al, 1998; Schagen et al, 1999; Schagen et al, 2002; Weiss et al, 2009; Poppelreuter et al, 2009;

Iconomou et al, 2004; Schagen et al, 2008; Hermelink et al, 2007; Hermelink et al, 2010) (See Chapter 3, Table 3.1). Bray and colleagues (2018) found that the EORTC QLQ-C30 was the most commonly used questionnaire (up until 2017), and was included in 33 of the 101 reviewed studies. The use of different measures makes comparisons across the studies highly problematic.

The FACT-Cog has been increasingly used (Downie et al, 2006; Vardy et al, 2006; Lange et al, 2014) since the mid-2000s. It is the first measure to be developed and validated with a sample of adults with cancer (Wagner et al, 2009). As mentioned in Chapter 2, it is a self-report measure that was developed as part of the FACT measurement system to assess the nature and severity of cognitive deficits among cancer patients as well as the impact of these deficits on patients' QoL. It has four subscales: symptoms of perceived cognitive impairments (PCI) (20 items), perceived cognitive abilities (PCA) (9 items), overall quality of life in relation to cognition (CogQoL) (4 items), and comments made by others (Oths) (4 items). Each item is rated on a seven point Likert scale according to how accurate the statement has been over the past week. Whilst higher scores indicate fewer symptoms (on PCI), better cognitive abilities (on PCA), better QoL (on overall QoL in relation to cognition), and more positive comments from others, there is no universally accepted definition of what constitutes a cognitive symptom or a cut-off score for the FACT-COG or its subscales (Vardy et al, 2017).

There appear to be fewer studies that have used interviews and/or focus groups to examine SCI. A search of the literature produced just 20 qualitative studies (using interviews and/or focus groups) since the early 2000's that have explored patients' experiences of cognitive change in depth. These are displayed in Table 4.1.

Table 4.1: Summary of interview and focus group studies in relation to perceptions of cognitive impairment since 2000

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
1	Becker et al 2015	Cross sectional PROMIS scale & Focus group or interview	Breast (n=10)	Explored perceptions about cognitive functioning while receiving treatment in a community oncology setting in Texas	6 participants completed active treatment the previous year, 2 completed treatment > 1 year ago, and 2 still on treatment	Content analysis procedure - informed by Sandelowski's (2000) approach to qualitative description	6 major themes: Cognitive problems Effects on employment Emotional response Search for answers Coping mechanisms The providers role
2	Boykoff et al 2009	Cross sectional Interview; focus group Four focus groups: 6–8 in each Plus one in-depth interview (1–3 hours) with each participant	Breast (n=74)	Exploratory pilot study	≥1 year post end of adjuvant RT and/or CT	Ethnographic content analysis (referred to by Crabtree and Miller as *template text analysis*.)	Survivors report diminished QoL and daily functioning resulting from chemobrain. No categorization of type of cognitive changes but problems with memory, reading comprehension, and

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
							speed of processing were noted. Cognitive changes associated with significant negative outcomes e.g. diminished QoL and work ability.
3	Cappiello et al 2007	Cross sectional Interview (Part of a larger study)	Early stage breast (n=20)	To describe the information and support needs of participants as a basis for developing specific interventions to meet the needs of this population.	7 - 60 months post end of treatment	Analysis not described	
4	Cheung et al 2012	Cross sectional Focus group: 4 English speaking 4 Chinese	Breast (n=43)	To gather in-depth descriptions from multi-ethnic Asian BC patients on perception and experience of cognitive changes,	Completed anthracycline-based CT within past 12 months	Focus group discussions were analysed using Thematic Analysis. Open-ended discussion guide	74 open codes were created and categorized into three main broad themes:

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
		speaking groups conducted on 1 day (60–80 minutes) Plus short self-administered questionnaire re: (i) demographics, (ii) perception of top 5 contributing factors of cognitive changes (iii) how receptive they were on a scale of 1 to 10, to receive CT if CT was proven to be associated with neurocognitive toxicity		impact on family and working lives and coping strategies		and data-driven analytic methods were based on elements of grounded theory.	1. participants' experience with cognitive changes 2. impact of cognitive changes 3. coping strategies.
5	Downie et al 2006	Cross sectional	Breast (n=21)	Examination of relationship between experience with fatigue,	Receiving CT - had received between	Transcripts of the interviews were analyzed for themes, symptoms,	20 out of 21 patients reported difficulty with recent memory. Participants described

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
		Semi structured interview Preceded by: FACT-G FACT-F FACT-ES HSCS.		menopausal symptoms and cognitive performance. Goals of the interview were to (i) gather descriptive information about the nature of the symptoms; (ii) assess frequency and severity of symptoms and (iii) gain a better understanding of the meaning and subjective impact of symptoms within patients' day-to-day lives.	3 and 6 cycles of treatment. Assessments took place 2 to 6 weeks after the previous intravenous CT.	and impact of symptoms. Initially two team members discussed themes and ratings emerging from the interviews, and developed a coding system.	increased forgetfulness (of names, words, places and appointments) and slower memory retrieval. Cognitive problems were intermittent and unpredictable. Problems with memory were reported to affect all aspects of life. At work they interfered with productivity, and at home patients complained about misplacing objects and forgetting whether chores had been completed
6	Fitch et al 2008	Cross sectional	Breast (n=15) CRC (n=8)	Exploratory study to understand and document experiences with	Started CT ≥ 6 months previously	Content analysis (Speziale & Carpenter, 1999) using all interviews,	Descriptions of cognitive changes provided clear evidence that the changes could affect

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
		Interview	Gyn (n=3) Hem (n=4) Pancreas (n=1) Lung (n=1)	changes in cognitive functioning following treatment		including pilot interviews.	daily living, social and work-related activities. Approx. ¼ of participants expected the changes to be temporary; the rest were uncertain or expected it to be permanent. Experienced emotional distress was linked to whether or not the cognitive changes interfered with participants doing something that was of importance to them. Participants used a variety of strategies to cope with the changes.
7	Kanaskie & Loeb 2015	**Longitudinal** (short interval)	Breast (n=7) aged 42 – 59	To better understand the lived experience of	Had completed standard CT	Van Manen's approach to interpretive phenomenological	Five essential themes were identified:

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
		2 in-depth semi-structured interviews 1 month apart and a written journal		cognitive change following CT and to more fully elucidate the impact of the phenomenon on personal and social relationships and how women cope with these changes in relation to their daily roles and responsibilities.	within past 12 months	research was used to uncover the meaning of the lived experience of cognitive change following CT	1. noticing the difference 2. experiencing cognitive changes 3. interacting socially 4. coping and 5. looking forward
8	Mitchell T 2007	**Longitudinal** Interview & diary entries	Mixed cancer patients (not described) (n=19)	To: 1. identify common and unique symptoms of social and emotional distress in individuals receiving CT; 2. illuminate patients' journeys through the process	Participants met with their researcher up to 10 times during treatment, depending on individual treatment regimes.	A modified phenomenological analysis framework	Eight major themes emerged: 1.striving for normality 2.role of significant others 3.feeling up/feeling down 4.flagging 5. being sociable

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
				of receiving CT treatment; 3. describe common and unique strategies employed by individuals to cope with the social and emotional effects of toxicity.			6. anxiety, 7.chemotherapy process, and 8. participating in the research. Concentration and memory loss were sub themes of flagging.
9	Mitchell & Turton 2011	**Longitudinal** Interview	Breast (n=1) others not described (n=3)	Initial study exploring the psychosocial effects of CT toxicity from patients' perspectives. To capture experiences and perceptions of: 1. CI as told by people receiving CT and	T1: Halfway through treatment, and T2: on completion of treatment. All 4 participants had or were due to have ≥ 4 months of CT	A descriptive phenomenological approach was employed (Giorgi 1985)	Not provided

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
				2. Concentration and memory impairment.			
10	Munir et al 2010	Cross sectional Focus group Semi-structured interviews with two focus groups (n = 6, n = 7) Plus CFQ -25	Breast (n=13)	To investigate women's awareness of CRCI, perception of cognitive limitations in carrying out daily tasks and subsequent return to work decisions and perceptions of work ability.	Completed CT between 12 months to 10 years ago	All interviews were transcribed verbatim and analysed using template analysis (Crabtree & Miller 1992).	Four main themes: 1. awareness of cognitive changes during and following CT, 2. cognitive ability and confidence in return to work 3. impact of cognitive changes on work ability and 4. information on the cognitive side effects of CT
11	Munir et al 2011	Phased study Semi structured interview	Breast (n=31)	To examine the need for interventions related to perceived cognitive problems from the	3 phases of data collection 4 months after the end of CT treatment:	First, quantitative content analyses were used to quantify & generate frequencies on	Three major themes: 1. Awareness of cognitive problems 2. Information and support received

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
		Plus: CFQ BDI Fatigue		perspectives of patients and of healthcare staff. In particular, the study examined whether cognitive interventions were required to help patients manage return to work and maintain satisfactory cognitive function at work.	(1) Semi-structured interviews with patients with BC recruited from a NHS hospital breast cancer clinic, (2) semi-structured interviews with health professionals involved in care of the women participating in the study, and (3) intervention validation questionnaire sent to participants interviewed in phase 1.	interviewees' statements on types of (1) cognitive changes experienced, (2) information received from healthcare professionals, and (3) info/support required. Descriptive statistical analyses, were applied. Qualitative content analysis was also used. Mixed method study	3. Information and support required

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
12	Myers JS 2012	Cross sectional Interview, Focus group	Breast (n=18)	To provide an in-depth description of the experience of CRCI and identify related information that women would find useful prior to CT and at the onset of cognitive changes.	Within 6–12 months of having completed CT	Qualitative content analysis and inductive analysis procedures were used to prepare, organize, and report the data (Elo & Kyngas, 2007).	'Life with chemobrain' was identified as the overarching theme. Three subthemes: 1.How I changed, 2.How I cope, and 3.How to teach me Most women reported problems with short-term memory, focusing, word finding, reading and driving.
13	Player et al 2014	Cross sectional Semi-structured individual telephone and face-to-face	Breast (n=9) 40–70 years old at time of diagnosis	To explore impact of chemobrain on daily functioning by examining the experiences as described by women who received treatment. Specific objectives were to:	Undergoing or had completed CT and self-identified experiencing 'chemobrain' according to the definition used earlier by Cheung et al. (2011).	A descriptive phenomenological methodology, a flexible exploratory design (Knaack, 1984; Marshall, 1996). Data were analysed using thematic analysis (Braun &	Six themes: 1. uncertainty about the origin of the chemobrain experience; 2. persistent but inconsistent impacts on function;

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
		interviews (lasting between 40 and 90 minutes)		(i) describe how chemobrain may be experienced by Australian women; (ii) explore areas of daily life that were most commonly affected, and needed support; and (iii) identify the strategies that women found helpful in minimising the effects of chemobrain.		Clarke, 2006). A field diary was kept by the researcher, with reflections and comments included in data collection & analysis phases (Groenewald, 2004). Data analysis involved open-reading of the transcript to understand the women' expression and meaning in the broadest context (Wertz, 2005), followed by line-by-line coding of each transcript and categorising data according to emerging patterns and themes.	3. simple function turned complex; 4. losing functional independence in family life; 5. strategies to maintain function; and 6. need for recognition of subjective experience of cancer treatment.

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
14	Potrata et al 2009	Cross sectional Interview Part of a larger programme of research on symptom experiences of eight cancer diagnostic groups.	Mylemoa (n=15)	To obtain a more in-depth understanding of CI and concerns as described by patients with multiple myeloma and the strategies used to cope with them.	Had received at least one treatment for multiple myeloma (including thalidomide, bortezomib, CT, RT, allogeneic and/or autologous stem cell transplant) on its own or in combinations. Less than 1 year from diagnosis, between 1–5 years and more than 5 years after initial diagnosis.	Grounded theory approach (Charmaz 2000)	Various cognitive impairments, e.g. problems with short-term memory, poor recall and lack of concentration were observed and/or expressed in at least 10 out of 15 patients, all of them long(er)-term survivors. In some patients cognitive impairments significantly interfered with personal and professional lives, and for some patients these were described as permanent. Patients used various coping strategies, from denial, taking notes, writing diaries, reading simpler texts, using talking books and videos, to using systems for

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
							counting medication to cope with cognitive impairment.
15	Raffa & Martin 2010	Cross sectional Interview	Breast (n=1)	Case study about the experience of 'chemo-fog', chemo-brain'	15 years after CT	Not described	Symptoms are usually difficult to describe and involve domains of cognition such as attention, concentration, memory, speed of information processing, multitasking, or ability to organize information. Deficits are reported to persist. The magnitude of the negative impact on QoL depends, as does the condition itself, on multiple and varied factors.
16	Rust & Davis 2013	Cross sectional Focus group	Breast (n=24)	To explore issues faced by underserved African American breast cancer survivors, their	Completed CT and radiation at least one year prior to the study	Analysis was based on grounded theory (Tavakol, Torabi, & Zeinaloo, 2006). Participants were	Four themes: 1. the concept of chemobrain,

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
				experiences with CI from chemobrain, and the impact of chemobrain on QoL.		asked open-ended questions to elicit conversation regarding the issues they faced, their experiences with CI, and the impact of chemobrain on their lives. Open coding involved examining the data in discrete parts for differences and similarities, and then identifying themes within the data. Data was then coded into categories and salient themes developed (Miles & Huberman, 1994; Rubin & Babbie, 2008).	2.variability among individuals, 3.stigma of chemobrain, 4.methods of coping

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
17	Shilling & Jenkins 2007	**Longitudinal** Structured interviews (part of an objective study)	Breast (n=142)	Compared/looked at relationship between objective impairment and subjective impairment.	T2: 4 weeks after the final CT session (n=93) 6 months in the non-CT group n=49 T3: 12 months after the final CT session (n=85) 18 months in the non-CT group: (n=41).	Not described	Quotes illustrate the types and extent of problems faced by these women. Main findings of CT patients: Patient noticed changes in: Memory: 83% at T2; 60% at T3 Concentration 78% at T2; 45% at T3 Family and friends noticed change in patient's: Memory 53% at T2; 39% at T3 Concentration: 32% at T2; 15% at T3

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
							Patient concerned about changes in: Memory 34% at T2, 39% at T3; Concentration 28% at T2; 40% at T3
18	Skoogh et al 2012	Cross sectional Open interview format	Testicular (n=40)	To learn more about possible long-term effects of CT in everyday activities related to cognitive demands. Focused on specific activities and behaviour in everyday life that may depend on cognitive function.	On average 15 years post CT	Interviews were recorded and transcribed to identify distinct and concrete behaviour elements such as "word dropping" or "looking for things". These elements were then categorised into themes such as "communicating" and "forgetfulness".	Identified 59 questions mainly reflecting one specific cognitive domain: 6 were judged to reflect attention, 26 memory, 5 visual-spatial ability, 7 language, 2 speed and 13 executive function.
19	Von Ah D et al 2013	Cross sectional	Breast (n=22)	To obtain a better understanding of breast cancer	All at least 1 year post CT treatment	A conventional content analysis approach was used	Six major domains: short-term memory, long-term memory,

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
		Interview (Six open-ended questions)		survivors' experiences of perceived CI, its trajectory, and its impact on relationships, daily functioning, work and overall life satisfaction after breast cancer diagnosis and treatment		(Hsieh and Shannon, 2005; Sandelowski, 2000). Codes were data-derived and research questions drove the analysis (Hsieh and Shannon, 2005).	speed of processing, attention and concentration, language and executive functioning. All survivors found these impairments frustrating, and some also reported these changes as detrimental to self-confidence and social relationships.

	First author & year	Study design and methods	Type of cancer	Aims/objectives of study	Time of assessment	Analysis used	Major themes
20	Wagner et al 2009	Cross sectional Interview (8 patients), Focus group (11 patients)	Breast (n=10) Lung (n=4) Oesophagus (n=2) Prostate (n=1) Myeloma (n=1) Liver (n=1)	Two aims: Phase 1: to solicit & record descriptions of CI from oncology patients who reported this concern, oncologists & oncology nurses. (For the development of a questionnaire to assess CI using language relevant to patients.) Phase 2: to evaluate psychometric properties of individual items generated in phase 1.	Completed 3 or more cycles of CT within the previous 6 months and had reported a disruption in cognitive function to an oncology healthcare provider.	Thematic content analysis by 3 independent reviewers. Themes identified from provider interviews were aggregated with those generated from patient focus groups & interviews. These themes were used to generate items for the FACT -Cog measure.	Patients reported deficits in: word-finding, forgetfulness, lack of mental clarity, impaired concentration, delayed reaction time, and psychomotor slowing. Patients described these deficits as frustrating and depressing - they interfere with work and ability to drive.

Key: CT: chemotherapy; CI: cognitive impairment; CRCI: chemotherapy related cognitive impairment; BC: Breast Cancer; PROMIS: Patient-Reported Outcomes Measurement Information System; FACT-G: Functional Assessment of Cancer Therapy: General; FACT-F: Functional Assessment of Cancer Therapy: Fatigue; FACT-ES: Functional Assessment of Cancer Therapy: Endocrine Subscale; HSCS: High Sensitivity Cognitive Screen; CFQ -25: The Cognitive Failures Questionnaire – 25; CFQ: The Cognitive Failures Questionnaire; BDI: Becks Depression Inventory

4.5 Trajectory and cognitive domains

4.5.1 Onset

As with the OCI studies, although early cross sectional studies such as van Dam and colleagues (1998) found evidence of SCI post-chemotherapy treatment, it was not until the early 2000s when studies properly examined the onset of such impairments.

4.5.2 Pre-chemotherapy

In 1999, Cimprich was one of the first researchers to concentrate solely on pre-surgery assessments. In her study, she found that only 27% of newly diagnosed breast cancer patients rated themselves as cognitively well functioning when performing key activities. Similarly, to the findings regarding OCI, SCI has been found to exist in a subset of cancer patients prior to the commencement of chemotherapy treatment (Sanford et al, 2014; Skaali et al, 2011; Hermlink et al, 2015). For example, Skalli and colleagues (2011) found that 16% of testicular cancer patients reported SCI affecting daily functioning after surgery and prior to the start of any additional treatment. However, Vardy and colleagues (2017) found that patients with CRC reported cognitive symptoms at rates commensurate with those in the general population prior to chemotherapy treatment.

4.5.3 Course

As with OCI, in the studies that found SCI there is conflicting data regarding its course**.**

In a purely subjective longitudinal study (i.e. one that used only a brief clinical interview and self-report questionnaires but no NP measures), of the 595 participants undergoing treatment for solid tumours, Kholi and colleagues (2007) found that problems with

concentration were reported by 48% of patients (5% severe) prior to the commencement of chemotherapy treatment (T1); 67% (18% severe) during treatment (T2) and 58% (8% severe) at 6 months following chemotherapy treatment (T3). Problems with memory were reported by 53% at T1 (4% severe), 67% at T2 (18% severe), and 68% at T3 (11% severe). Whilst there were cognitive problems reported prior to chemotherapy treatment, it was found that patients tended to report SCI more during and after chemotherapy (Kohli et al, 2007) with the course of SCI being reported as worse during chemotherapy treatment.

A later longitudinal study that examined the cognitive effects of chemotherapy in 61 older post-menopausal women with breast cancer also found that a higher percentage of women in the chemotherapy group reported SCI after chemotherapy, with 27% pre-chemotherapy treatment (T1), 43% 6 months later/within 1 month of completing chemotherapy (T2) and 46%, six months after T2 (T3). However, the percentage of those reporting memory problems in the non-chemotherapy group did not change much, with 32% at T1, 35% at T2 and 31% at T3 (Tagar et al, (2010).

These two studies contrast with Shilling & Jenkins (2007), who found that self-reported difficulties decrease over time. They found that 71% and 61% of participants reported problems with memory at one and six month's respectively post-chemotherapy treatment, 64% reported problems with concentration one month after chemotherapy, and 42% six months after the end of chemotherapy treatment. Quesnel and colleagues (2009) study also found that patients receiving chemotherapy treatment reported more cognitive difficulties than those who did not receive it at the post-treatment assessment, followed by a return to the baseline level at the 3 month follow-up evaluation. In a

systematic review, Hutchinson and colleagues (2012) found that the course and duration of SCI is unclear.

4.5.4 Duration

Perceived changes in memory and attention attributed to CRCI have been reported to exist immediately following chemotherapy treatment and up to a year later (Hutchinson et al, 2012). As with OCI, there are studies that suggest that SCI can persist for up to 10 years following cancer diagnosis (Ahles et al, 2002).

Post-2005 cross sectional and longitudinal studies that used the FACT-Cog to measure SCI in patients with cancer found that participants self-reported on-going SCI for multiple years following chemotherapy treatment. For example, Von Ah and colleagues (2009) cross sectional study in breast cancer found that participants self-reported on-going symptoms for a mean period of 5 years after adjuvant chemotherapy (Von Ah et al, 2009). Similarly, Vardy and colleagues' (2017) longitudinal study exploring SCI in patients with CRC who either did or did not receive chemotherapy found that cognitive symptoms increased in patients who received chemotherapy, peaked just after completing treatment and continued at the higher level for 2 years after diagnosis.

4.6 Overview of affected cognitive domains

Patients with cancer (particularly those with breast cancer) often complain of problems with memory and concentration (Phillips & Bernhard, 2003). In the context of the "cancer and cognition" literature, reports of SCI have been described as patients having difficulties with attention, concentration and memory (Wagner et al, 2009; Boykoff et al, 2009; Downie et al, 2006; Cappiello et al, 2007; Cheung et al, 2012; Mulrooney, 2008;

Munir et al, 2010; Munir et al, 2011; Myers, 2012; Von Ah D et al, 2013; Rust & Davis, 2013; Fitch et al, 2008). Downie and colleagues (2006) also found that 78% of breast cancer participants reported problems with language. Bray and colleagues (2018) systematic review found that not all of the included studies specified particular cognitive symptoms reported by participants, although when they were described, they predominantly involved reports of deficits in memory.

The most frequently reported cognitive changes in interview and/or focus group studies appear to be in memory during chemotherapy treatment (Downie et al, 2006; Mitchell, 2007) and up to 12 months after the end of chemotherapy treatment (Myers, 2012; Potrata et al, 2009; Shilling & Jenkins, 2007; Von Ah, 2013). For example, almost all of the breast cancer patients receiving adjuvant chemotherapy treatment (20 of 21) interviewed for Downie and colleagues' study (2006) reported difficulty with recent memory during chemotherapy treatment. They described increased forgetfulness of names, words, appointments and slower memory retrieval (Downie et al, 2006). Similarly a few years later Von Ah and colleague's (2013) found that all of the 22 breast cancer participants who had undergone chemotherapy treatment at least 1 year earlier, reported short term memory impairments, 91% (n=20) reported long term memory impairments and 55% (n=12) reported issues with attention and concentration.

4.7 Further issues affecting studies of both OCI and SCI in cancer populations

4.7.1 Attrition

From both the objective and subjective point of view, the difficulties encountered interpreting research in this area due to the methodological issues are further

complicated by the high rates of attrition encountered in such studies. Attrition is often a result of the advancement of residual disease, death or participants' reluctance/unwillingness to discuss their cancer at follow-up as this can raise negative thoughts and feelings regarding a possible relapse of the disease (Jansen et al, 2008; Hodgson et al, 2013).

4.7.2 Confounds

As mentioned above, a number of relatively recent studies have found that a percentage of patients with solid tumours have OCI (Wefel et al, 2004; Hurria et al, 2006; Hermelink et al, 2007; Jansen et al, 2008; Lange et al, 2014; Mandelblatt et al, 2014; Hermelink et al, 2015; Vardy et al, 2015) and/or SCI (Cimprich, 1999; Mehlsen et al, 2009) even before starting adjuvant chemotherapy treatment. This could be attributed to other contributing factors as discussed in Chapter 2, Section 2.4 or perhaps there are common risk factors for both the development of cancer and cognitive changes?

As can be seen from the studies discussed in this chapter and Chapter 3, the mechanisms underlying CRCI (whether objective or subjective) are still not well understood (Ahles & Saykin, 2007, Vardy et al, 2008 and Walker et al, 2012).

4.8 Relationship between OCI and SCI

As mentioned, studies examining cognition in patients with cancer often include both an objective and subjective measure of cognitive function (41 out of 77 in Table 3.1). However, this does not always mean that an association is examined. For example, Bray and colleagues (2018) found that the association between self-reported cognitive

symptoms and NP results was not reported in more than half of the studies (i.e. >50 out of 101 studies) included in their review.

Even when it is examined, few studies have found a significant correlation between these measures (Hutchinson et al, 2012). The majority of studies (that examined the relationship listed in Table 3.1) report no association between OCI and SCI (e.g. Cull, Hay, Love, Mackie, Smets, & Stewart, 1996; Klepstad, Hilton, Moen, Fougner, Borchgrevink, & Kaasa, 2002). In Bray and colleagues (2018) systematic review, they found that 31 studies showed a lack of association between self-reported cognitive symptoms and NP results. They described how a total of 14 included studies reported a significant association between OCI and SCI (correlation coefficients from 0.22 to 0.57) but found that the association was often restricted to a limited number of cognitive domains tested in the NP assessment (Bray et al, 2018).

Patients frequently report that their own perception of the level of cognitive impairment is greater than that detected by NP assessments (van Dam et al, 1998; Schagen et al, 1999; Ahles et al, 2002; Castellon et al, 2004; Donovan et al, 2005; Cull et al, 1996; Servaes et al, 2002; Poppelreuter et al, 2004).

SCI is often associated with anxiety and/or depression and/or fatigue (van Dam et al, 1998; Ahles et al, 2002; Jenkins et al, 2006; Cimprich et al, 1999;Cimprich et al, 2005) rather than OCI. Bray and colleagues (2018) reported that 43 out of 44 studies found a moderate to strong association between self-reported cognitive function and other patient-reported outcomes. The main associations were between self-reported cognitive function and mood disturbance, fatigue and psychological distress (Bray et al, 2018).

4.9 Impact of CRCI on QoL

Patients' perceptions of impairment are important due to the potential impact these may have on QoL (Hutchinson et al, 2012). Deficits in perceived concentration and memory can have a detrimental effect on an individual's daily living, social and work related activities (Fitch, Armstrong, & Tsang, 2008). In 2009, Boykoff and colleagues interviewed 74 breast cancer patients who had completed treatment at least 12 months prior to the interviews, in order to explore the psychosocial ramifications of CRCI. Study results included descriptions of the general psychosocial influence of perceived cognitive changes, effect on interactions with healthcare providers, and consequences for social networks and work performance. It highlighted the fact that patients report diminished QoL and daily functioning as a consequence of CRCI. This corroborated Shilling and colleagues (2005) findings that described how perceived cognitive impairment during chemotherapy can have a 'knock-on' effect on patients' QoL and may reduce their ability to make a smooth transition from treatment back to activities of normal everyday life such as returning to work (Mitchell & Turton, 2011). Less is known however about the relationship between OCI and HRQoL which is more closely examined in the following Chapter.

4.10 Summary

The presence, extent and course of any cognitive impairment (objective or subjective) and whether it causes observable difficulties for patients with solid tumours remain unclear.

To date, most research examining CRCI has focused on only one type of cancer (Wefel et al, 2011) with varying results. Studies have mostly been concerned with female breast

cancer, making the results less generalizable to people with other types of cancer (de Ruiter et al, 2011; Skaali, Fosså, & Dahl, 2011). Research in only the female breast cancer population has also prevented an examination of possible gender differences. Few studies have been conducted in any other cancer populations, such as testicular cancer (Schagen et al, 2008), ovarian cancer (Correa & Hess, 2012), and prostate cancer (Nelson et al, 2008). Therefore, more longitudinal research is required in additional solid tumour cancer populations to fully understand the extent and course of OCI and/or SCI in these populations. Such studies will help to determine whether CRCI is a universal phenomenon or is more pronounced in the female breast cancer population. Furthermore, studies in other cancer populations will improve understanding of whether the different treatments (e.g. multi- and single-agent chemotherapies) for different cancers work by different mechanisms, which lead to OCI and/or SCI. It would be extremely helpful if research in this area could clarify which specific treatments might be expected to be detrimental and how long any specific side effects might last (Anderson-Hanley et al, 2003). Not only would this knowledge enable researchers to identify risk factors including disease-specific factors, demographic factors, psychological factors, and genetic factors (Janelsins et al, 2014), but it would also allow patients to make informed treatment choices and prepare for any potential impact on work and relationships (Anderson-Hanley et al, 2003).

Moreover, the exact mechanism(s) involved in chemotherapy-related OCI and/or SCI are currently unclear. These inconsistent results are likely due to methodological issues (e.g., relatively small sample sizes, cross sectional designs, use of different NP tests, different reference data and performance cut offs for classifying cognitive impairment (Shilling, Jenkins, & Trapala, 2006)) and differences in study populations (stage and

severity of cancer, different chemotherapy treatment regimens (dosage and drugs) as well as additional varying adjunctive treatments).

This discursive review has also highlighted the need for additional more focused systematic reviews of the literature, which will identify studies examining whether there is a relationship between HRQoL and objectively measured cognitive changes related to chemotherapy treatment. This is the subject of the following chapter.

Chapter 5: Health-related quality of life and its association with objective cognitive changes in cancer patients who have solid tumours.

5.1 Introduction

The end of Chapter 4 highlighted the need to identify studies that specifically explore the relationship between HRQoL, and OCI in order to establish a broader picture of the consequences of CRCI. This chapter provides such an examination of the literature. It synthesises and reviews the primary research studies that have aimed to measure the relationship between OCI in patients with solid tumours who are undergoing or have had chemotherapy treatment and their HRQoL outcomes.

5.2 Background

As mentioned in Chapter 1, the effectiveness of chemotherapy drugs in treating a range of cancers has improved significantly in recent decades. Whether used alone, or in combination with other treatments or therapies, the result has been a marked reduction in disease recurrence and an increase in survival times. Not only has improved treatment contributed to improved survival but screening, and early detection of disease have also improved outcomes (See Chapter 1) (Fardell, Vardy, Shah, & Johnston, 2011). Despite these strides forward, no pharmaceutical treatments are devoid of side effects. Chemotherapy drugs are no exception with a decline in cognitive function being one of the commonly reported side effects and the focus of this thesis. The evidence and estimates of the numbers of patients affected by self-reported and objective assessment of cognitive decline were discussed in the previous chapters. As discussed in the

previous chapters the "cancer and cognition" research has numerous methodological difficulties.

5.3 HRQoL

As discussed in Chapter 4, HRQoL is a multi-dimensional construct specifically related to health and illness (Kirshner & Guyatt, 1988; Cella et al, 1993). HRQoL encompasses the subjective perceptions of the positive and negative aspects of cancer patients' symptoms, including physical, emotional, social, and cognitive functions as well as disease symptoms and side effects of treatment (Bottomley, 2002; Leplege & Hunt, 1997).

With the increase in survival times HRQoL has become a meaningful outcome measure for patients diagnosed with cancer (Arndt, Merx, Stegmaier, Ziegler, & Brenner, 2004). An understanding of a possible link between objective and/or subjective CRCI and the impact on various domains of HRQoL is necessary to fully understand the potential consequences of cancer and adjuvant chemotherapy treatment. Such knowledge may be a helpful catalyst in the development of more appropriate interventions designed to improve the process of coping and adjustment of these patients (Ahles, Saykin, Furstenberg, et al, 2005).

A review of the literature to date revealed that HRQoL is often assessed at the same time as OCI in a large proportion of "cancer and cognition" studies (i.e. approx. 50% of the studies listed in Chapter 3, Table 3.1). The two most commonly used tools to assess HRQoL in the "cancer and cognition" literature are the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EROTC – QLQ C30) (EORTC Quality of Life Group, 2002)(Aaronson et al, 1993; Kayl et al, 2008); or one or

more of the questionnaires from the Functional Assessment of Cancer Treatment (FACT) battery (Functional Assessment of Chronic Illness Therapy, 2007) (Wagner, Sweet, Butt, Lai & Cella 2009). Both the EORTC – QLQ C30 and FACT-G are generic core HRQoL questionnaires supplemented by a range of tumour-, treatment- or symptom-specific 'modules' as required (e.g. the FACT-B for breast cancer; FACT-C for colorectal cancer (CRC)).

The EORTC – QLQ C30 is a 30 item self-report questionnaire designed to assess the HRQoL of patients with cancer participating in international clinical trials. It is composed of multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status/QoL scale, and six single items. Whereas the FACT-G (now in Version 4) is a 27-item compilation of general questions divided into four primary QOL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. A comparison of the EORTC QLQ-C30 and FACT-G characteristics is presented in Table 5.1.

Table 5.1. A comparison of QLQ-C30 and FACT-G characteristics (Luckett et al, 2011).

	EORTC QLQ-C30	**FACT-G**
Number of items	30	27
Response options	Likert scales (4 or 7 options)	Likert scale (5 options)
Recall period	Past week	Past 7 days
Item format	Questions	Statements
Item organisation	Items are not always grouped into scales and never explicitly so	Item are grouped into scales
Scaling	Five 'functioning' scales, measuring:	Four 'well-being' subscales, measuring:

	EORTC QLQ-C30	**FACT-G**
	• Physical functioning (PF; 5 items) • Role functioning (RF; 2 items) • Emotional functioning (EF; 4 items) • Social functioning (SF; 2 items) • Cognitive functioning (CF; 2 items)	• Physical well-being (PWB; 7 items) • Social/family well-being (SWB; 7 items) • Emotional well-being (EWB; 6 items) • Functional well-being (FWB; 7 items, including global QoL item)
	One three-item symptom scale measuring fatigue.	Overall FACT-G score (total of all 27 items)
	Two two-item symptom scales measuring pain, nausea, and vomiting.	
	Six single-item symptom scales measuring dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial impact.	
	Overall global health status/QoL scale (2 items)	
Time to administer	11 min	5 to 10 minutes
Administration	Self, interviewer, computer	Self, interviewer, computer

As can be seen in Table 5.1, both instruments have subscales measuring key aspects of HRQoL (i.e. physical, emotional, social and functional), however the EROTC –QLQ C30 also provides brief scales for cognitive functioning, financial impact and a range of symptoms that are either not assessed by the FACT G or are embedded within its wellbeing scale (Blazeby, 2005; Luckett, 2011). This difference is further highlighted by the fact that EROTC-QLQ C30 provides 5 "functioning" scales and 10 symptom scores compared to FACT-G, which only gives five summary scales (4 "well-being" and 1 overall scale) (Luckett, 2011). There are also differences between the two batteries' social

domains. Conroy and colleagues (2000) found that EROTC QLQ–C30's social functioning scale assesses the impact on social activities and family life whereas the FACT–G social well-being subscale focuses on social support and relationships. Whilst both scales are widely used, they each measure markedly different aspects of HRQoL so very often a direct comparison of results between studies examining HRQoL is not possible given that they use different scales (Kemmler et al, 1999).

5.4 OCI and HRQoL

Prior to undertaking this systematic review, the Cochrane Library was searched for reviews on the subject matter. This revealed four meta-analyses all of which reviewed studies that examined cognitive impairment arising from chemotherapy treatment (Jim, 2012; Lindner, 2014; Jansen, 2007; Jansen, 2005). There was also one systematic review that looked at the effectiveness of psychosocial interventions for cognitive dysfunction in cancer patients who received chemotherapy (Hines, 2014) and one critique of the literature on CRCI in women with breast cancer (Jansen, 2005). Taken together, the reviews support the hypothesis that there is a risk of chemotherapy having a small to moderate negative impact on some cognitive domains (Jansen, 2005; Jim, 2012) in a proportion of cancer patients. However, as demonstrated in Chapter 3, given the considerable differences between studies (in terms of participants, disease severity, outcome measures and design) it is not possible to determine from the reviews how long the deficits last or who is at greatest risk. All reviews suggest that if the heterogeneity between future studies can be reduced, valuable information may be gained which could effectively inform suitable interventions for decreasing the effects of CRCI and potentially improving HRQoL (Lindner, 2014).

5.4.1 Aims

The primary aim of this systematic review was to identify and synthesise research concerned with the relationship between objectively measured cognitive impairment and HRQoL in adult patients who received chemotherapy for treatment of solid tumours. It also aimed to establish whether particular OCIs are associated with specific aspects of HRQoL.

5.4.2 Methods

5.4.2.1 Inclusion and exclusion criteria

The search was limited to papers published in English post-1980, as this period coincides with a prevalence of reporting and systematic investigation of CRCI (van Dam et al, 1998).

Articles were restricted to those that had recruited patients aged 18+ years with a solid tumour such as breast, ovarian, CRC, prostate, and lung treated with chemotherapy. Studies of patients with brain tumours and central nervous system tumours were excluded because of the inherent effects of the tumour on cognition, as well as the fact that treatments often involve brain irradiation and surgical interventions that are known to cause additional direct effects on brain tissue secondary to the lesions (Roman & Sperduto, 1995; Weitzner & Meyers, 1997) and consequent changes in neuropsychological functioning (Anderson-Hanley et al, 2003).

Included studies were required to be full papers that assessed both objective cognition and HRQoL using standardised measures. In addition, to be included, studies needed to examine (by quantitative measurement) and/or report on the relationship between such

objectivelymeasured cognitive deficits (global cognitive deficits and/or domain specific ones) and (global or domain specific) measures of HRQoL. Reviews, commentaries, case reports, dissertations, and conference abstracts were all excluded.

5.4.2.2 Search Strategy

On 6th June 2016 the following electronic databases were searched:

- Web of Science Direct
- Pubmed
- Medline, Embase, PsycINFO and PsycARTICLES through OVIDSP
- CINAHL through EBSCO

using a combination of search terms that included all known terms for cancer, such as neoplasms and oncology. Treatment terms included chemotherapy and "systemic treatment"; the HRQoL and cognition terms included are fully set out in Figure 5.1. The researcher agreed the search terms with a specialist librarian and the supervisory team.

The following search strategy was used to obtain the initial list of articles:

Figure 5.1: Search terms used to find suitable studies for the systematic review

Cancer terms	Impairment terms	Treatment terms	Outcome
Cancer	Cognition	Chemotherapy	Quality of life (QoL)
Oncology	Cognitive impairment	Systemic treatment	Well being
Neoplasm	Cognitive deficit		Health related QoL

Cancer terms	Impairment terms	Treatment terms	Outcome
	Cognitive function		
	Cognitive decline		
	Cognitive failure		
	Chemobrain		
	Chemofog		
	Memory		
	Executive function		
	Processing speed		

The Boolean phrase 'OR' was placed between the terms listed vertically and the Boolean phrase 'AND' placed between those terms listed horizontally in the table. A combination of both text words and indexed terms (such as MeSH) were applied in each database. Search terms were modified as necessary for each electronic database searched. The reference lists of all included articles were also searched for additional studies.

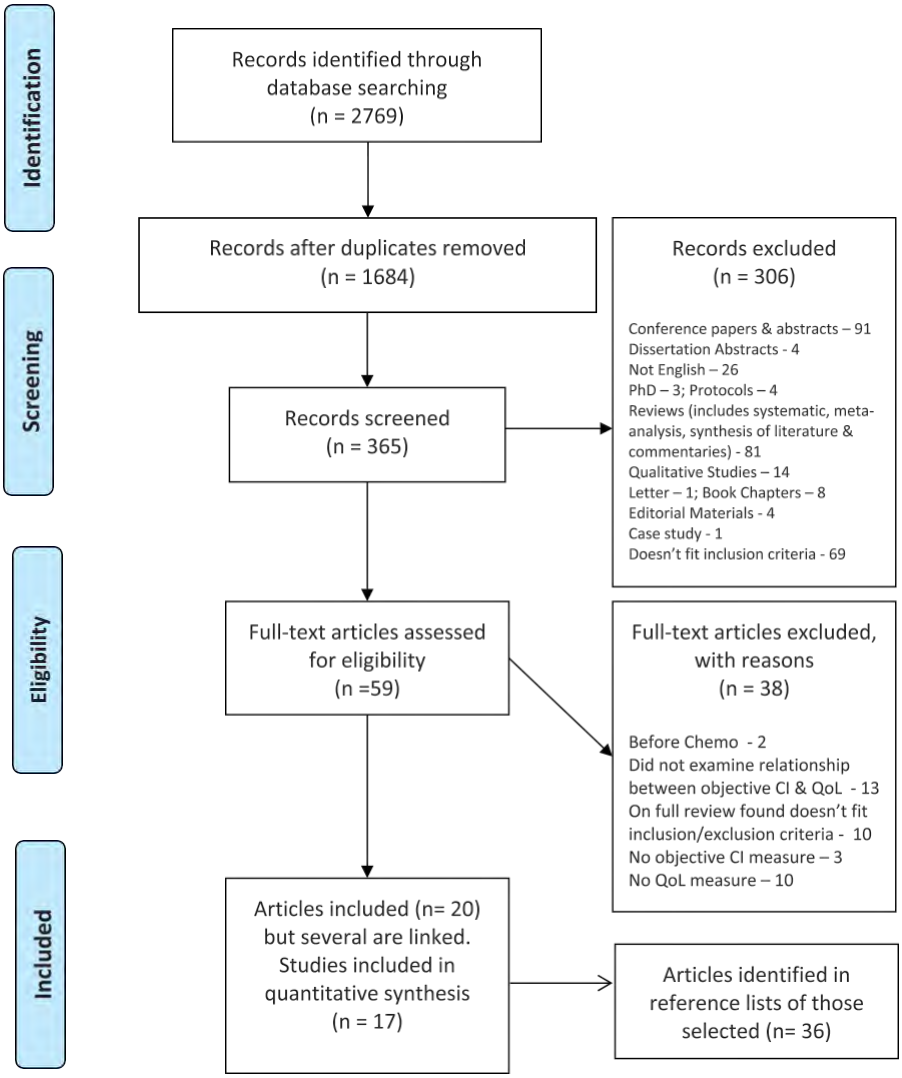
Articles published between 7 June 2016 and 1 July 2018, were also identified and the findings from these studies are summarised in Section 5.6.

5.4.2.3 Study selection

Once searches had been conducted and duplicates removed, retrieved articles were screened by title and, if eligibility was unclear from the title alone, the abstracts were

screened. The researcher assessed the abstracts using the eligibility criteria. A member of the supervisory team also independently screened 10% of all titles and abstracts retrieved using the search strategy to identify studies that potentially met the inclusion criteria. A list of the independently screened studies were crosschecked by the researcher for any areas of disagreement, of which there were none. All remaining articles were retrieved in full and screened for eligibility by the researcher, who then selected the relevant articles and crosschecked the relevance of these articles with the supervisory team. In total, 17 studies met the inclusion criteria (see Fig. 5.2).

Figure 5.2: Flow chart of study selection



5.4.2.4 Data Extraction

A data extraction form for this systematic review was developed by the researcher (Appendix D) and used to record general study details such as:

- Authors, year of publication and country
- Study design
- Research question
- Disease characteristics – type of cancer and severity
- Treatment regime – surgery, chemotherapy, radiotherapy, combination treatments
- Participant characteristics
- Inclusion/exclusion criteria
- Objective cognitive, HRQoL and other measures used – detail regarding characteristics of measures used, the time at which they were all administered
- Results – analysis used, number of participants withdrawn, results of analysis
- Limitations and/or anything else of note

The data extraction form was piloted against five papers and was refined thereafter. The researcher and supervisory team agreed on the final form.

5.4.2.5 Quality Assessment

As there is currently no agreed "gold standard" appraisal tool for observational studies, a quality-scoring tool was developed on the basis of methodological quality assessment checklists from the NICE *Methods for the development of NICE public health guidance* (Sanderson et al, 2007; Lang & Kleijnen, 2011). Valid criteria (items) were selected from

the NICE checklists and adapted for the purposes of this review in order to ensure that the 5 recommended aspects of internal validity (i.e., a clearly focused question, selection of subjects, assessments, confounders, and statistical analysis), together with an overall assessment of the study, were addressed in the evaluation of quality. A total of 16 items were included that covered all aspects considered necessary to evaluate the quality of the evidence in relation to the research question: *Is there a relationship between objectively measured cognitive changes in patients with solid tumours undergoing chemotherapy treatment and their health-related quality of life outcomes?* (Appendix E). Authors of original papers were emailed to obtain any missing data or details so that the quality of the study could be evaluated, rather than relying on the published paper.

The overall assessment for each paper was calculated by considering all 16 items and then attributing scores between zero and four to the overall assessment of the study, considering the extent to which each study was internally and externally valid. The higher the score, the less bias in the study and the more external validity. Two studies had the highest overall rating score of 4 (Vearncombe et al, 2009; Vardy et al, 2015), five studies scored 3 (Tchen/Mar Fan et al, 2005; van Dam et al, 1998; Reid-Arndt et al, 2010; Jenkins et al, 2006; Schagen et al, 1999), nine scored 2 (Cruzado et al, 2014; Hess et al, 2015; Wefel et al, 2004; Reid-Arndt et al, 2009; Wefel et al, 2010; Hurria et al, 2006; Freeman et al, 2002; ;Mehnert et al, 2007; Whitney et al, 2007) and one was rated 0 (Iconomou et al, 2004). Each included study was assessed by the researcher. Another member of the supervisory team then independently coded the quality of the studies to check the reliability of the quality assessment. Agreement between the coders was substantial ($\varkappa = 0.675$) and the researcher's final score was

used. Although the methodological quality of each study was evaluated and discussed, studies were not eliminated from this review because of poor quality.

5.4.3 Results

5.4.3.1 Identified studies

Database searches identified 2769 citations, and 36 additional citations were retrieved from reference lists. Screening of titles and abstracts identified 365 potentially eligible articles (Figure 5.2).

The full texts of 59 papers were reviewed, 20 satisfied the inclusion criteria. An examination of the reference lists did not identify any additional papers that met the inclusion criteria. Several papers were linked and consequently treated as a single study (works of Tchen et al 2003 and Fan et al 2005 were linked; Shilling et al 2005 and Jenkins et al, 2006 were linked; and Vardy et al 2014 & 2015 were linked). This resulted in the final inclusion of 17 studies, whose main characteristics are presented in Table 5.2.

Table 5.2: Summary of characteristics of studies in the systematic review

Study & Country	Design	Sample Characteristics	Time of assessments and questionnaires	Operational Definition of Cognitive Impairment (CI)	Other Measures	Overall quality rating score**
Cruzado, 2014 *Spain*	Longitudinal (Single Site)	CRC	T1: pre-CT (n=81) T2: pre last-CT (n=73) T3: 6 months post last CT (n=54)	Raw scores converted into z scores (mean=0, SD=1) using published normative data adjusted for age, education, and gender. CI: (1) z scores of ≤−1.5 for more than one test; OR (2) z scores of ≤−2.0 for just one test.	HADS BFI 3 Hemoglobin levels	2
Freeman, 2002 *USA*	Cross sectional (Single Site)	Breast	2 groups G1: after 4 cycles CT (n=8) G2: 6 to 12 months after CT (n=9)	ANOVA to determine whether the 2 groups significantly differed in their cognitive performances.	CES-D Symptom Checklist 90- Revised Social Support Appraisal Scale 1 item re overall cognitive function 1 item re motional function	2
Hess, 2015 *USA*	Longitudinal	Ovarian	T1: pre-CT (n=231) T2: prior to 4th cycle CT (n=218) T3: 3 weeks post CT (n=208)	Impaired cognitive domain for each patient = the increased cognitive domain score from baseline for processing speed or motor reaction; and a decreased score for attention domain ≥1.5 standard error of measurement.	FACT – Ntx HADS PAF	2

Study & Country	Design	Sample Characteristics	Time of assessments and questionnaires	Operational Definition of Cognitive Impairment (CI)	Other Measures	Overall quality rating score**
			T4: 6 months post CT (n=169)	A cognitive index score (CIS) for each patient = total number of impaired cognitive domains at a time point. CIS ≥ 2 during CT = possible or probable acute CI. If retained > 6 months = persistent CI		
Hurria, 2006 *USA*	Longitudinal (Single Site)	Breast	T1: pre CT (n=28) T2: 6 months post CT (n=28)	Raw scores for each test converted into standardized scores using published normative data. CI: 2 ≥ SDs below published norms on ≥ 2 test	ADLs IADLs KPS Comorbid medical conditions GDS	2
Iconomou, 2004 *Greece*	Longitudinal (Single Site)	Lung (n=22), Breast (n=26), CRC (n=25), genitourinary (n=12) other (n=17)	T1: pre CT (n=102) T2: end of CT (n=80)	MMSE < 24	HADS	0
Mehnert, 2007 *Germany*	Cross-sectional	Breast	3 groups: G1: high-dose CT (n=24) G2: standard-dose CT (n=23) G3: early stage cancer no CT (n= 29)	CI = z ≤ -1.4 SD below the mean of zero in 1 test parameter. Global CI score = four or more test parameters in the impaired range	FEDA MFI-20 (German version)	2

Study & Country	Design	Sample Characteristics	Time of assessments and questionnaires	Operational Definition of Cognitive Impairment (CI)	Other Measures	Overall quality rating score**
Reid-Arndt, 2009 *USA*	Cross sectional	Breast	1 month post CT (n=46)	Raw test scores converted to z-scores utilizing age, education, and gender-based normative data. An average of each person's z-scores for tests comprising each domain was computed Decline in cognition = (domain composite z score) – (WRAT -3 Reading z score)	WRAT-3 reading subtest Hesitation Scale POMS-SF Social Role Functioning questionnaire CIQ	2
Reid-Arndt, 2010 *USA*	Longitudinal	Breast	T1:1 month post CT (n=46) T2: 6 months post CT (n=39) T3: 1 year post CT (n=33)	Individual test scores converted to z-scores utilizing age, education, and gender based normative data. Subtle CI = > 1 SD below the normative data mean, Severe CI = 1.5-2+ SD below the mean.	Hesitation Scale POMS-SF BDII-II Social Role Functioning questionnaire	3
Schagen, 1999 Netherlands	Cross sectional	Breast	2 groups: G1: approx. 1.9 years post adjuvant CT (n= 39) G2: no CT but matched for age & time since treatment (n=34)	CI = 2 ≥ SDs below the mean of the control group Overall impairment score (OSCI) for each individual patient = total number of tests on which the patient was impaired.	Semi structured interviews re subjective cognitive functions HSCL – 25	3

Study & Country	Design	Sample Characteristics	Time of assessments and questionnaires	Operational Definition of Cognitive Impairment (CI)	Other Measures	Overall quality rating score**
Jenkins, 2006 *UK*	Longitudinal	Breast	3 groups at each time points: G1: CT (n= 85) G2: Non CT (n= 43) G3: Healthy controls (n=49) T1: G1 assessed 21-83 days post-surgery; G2 assessed 22 -92 days post-surgery T2: 4 weeks post CT or 6 months T3: 12 months post CT or 18 months	Group comparisons on cognitive test scores were made at T1 & T2 using one way and repeated measures ANOVA, Chi-squared or Mann-Whitney U tests as appropriate. A reliable change index (RCI) (Jacobson & Truax method) was calculated for each cognitive measure using the baseline and follow up data of the control subjects.	All participants screened for dementia using info & orientation subtest of WMS III. NART Broadbent Cognitive Failures Questionnaire GHQ 12	3
Fan, 2005 *Canada*	Longitudinal	Breast	T1: After 3 cycles of CT G1: resectable breast cancer patients (n=104) G2: healthy women (n=102) T2: 1 year after T1 G1: resectable breast cancer patients (n=91) G2: healthy women (n=81) T3: 2 years after T1 G1: resectable breast cancer patients (n=83)	Overall classification of cognitive functioning was evaluated by the HSCS using an interpretive algorithm.	Blood test for measurement of serum estradiol, follicle stimulating hormone and luteinizing hormone FACT F	3

Study & Country	Design	Sample Characteristics	Time of assessments and questionnaires	Operational Definition of Cognitive Impairment (CI)	Other Measures	Overall quality rating score**
			G2: healthy women (n=81)			
van Dam, 1998 *Netherlands*	Cross-sectional (Single Site)	Breast	3 groups assessed approx. 2 years after last non-hormonal therapy: G1: high dose CT (n=34) G2: standard dose CT (n=36) G3: No CT (n=34)	Test scores were converted into standardised z scores by use of the mean test score of the control group. A mean overall composite z score was computed. CI = 2 SDs below the mean of the control group on a test. Overall CI score was calculated for each individual patient by counting all tests on which the patient was impaired.	DART Semi structured interviews HSCL-25	3
Vardy, 2015 Canada & Australia	Longitudinal	CRC	T1: Pre CT G1: CT (n=173) G2: no CT (n = 116) G3: metastatic (n = 73) G4: HC (n= 72) T2: 6 months G1: CT (n=137) G2: No CT (n=90) G3: metastatic (n = 52) G4: HC (n=72) T3: 6 months	Raw scores converted to demographically corrected T or Z scores (based on age, education, and sex), and a deficit score ranging from 0 (no impairment, T score > 39) to 5 (severe impairment, T score < 20) was derived. Deficit scores were averaged to determine Global Deficit Scores (GDS) to reflect overall cognitive performance. CI: 1) GDS more than 0.5; and	GHQ-12 Blood tests included CBC, creatinine, liver function tests, carcino-embryonic antigen, sex hormones, selected cytokines, markers	4

Study & Country	Design	Sample Characteristics	Time of assessments and questionnaires	Operational Definition of Cognitive Impairment (CI)	Other Measures	Overall quality rating score**
			G1: CT (n=118) G2: no CT (n = 87) G3: metastatic (n = 41) G4: HC (n=70) T4: 6 months G1: CT (n=99) G2: no CT (n=72)	2) 2 ≥ SDs below healthy controls on > 1 cognitive test or ≥1.5 SDs below healthy controls on ≥ 2 tests.	of blood clotting and apolipoprotein genotyping	
Vearncombe, 2009 *Australia*	Longitudinal	Breast	T1: After surgery pre CT G1: CT (n=138) G2: no CT (n = 21) T2: 4 weeks post CT G1: CT (n = 138) G2: no CT (n=21)	Impairment on specific cognitive tests = significant decline identified using the Reliable Change Index (corrected for practice, RCIp). Impairment in each cognitive outcome measure was a decline of > 1.96 SD. "Multiple Test Decline" = significant decline on ≥ 2 cognitive tests. Cognitive change = T2 - T1 for each cognitive test.	HADS NART-2 FACT F	4

Study & Country	Design	Sample Characteristics	Time of assessments and questionnaires	Operational Definition of Cognitive Impairment (CI)	Other Measures	Overall quality rating score**
Wefel, 2004 *USA*	Longitudinal (Single Site)	Breast	T1: pre CT (n=18) T2: 6 months post CT (n=18) T3: 1 year post CT (n=15)	Raw scores were converted into z scores (mean=0, SD=1) using published normative data adjusted for age, education, and gender. CI: (1) z scores ≤ −1.5 for more than one test OR (2) z scores ≤ −2.0 for just one test. The reliable change index (RCI) was used to determine the frequency of change in cognitive function from one assessment to the next.	MMPI	2
Wefel, 2010 *USA*	Longitudinal (Single Site)	Breast	T1: pre CT (n=42) T2: 2.9 months after T1(n=37) T3: 7 months after T1 (n=33) T4: 13.1 months after T1 (n=28)	Same as Wefel, 2004	BDI STAI	2

Study & Country	Design	Sample Characteristics	Time of assessments and questionnaires	Operational Definition of Cognitive Impairment (CI)	Other Measures	Overall quality rating score**
Whitney, 2007 USA	Longitudinal	Non-small cell lung cancer Stage 3A or 3B.	T1: pre CT T2: 1 month post CT T3: 7 months post CT (n=9)	Raw scores converted into z scores (mean=0, SD=1) using published normative data adjusted for age, education and gender. CI: (1) z scores ≤ −1.5 for more than one test OR (2) z scores ≤ −2.0 for just one test. RCI was used to determine the frequency of change in cognitive function from one assessment to the next.	Premorbid VIQ PHQ BFI Computed tomography imaging of the head	2

Key: CI: Cognitive impairment; CRC: Colorectal Cancer; CT: chemotherapy; S.D: standard deviation; ANOVA: Analysis of variance.

BF13: Item 3 of Brief Fatigue Inventory; HADS: Hospital and Depression Scale; CES-D: Centre for Epidemiological Studies Depression Inventory; FACT – ntx: neuropathy scale; PAF: patients perceptions of cognition; ADLs: activities of daily living; IADLs instrumental activities of daily living; KPS: Karnofsky performance status; Comorbid medical conditions: Charlson Comorbidity Index; GDS: Geriatric Depression Scale; FEDA: self-perceived cognitive deficits; MFI-20: Multidimensional fatigue inventory; WRAT-3: The wide range achievement test-3; POMS-SF: Profile of Mood States –Short Form; CIQ: Community Integration Questionnaire; BDI-II: Becks Depression Inventory-Second Edition; HSCL-25: The Hopkins symptom checklist – 25; DART: Dutch Adult Reading Test; GHQ12: General Health Questionnaire 12; NART-2: National Adult Reading Test version 2; FACT F: Functional Assessment of Chronic Illness Therapy - Fatigue subscale; MMPI: Minnesota Multiphasic Personality Inventory; STAI: State Trait Anxiety Inventory; Premorbid VIQ: American version of the Nelson Adult Reading Test; PHQ: Patient Health Questionnaire.

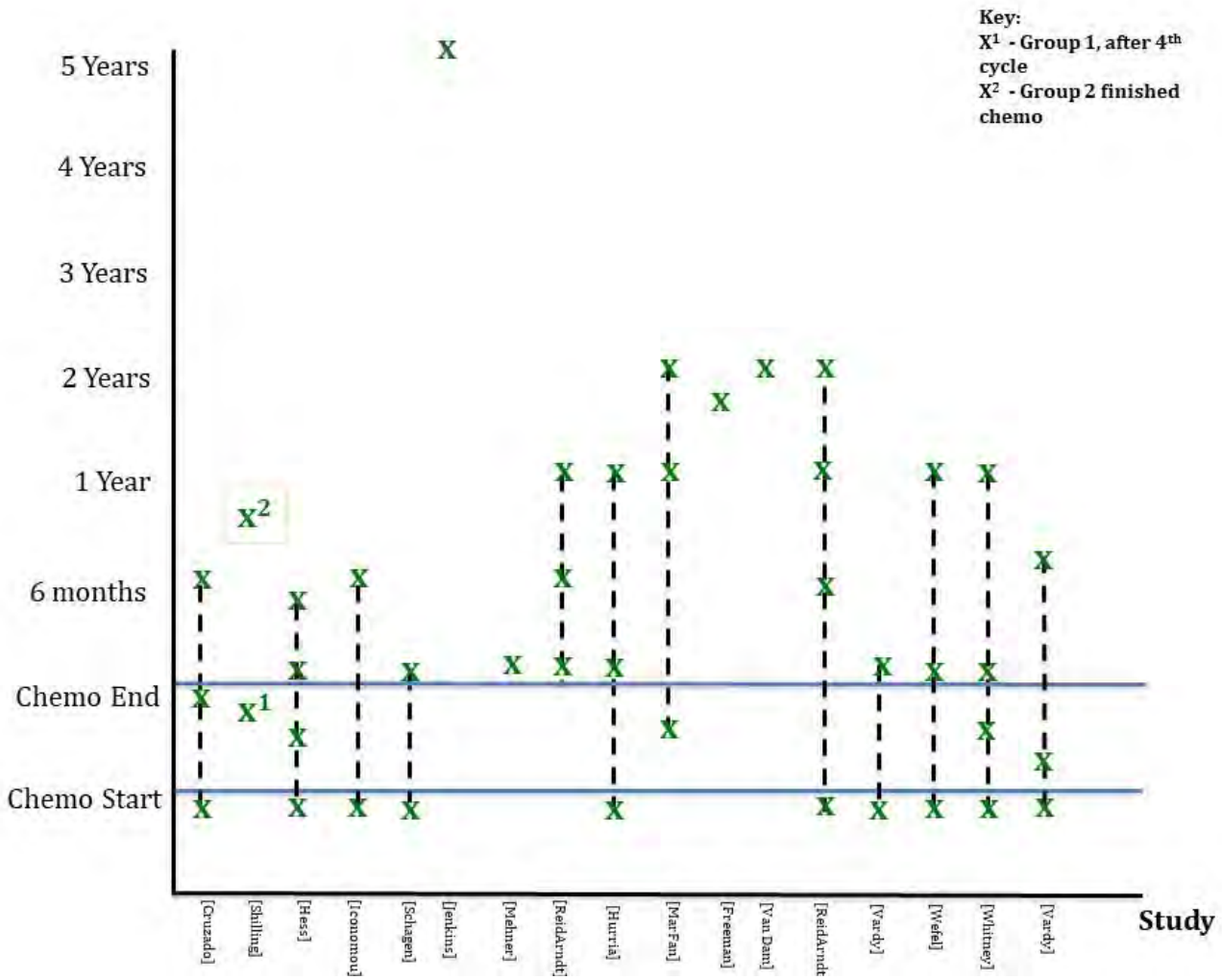
** The overall rating scores ranged from 0 (low) to 4 (high) and were obtained by adding together the scores for each of internal validity and external validity. The higher the score the less bias there is in the study and the more external validity. Each of internal validity and external validity had a possible score of 0, 1 or 2 (0 – no criteria fulfilled; 1 some of the criteria had been fulfilled; 2 all or most of the criteria have been fulfilled).

5.4.3.2 Designs used in the included studies

As can be seen in Tables 5.2 and 5.3 the included studies used a wide range of designs. This variation may also have contributed to the divergent set of results seen in the 17 studies particularly if they were examining any potential relationships at different points in time and in different patient groups.

Eleven studies (65%) (Hurria, 2006; Mehnert, 2007; Reid-Arndt 2009; Reid-Arndt 2010; Shilling 2005; Jenkins, 2006; Tchen/Mar Fan 2005; Vearncombe, 2009; Wefel 2004; Wefel 2010) were exclusively women with breast cancer; one was a mixed solid tumour patient group (Iconomou, 2004), two examined CRC patients (Cruzado, 2014) and one examined lung cancer patients (Whitney, 2008). In addition to variations in study samples, there were many differences in the designs and measurement points across the studies (Figure 5.3) that make it difficult to draw overall conclusions from this body of work. Twelve studies (Cruzado et al, 2014; Hurria et al 2006; Iconomou et al, 2004; Reid-Arndt et al , 2010; Shilling et al, 2005; Jenkins et al, 2006; Mar Fan et al, 2005; Vearncombe et al, 2009; Wefel et al 2004; Wefel et al 2010; Whitney et al, 2008) were longitudinal, with ten (59%) having baseline assessments before chemotherapy treatment. Four of the longitudinal studies with pre-treatment assessments (Cruzado et al, 2014; Hess et al, 2015; Vardy et al, 2015; Wefel et al, 2010) also examined cognition during chemotherapy treatment. Follow-up periods varied across the studies, ranging from end of treatment (Iconomou et al, 2004) to 2 years post treatment (Mar Fan, 2005). One longitudinal study assessed cognition at three time points but not until after treatment had finished (Reid-Arndt et al, 2010).

Figure 5.3. Pictorial representation of measurement time points in the studies included in the systematic review



Eight studies (Freeman et al, 2002; Jenkins et al, 2006; Mar Fan et al 2005; Mehnert et al, 2007; Schagen et al, 1999; van Dam, 1998; Vardy et al, 2015; Vearncombe et al, 2009) included more than one group. Three compared groups with different types of treatment or stages of disease (e.g. standard dose chemotherapy compared to high dose (Mehnert et al, 2007; van Dam et al, 1998; Vearncombe et al, 2009). Two studies (Mehnert et al, 2007; Vardy et al, 2015) compared the different chemotherapy groups to an early stage cancer group who did not need chemotherapy; three studies compared

chemotherapy patients to healthy controls (Shilling et al, 2005/Jenkins et al, 2006; Tchen et al, 2003/Mar Fan et al 2005; Vardy et al, 2015). The healthy control groups were peer nominated (i.e. friends and family of the patient participants'). The healthy controls were a useful comparator as they were matched for age and socioeconomic status, in all three studies. However, it is important to note that the cognitive evaluation in the patient group may be confounded by the stress associated with a cancer diagnosis and consequent surgery (Vardy et al, 2007). This raises the questions as to whether a healthy control group is the ideal comparator in this context. In an approach that attempted to cover this issue well Jenkins et al (2006) included both a non-chemotherapy group (who had had surgery and had started endocrine therapy) as well as healthy controls (made up of friends and family of the patient participants, who may have also been stressed by the fact that a family member had received a cancer diagnosis for which they were being treated), which is considered to be ideal (Wefel et al, 2011).

Eight studies recruited participants from one hospital site (Cruzado et al, 2014; Freeman et al, 2002; Hurria et al, 2006; Iconomou, 2004; Schagen et al, 1999; van Dam et al, 1998; Wefel et al 2004; Wefel et al 2010). The remaining nine studies recruited from two or more sites making these results potentially more generalisable. In one case, however, (Whitney et al, 2008) which was a multi-site study had a small sample size of 14. This could be because it was a lung cancer sample, with quite an advanced disease stage. Of the eight single site studies, four had sample sizes of fewer than 50 participants despite long recruitment periods. For example, Hurria et al, (2006) only recruited 28 breast cancer participants over 2 years and Freeman et al (2002) was a pilot study with only 17 participants. In contrast, two single site studies (Cruzado et al

(2014) and Iconomou et al (2004)) recruited in excess of 80 participants each (81 and 102 respectively), but both had high attrition rates (33% and 21% respectively) and neither was sufficiently powered. Overall, 59% of studies (Cruzado et al, van Dam et al, 1998; Reid-Arndt et al 2009; Reid-Arndt et al, 2010; Wefel et al, 2010; Freeman et al, 2002; Mehnert et al, 2007; 48, Iconomou et al 2004; Vearncombe et al, 2009) were underpowered and/or did not provide sample size justifications.

5.4.3.3 Defining OCI

The calculation and operational definition of what constitutes cognitive impairment varied widely across studies (see Table 5.1). More than half of the studies (n = 10) converted the raw neuropsychological scores into standardised z-scores (mean = 0, SD = 1) using published normative data adjusted for age, education, and gender. However, the number of tests and the extent to which these z-scores had to deviate to constitute cognitive impairment varied across the studies. Definitions of cognitive impairment included z-scores of ≤ −1.4, −1.5, and −2 standard deviations (s.d) below the mean in between one and four tests. For example, Hurria et al (2006) classified participants as having cognitive impairment if they scored 2 or more s.d's below published norms on two or more discrete tests, whereas Reid-Arndt and colleagues (2010) classified participants as having 'subtle' cognitive impairment if they scored 1 s.d below normative data mean, while more 'severe' impairment was defined as 1.5 - 2 plus s.d's below the mean. (See Table 5.2 for the full list of operational definitions used.) The extent of OCI has been shown to be dependent on the method of analysis (Shilling et al, 2006). As a consequence of the differences across the included studies, it is not possible to provide a simple estimate of the prevalence of OCI in patients treated with adjuvant chemotherapy (See Chapter 3 for a fuller discussion). Nevertheless, ignoring these

methodological differences, all but two of the included studies in this review (Freeman et al, 2002; Iconomou et al, 2004) reported statistically significant OCI in some patients undergoing adjuvant chemotherapy treatment.

5.4.3.4 Affected cognitive domains and assessment of OCI in the included studies

The cognitive domains most affected varied widely across the studies included in this review. Four studies (Cruzado et al, 2014; Shilling et al, 2005 and Vearncombe et al, 2007; Vardy et al, 2015) reported verbal memory as being most affected and 6 studies (Wefel et al, 2004; Vardy et al, 2015; Reid-Arndt et al 2009; Reid-Arndt et al, 2010; Wefel et al, 2010; Schagen et al, 1999) found that the most common domains showing decline were processing speed and executive function. Two studies (Freeman et al, 2002; Iconomou et al, 2004) reported that objective cognitive performance remained constant throughout treatment.

It is not surprising that cognitive decline was found across so many different domains in the included studies. As shown in Table 5.3, multiple tools were used, and many different cognitive domains as reported by the authors were measured. Not only did the studies assess different areas of cognition but they also used different tests to assess the same domains. Overall, there were more than 54 different measures used across 17 studies to tap a variety of cognitive domains. Most of the studies (n=15) used a battery of neuropsychological tests assessing a range of domains. The different psychometric qualities of each of the measures may have influenced the conclusions drawn regarding the cognitive domains most affected by chemotherapy treatment. For example, no impairment was reported by Iconomou and colleagues (2004) who used the Mini–

Mental State Examination (MMSE), which has been criticised for not being sensitive enough to detect subtle cognitive changes (Rugo & Ahles, 2003; Brown et al, 2003).

This problem of diversity of assessments used has been recognised by the ICCTF as an issue that needs consideration in future research (Wefel et al, 2011). In an attempt to bring some homogeneity to all studies, the ICCTF recommended that in future trials 3 core neuropsychological assessments (the Hopkins Verbal Learning Test–Revised, Trail Making Test, and the Controlled Oral Word Association of the Multilingual Aphasia Examination)(Benedict, 1998; Reitan, 1992; Benton & Hamsher, 1989; Mitrushina et al, 2005; Strauss, Sherman & Spreen, 2006) be used to measure learning and memory, processing speed, and executive function, supplemented with additional tests of working memory capacity, on the basis of the researchers own preferences (Wefel et al, 2011). This was justified by the assertion that research has shown that the domains assessed by these tests are most affected by chemotherapy treatment (Wefel et al, 2011). However, no study included in this review that was undertaken post- ICCTF's recommendations used the entire core battery to assess neuropsychological impairment although three earlier studies did (Freeman et al, 2002; Hurria et al, 2006; Wefel et al, 2010).

5.4.3.5 Assessing HRQoL

As mentioned in Section 5.2, HRQoL was assessed at the same time as cognition in all studies included in this review. As with the neuropsychological assessments, some studies analysed only global HRQoL scores (Mar Fan et al, 2005; Hess et al, 2015; Wefel et al, 2010; Iconomou et al, 2004) whereas others extended the analysis to the subscales of the HRQoL measure (Cruzado et al, 2014; van Dam et al, 1998; Reid-Arndt et al, 2009;

Reid-Arndt et al, 2010; Whitney et al, 2007; Schagen et al, 1999; Vearncombe et al, 2009). As can be seen in Table 5.3, five studies assessed HRQoL using the EORTC–QLQ C30; the remaining studies used one or more of the questionnaires from the FACT battery. Therefore, as with the cognitive domains measured, a direct comparison of results between studies using different scales is not possible (Kemmler et al, 1999).

5.4.3.6 The relationship between OCI and HRQoL

Only three (Mehnert et al, 2007; Vearncombe et al, 2009; Reid-Arndt et al, 2010) out of the 17 included studies found a significant relationship between OCI and HRQoL. Whilst all three studies examined the inter-relationships between various domains of HRQoL and specific impaired cognitive domains, Mehnert (2007) and Reid-Arndt (2010) specifically examined the presence of post treatment cognitive deficits whereas Vearncombe (2009) examined deficits over the course of treatment.

The significant relationships were different in all three studies. For example, Mehnert et al, 2007 found that objective measures of verbal memory were associated with poorer HRQoL (as measured by EROTC QLQ C30) five years after treatment. Reid-Arndt et al, (2010) reported that poorer functional wellbeing (as measured by FACT B) was significantly associated with verbal fluency at twelve months post chemotherapy treatment (even though only a very small proportion of study participants demonstrated any OCI). The third study, Vearncombe et al, (2009) found that lower functional wellbeing pre-chemotherapy treatment as measured by FACT B significantly contributed to changes over the course of treatment in the cognitive domains of attention and executive function rather than declines in well-being affecting cognitive functioning shortly after finishing chemotherapy treatment. By examining specific

domains of each of HRQoL and cognition, these three studies were arguably able to identify the more subtle effects of any relationships although none of them was without their limitations as detailed in Section 5.3.6 below.

Mehnert and colleagues (2007) examined cognitive functioning in three different treatment groups (high dose chemotherapy; standard dose chemotherapy and non-chemotherapy group) approximately five years after chemotherapy treatment (see Table 5.3). They reported a range of significant relationships between cognition and HRQoL across all of the groups, more specifically:

i) in the standard dose group: impairment in working memory was significantly correlated with lower levels in physical functioning (PF) and emotional functioning (EF) group as measured by the EROTC-QLQ C30; impairment in simple reaction time was associated with lower social functioning (SF) and impairment in global attention was significantly correlated with lower levels of EF;

ii) in the high dose group: impairment in global executive functions was correlated with PF and SF; impairment in simple reaction time was associated with lower role functioning (RF) and impairment in selective attention was significantly correlated with lower levels of EF and SF;

iii) in the non-chemotherapy group: impairment in simple reaction time and verbal learning was correlated with lower levels in RF and impaired verbal recognition with lower levels in PF.

None of the remaining studies included in this review reported any correlation between overall OCI and overall HRQoL or between any of the specific domains. However, Hurria

and colleagues (2006) did observe in the discussion section of their paper that those participants with the most dysfunction who improved also showed an improvement in overall global QoL. Unfortunately, no statistics or specific details were provided to back up this assertion.

Table 5.3: Summary of measures used in the included studies, cognitive domains as defined by the authors, and the relationship between OCI and HRQoL

First Author & year	OCI	HRQoL Measure	OCI/ HRQoL Signif correl-ation?	Cognitive Domain Measured									
				Processing speed	Memory			Attention		Learning	Executive Function	Self-regulation & planning	Spatial Function	Language / Verbal Function
					Verbal	Visual	Working	Attention	Visual motor/ psychomotor function	Verbal				
Cruzado 2014	✓	EORTC QLQ C30	X		Subtest of Barce - lona Test – Imm Mem, Imm Mem-Q, Delayed Mem, Delayed Mem-Q			TMT A*	WAIS-R digit symbol		Stroop C-W, colour & word; TMT B*			
Freeman 2002	X	FACT B	X	TMT A* & B* PASAT Stroop Word, Colour, C-W COWAT	TMT B* Category Test HVLT-R* WMS III- Faces I & II RBANS			TMT A* &B* Category Test HVLT-R* Faces I & II PASAT RBANS Stroop Word, Colour, C-W COWAT	TMT A* &B* Grooved Pegboard RBANS Sensory Perceptual Exam		TMT B* Category Test PASAT Stroop C-W			HVLT-R* RBANS COWAT
Hess 2015	✓	FACT O	X	CRT				CRT	CRT					
Hurria 2006	✓	FACT B	X		HVLT –R*	RCFT		TMT A*	WAIS-III digit symbol, TMT A & B		TMT B*, Stroop colour & word, COWAT*		WAIS-III Block Design, RCFT	WRAT – 3 Reading subtest, Boston naming test, COWAT*
Iconomou 2004	X	EORTC QLQ C30	X					MMSE						MMSE

First Author & year	OCI	HRQoL Measure	OCI/ HRQoL Signif correl-ation?	Cognitive Domain Measured										
				Processing speed	Memory			Attention		Learning	Executive Function	Self-regulation & planning	Spatial Function	Language / Verbal Function
					Verbal	Visual	Working	Attention	Visual motor/ psychomotor function	Verbal				
Mehnert 2007	✓	EORTC QLQ C30	✓		VLMT – Form A	ROCFT	WMS-R	TMT A & B*, TAP, Test D2			RWT, LPS-3, LPS -4			
Reid-Arndt 2009	✓	FACT B	X		WMS-III Logical Memory I & II, Visual Reproduction I & II, Rey AVLT Delayed Recall				WAIS-III digit span, TMT A*		TMT B*, Stroop			COWAT*, Category Fluency
Reid-Arndt 2010	✓	FACT B & 1 single item question ('in general, how satisfied are you with your overall quality of life')	✓	TMT A & B*	WMS-III Logical Memory I & II, Rey AVLT Delayed Recall & Trials 1-5						Stroop			COWAT*, Category Fluency
Schagen 1999	✓	EORTC QLQ C30	X	FVRT; FBCT; FVST	RAVLT	RCFT WMS-R Visual Reproduction – imm, delayed & recall		D2 WAIS- digit symbol WAIS- digit span	FFTT TMT A*		TMT B*, Stroop			Word fluency subtest from S.A.N test
Shilling/ Jenkins 2005/2006	✓	FACT B & ES (patients only)	X	Letter cancellation task	WMS logical memory, imm & delayed, RAVLT recall 1-7	RCFT	WMS III - spatial span, letter/ number sequencing				Stroop			

First Author & year	OCI	HRQoL Measure	OCI/ HRQoL Signif correl-ation?	Cognitive Domain Measured										
				Processing speed	Memory			Attention		Learning	Executive Function	Self-regulation & planning	Spatial Function	Language / Verbal Function
					Verbal	Visual	Working	Attention	Visual motor/ psychomotor function	Verbal				
							& digit span							
Tchen/ Mar Fan 2003/2005	✓	FACT-G Version 4 FACT ES	X	HSCS				HSCS, CPT	HSCS, TMT A &B*			HSCS	HSCS	HSCS
van Dam 1998	✓	EORTC QLQ C30	X	FVRT; FBCT; FVST	REY15 words	Complex figure		D2 test WAIS- digit symbol WAIS- digit span	TMT A* FFTT		Stroop TMT B*		RCFT (copy)	Word Fluency subtest from the DAST
Vardy/ Vardy 2014/2015	✓	FACT G	X	WAIS III Digit Symbol TMT A & B*	HVLT-R* CANTAB - VRM	BVMT-R	CANTAB - SWM	CANTAB - RVP	CANTAB – MOT & RVP & RTI	CANTAB - VRM				
Vearncombe 2009	✓	FACT G	✓	SDMT	AVLT	WMS-III Visual Reproduction – imm, delayed & recognition	WAIS-III Backward digit span	TEA Visual Elevator & Telephone search	Purdue Pegboard		WAIS-III Matrix Reasoning Stroop, DKEFS Card sorting, COWAT*			
Wefel 2004	✓	FACT B	X	WAIS-R Digit Symbol, TMT A*	VSRT delayed recall, NVSRT delayed recall			WAIS-R Digit Span & Arithmetic	Grooved Pegboard	VSRT Long term storage, NVSRT Long term storage	TMT B*, Booklet Category Test, WAIS-R Similarities		WAIS-R Block Design	

First Author & year	OCI	HRQoL Measure	OCI/ HRQoL Signif correl-ation?	Cognitive Domain Measured									
				Processing speed	Memory			Attention		Learning	Executive Function	Self-regulation & planning	Spatial Function	Language / Verbal Function
					Verbal	Visual	Working	Attention	Visual motor/ psychomotor function	Verbal				
Wefel 2010	✓	FACT B	X	WAIS-R Digit Symbol, TMT A*	HVLT*			WAIS-R Digit Span		HVLT*	TMT B*, MAE COWA*			
Whitney 2008	✓	FACT L	X		HVLT—R*, RCFT			Gordon CPT	WAIS-block design		COWA* WCST-64			

Key: * = this is one of the ICCTF's recommended core neurological assessments. EORTC QLQ C30: European Organization for Research and Treatment of Cancer Quality of Life questionnaire; FACT O: For patients with Ovarian cancer; FACT G: Functional Assessment of Cancer Therapy – General; FACT B: For patients with Breast cancer; FACT ES: For patients with Endocrine Symptoms; FACT L: For patients with Lung cancer; Imm-Mem: Immediate memory; Imm-Mem-Q: Immediate memory-questions; Delayed-Mem: Delayed memory; Delayed-Mem-Q: Delayed memory-questions; TMT A & B: Trial Making Test Part A & Part B; WAIS-R Digit Symbol: Wechsler Adult Intelligence Scale Revised Digit Symbol; MMSE: Mini- Mental State Examination; CRT: Headminder Clinical Research Tool; WAIS-R Digit Span: Wechsler Adult Intelligence Scale Revised Digit Span; Stroop C-W: Stroop interference trial;

HVLT-R: Hopkins Verbal Learning Test – Revised; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; Category Test; PASAT: Paced Auditory Serial-Addition Task; COWAT/COWA: Controlled Oral Word Association Test; Grooved Pegboard; Sensory Perceptual Exam; RCFT: Rey-Osterrieth Complex Figure test; WAIS-III: Wechsler Adult Intelligence Scale –III; WRAT-3: The Wide Range Achievement Test, Third Edition; MMSE: Mini- Mental State Examination; VLMT: Auditory Verbal Learning Test – German modified version;ROCFT: Rey-Osterrieth complex figure test; TAP: Test battery for attentional performance; Test D2: D2 cancellation test;RWT: Regensburg Word Fluency Test; LPS: achievement measure test; WMS-III Logical Memory: Wechsler Memory Scale – third edition Logical Memory; WMS-III Visual Reproduction: Wechsler Memory Scale – third edition Visual Reproduction; Faces I & II: Facial Recognition Tests; RAVLT/Rey AVLT: Rey Auditory Verbal Learning Test; FFTT: Fepsy finger-tapping task; FVRT: Fepsy visual reaction test; FBCT: Fey binary choice test; FVST: Fepsy visual searching test; S.A.N Test: Letter cancellation test; HSCS: High Sensitivity Cognitive Screen; CPT: Continuous Performance Test; DAST: Dutch Aphasia Society Test; CANTAB Battery: RVP: Rapid Visual Information Processing; RTI: Reaction Time; VRM: Verbal Recognition Memory; SWM: Spatial Working Memory; MOT: Motor Screening; BVMT-R: Brief Visuospatial Memory Test Revised; SDMT: Symbol Digit Modalities Test; TEA: Test of Everyday Attention; Elevator & Telephone search; Perdue Pegboard; DKEFS: Delis-Kaplan Executive Function Scale; NVSRT: Nonverbal Selective Reminding Test; VSRT: Verbal Selective Reminding Test; Grooved Pegboard MAE COWA: Multilingual Aphasia Examination controlled oral word association; WCST-64: Wisonsin Card Sorting Test Conceptual Level Responses; Gordon CPT: Gordon Continuous Performance Test.

One of the reasons for a lack of significant relationships in the studies included in this review could have been that some of them used a global cognitive impairment score and/or a global HRQoL score (e.g. van Dam et al, 1998), thereby masking any more subtle relationships or associations that may have existed. For example, Tchen (2003)/Mar Fan et al (2005) and van Dam et al, (1998) calculated cognitive impairment by combining performance on cognitive tasks into one global impairment score. Tchen (2003)/Mar Fan et al (2005) reported that the overall classification of cognitive impairment by the HSCS was not correlated with HRQoL. Similarly, Iconomou et al (2004) reported that there was no significant relationship at baseline or after treatment between objective cognitive performance as measured by the MMSE and any of the QLQ-C30 subscales. In addition, Whitney et al (2010) did examine possible relationships between neuropsychological test results and HRQoL variables but did not find any statistically significant correlations at any of the three assessed time points.

5.4.3.7 Methodological quality of included studies

As mentioned above, the included studies used a wide range of designs and were of varying quality. Of the studies with the most robust methodological designs (Hess et al, 2015; van Dam et al, 1998, Vearncombe et al, 2009, Jenkins et al, 2006, Mar Fan et al, 2005; Vardy et al, 2015; Wefel et al, 2010), six were longitudinal. Five of the six had the largest sample sizes (Mar Fan et al, 2005; Hess et al, 2015, Vardy et al, 2015; Jenkins et al, 2006; Vearncombe et al, 2009), a total of 206, 231, 434, 177 and 159 participants respectively with one or more comparison group as outlined above.

Six studies were graded as having high internal validity (i.e. unbiased) (Jenkins et al, 2006; Mar Fan et al, 2003; Vearncombe et al, 2009; Reid-Arndt et al, 2010; Schagen et al,

1999; Vardy et al, 2015); ten as moderate and one as poor (Iconomou et al, 2004). Only three studies were graded as having high external validity (van Dam et al, 1998; Vardy et al, 2015; Vearncombe et al, 2009); thirteen as moderate and one as having poor external validity (Iconomou et al, 2004).

Methodological shortcomings mainly concerned three studies (Hurria et al, 2006; Jenkins et al, 2006; Wefel et al, 2010) that were exploratory in nature with no focussed objective. Seven studies (Cruzado et al, 2009; Freeman et al, 2002; Hess et al, 2015; Hurria et al, 2006; Reid Arndt et al, 2009; Reid Arndt et al, 2010; Vardy et al, 2015) failed to report the acceptance rate of invited participants, and eight (60%) of the longitudinal studies (Cruzado et al, 2009; Hess et al, 2015; Mar Fan et al, 2005; Vardy et al, 2015; Reid Arndt et al, 2010, Wefel et al, 2010; Whitney et al, 2008; Iconomou et al, 2004) had attrition rates exceeding 20%.

Of the three studies that reported a relationship between OCI and HRQoL one was cross-sectional (Mehnert et al, 2007) and two longitudinal in design (Reid-Arndt et al, 2010; Vearncombe et al, 2009). As mentioned above, the focus of each was slightly different. For example, Mehnert and colleagues (2007) examined neuropsychological impairment and HRQoL in high-risk breast cancer survivors 5 years after treatment. Whereas Reid-Arndt and colleagues (2010) examined the relationship 1 month after treatment and followed up the participants for another 12 months and Vearncombe et al (2009) investigated whether HRQoL significantly contributed to cognitive impairment reported after chemotherapy, examining cognition pre-treatment and 4 weeks post treatment.

In interpreting the quality of the studies that found a statistically significant relationship between OCI and HRQoL, Mehnert's cross-sectional study had a low quality rating (1), and therefore the results should be treated with caution. Both longitudinal studies (Vearncombe et al, 2009 and Reid-Arndt et al, 2010) received a higher overall quality score (3 and 4 respectively) suggesting that the results are more robust. All three studies examined OCI post treatment, although Vearncombe et al (2009) also assessed cognition prior to treatment.

5.5 Conclusions

This review set out to examine studies that explored the possibility of a direct relationship between the objectively measured cognitive effects related to chemotherapy treatment in cancer patients with solid tumours and their HRQoL. A critical examination of all identified studies exploring this relationship has shown that OCI is subtle and only occurs in a subset of cancer patients with solid tumours. The review established that there is limited evidence to suggest that such OCI following adjuvant chemotherapy is associated with poorer HRQoL.

Whilst a few studies showed significant associations between OCI and aspects of HRQoL (Reid-Arndt et al, 2010; Vearncombe et al, 2009) after chemotherapy treatment the majority found no such association. However, there are a number of reasons why caution is required when considering the number of OCI studies that failed to find any such relationship. One reason, for example is the fact that most of the studies included in this review did not set out to explore this relationship; rather it typically features as an exploratory post-hoc analysis. Consequently, the design and conduct of the study is not focussed on addressing this question (e.g. Hurria et al, 2006).

In addition, the tests used to assess objective cognition and the definition of impaired cognition were not performed or used consistently across studies, creating significant difficulties in making comparisons across studies. With regard to measuring objective cognitive decline, studies assessed a large number of cognitive domains and used an even larger array of tests. The criteria for the classification of OCI also varied widely. This is not an uncommon problem in the assessment of objective cognitive change. However, in an attempt to bring some uniformity to future studies there are now specific recommendations for defining OCI and the cognitive domains to be assessed along with recommended tools to measure any deficits (Wefel et al, 2011). It is hoped that there will be more homogeneity of neuropsychological assessments between studies in the future but this will take some time to be adopted. Going forward, consistent use of the recommended tests and definitions should provide a clearer picture of the type and extent of deficits suffered by different cancer patients undergoing chemotherapy treatment.

A similar issue also relates to the definition and questionnaires used to assess HRQoL. There are many instruments available for assessing HRQoL, from generic (measuring multiple concepts relevant to a wide range of patients) to specific (a disease, population or health dimension) (Davies, 2009). All of the studies in this review used one of two instruments - the EROTC – QLQ C30 or the FACT battery. As shown in the results it is hard to draw meaningful comparisons between the results obtained by these two measures as the EORTC system offers multiple specific scales and symptom scores, whereas the FACT system produces summary scales.

It should also be noted that although almost every study in this review found some type of cognitive impairment in a small subset of participants, this often improved for some patients after treatment (Hurria et al, 2006; Mar Fan et al, 2005; Wefel et al, 2004; Whitney et al, 2008). It is common with repeated assessments of neuropsychological performance using tests of the same design that individuals show some improvement even when alternate forms of the same test are used. In other words it is possible that improvements in neuropsychological test scores could have been a reflection of the effects of repeated exposure to the tests rather than clinically significant gains in cognitive function (Reid-Arndt, 2010). This emphasizes the need for a control or comparison group so as to be able to examine and compare the practice effects when repeatedly using these tests over time (Wefel, 2011). For example, Shilling et al, 2005 who used the reliable change index with corrections for observed practice effects on each measure and had a control group were able to examine this. They found that the chemotherapy participants that were classified as impaired on the basis of showing reliable cognitive decline on two or more measures were 2.25 times more likely than controls to be classified as showing cognitive impairment.

Finally, despite these methodological limitations, the studies were sufficiently robust to have established if a major impact of chemotherapy on HRQoL had occurred. A point further highlighted by Whitney et al (2008).

The secondary aim of this review was to examine which affected cognitive domains were related to which particular aspects of HRQoL. Here there was insufficient data to answer the question, as only three studies reported relationships between specific domains (Mehnert et al, 2007; Reid Arndt et al, 2010; Vearncombe et al, 2009). Although other studies may have examined this issue it is unclear whether any of them

examined it in any detail. Even amongst the three that did find specific relationships it was not feasible to draw any meaningful comparisons between them as they used different HRQoL measures. As shown in the results above, Mehnert (2007) used the EROTC QLQ-C30, which has more QoL scores than the FACT B, that was used by Reid-Arndt (2010) and Vearncombe (2009). It is therefore arguable that Mehnert (2007) was very likely to find more associations, although multiple comparisons could have led to an increase in Type I errors. On the other hand by using summary scores (as do the FACT measures) Reid-Arndt (2010) and Vearncombe (2009) could have missed the more subtle relationships (although it is worth noting here that Vearncombe et al, 2009 was also rated the best quality study). For example by combining scores into summary scores, it is possible to mask the fact that the small more individual HRQoL domains (as measured by EROTC QLQ-C30 such as pain, nausea/vomiting etc) may have significant associations with individual cognitive domains.

Even though Mehnert et al (2007) found that declines in specific cognitive domains (such as working memory, simple reaction time and global attention) were associated with poorer physical, emotional, and social functioning, this study had significant methodological limitations and as a result these findings can be largely discounted. They reported that patients who had received standard dose chemotherapy consistently had the lowest HRQoL.

5.6 Strengths and limitations of this review

This review is not without its limitations. For example all studies irrespective of quality were included because it is an under researched area. Most were of moderate quality at best and not necessarily methodologically robust enough to answer the review

question. Although small sample sizes have always been a problem for this area of research, almost every study (other than Jenkins et al, 2006; Mar Fan et al, 2005; and Vearncombe et al, 2009) was underpowered. As well as small sample sizes, studies examining CRCI also suffer from high rates of attrition (for example anywhere between 12% (Vearncombe, 2009) to 36% (Whitney, 2008)) as this can induce negative thoughts and feelings about possible relapse of disease or even death (Hodgson et al, 2013).

5.7 Update post June 2016

Whilst there has been an explosion of CRCI studies that have been published between June 2016 and August 2018 a scoping of the literature revealed that there were no more studies that fully examined the relationship between OCI and HRQoL.

5.8 Publications

This review has been published online by the journal Psycho-oncology on 23 November 2016. The published manuscript for this study is presented in Appendix F.

1. Dwek, M. R., Rixon, L., Simon, A., Hurt, C., & Newman, S. (2016). Is there a relationship between objectively measured cognitive changes in patients with solid tumours undergoing chemotherapy treatment and their health-related quality of life outcomes? A Systematic Review. Psycho-oncology, 24, 344-345.
2. Poster Presentation of Review at the 2015 World Congress of Psycho-Oncology in August 2015 Washington DC. (Please refer to Appendix G)

Chapter 6: Summary of the literature, rationale and aims of the present thesis

6.1 Summary of the literature

Chapter 1 highlighted the increase in survival rates of individuals diagnosed with CRC, its treatment, and the long list of possible side effects including cognitive impairment. Chapter 2 discussed cognition (objective and subjective), cognitive function in cancer patients with solid tumours, and highlighted the challenges involved in measuring cognition and cognitive impairment.

As discussed in Chapters 3 and 4, objective and subjective impairments in cognitive functioning have mostly been reported in a subset of patients with breast cancer, who have completed chemotherapy treatment. Impairments are reported to occur across a range of cognitive domains including attention, executive function and motor function when compared to normative data, disease specific groups and/or healthy control groups. Despite a plethora of research, there remains a lack of clarity around the extent, course, nature and duration of any cognitive impairment (objective and/or subjective). The extent to which CRCI extends to other solid tumours such as CRC also remains unclear.

The impact of CRCI on HRQoL in patients with solid tumour cancers has not been adequately explored as discussed in Chapter 5. The results of a systematic review of the literature (described in Chapter 5) showed that only a limited number of studies have examined the relationship between OCI and HRQoL. To address this gap in the literature, this thesis explored cognitive functioning (objective and subjective) in the CRC population and its relationship with HRQoL.

6.2 Methodological limitations of the existing literature

There were several methodological limitations in the studies reviewed to date. Some of the significant methodological issues that arose from the review of the literature are as follows:

1. Most research studies have explored cognitive function in patients with cancer after systemic treatment has been completed (Vardy, Wefel, Ahles, Tannock and Schagen, 2007).
2. Few studies have prospectively measured patients' cognitive function prior to the commencement of chemotherapy treatment and hence these studies do not have any baseline.
3. Few studies measured cognitive function over the course of chemotherapy treatment and beyond. This would have made it possible to identify changes occurring during and after treatment so as to establish whether any deficits detected persist after treatment.
4. Studies have often lacked a comparison/control group (e.g. patients diagnosed with the same cancer but who do not have chemotherapy treatment) against which to compare cognitive function scores. Most reviewed studies also had small sample sizes and/or were not informed by power calculations.
5. Most cognitive research to date has focussed on female patients with breast cancer. (There have only been a small number of CRC studies that examined CRCI.) This has precluded any exploration of gender differences in relation to cognitive decline.

6.3 Rationale for the present study

Further, longitudinal and adequately powered studies are required to examine CRCI in patients with solid tumours other than breast, which (as mentioned previously) make up the majority of studies in the research to date.

This study uses a mixed method approach across multiple hospital sites to address an area of research that has previously received little attention. Given the recent increased incidences of cancer, improved rates of survival (particularly CRC) and the increasing use of chemotherapy drugs to treat different types of cancer (Wefel, Vardy, Ahles and Schagen, 2011), the effect of CRCI would benefit from further research and investigation. The present study is designed to comprehensively investigate cognitive functioning in patients with CRC prior to and over the course of systemic treatment. Few studies have investigated and compared cognitive impairment in CRC across different domains of cognitive functioning and there are no studies to date (of which the researcher is aware) that have used a mixed methods approach.

This thesis utilised a set of core neuropsychological test measures including those recommended by the ICCTF (Wefel et al, 2011) in an effort to assess the extent to which cognitive impairment is a phenomenon associated with chemotherapy treatment. Importantly this study examined patients who had all been diagnosed with the same cancer (i.e. CRC), who all required and underwent curative surgery but only half of whom went on to have adjuvant chemotherapy treatment; allowing for a comparison between those who received adjuvant chemotherapy to those who did not on all measures. To examine the potential factors that may influence cognitive outcomes in

this patient group, a wide range of clinical, psychosocial and demographic variables were included in the study.

Impaired cognitive function (both objective and subjective) could affect patients' HRQoL and potentially prevent a return to work and/or a normal social life (Wefel et al, 2011). The relationship between the type and extent of impaired cognitive function and HRQoL was therefore examined. This work has the potential to contribute towards the development of specific supportive and rehabilitative interventions to improve the HRQoL for patients that may be impacted.

6.4 The current thesis

This thesis examines CRC, a solid tumour cancer with a high prevalence that affects both men and women almost equally. Patients with CRC have a relatively high survival rate, which is beneficial for a longitudinal study exploring the nature and trajectory of CRCI.

6.4.1 Sample size

Recruitment to each study component of this thesis (i.e. the quantitative study and the qualitative study) was led by a sample size calculation (see Chapter 7, Sections 7.4.1 and 7.4.2). To achieve the required samples the studies recruited participants from multiple hospital sites with the effect of increasing the generalisability of the findings.

6.4.2 Aims, objectives and research questions

Research question 1: What is the nature and extent of cognitive impairment in patients with CRC post-surgery but prior to adjuvant chemotherapy treatment?

Aim 1: This thesis aimed to establish whether cognitive impairment (objective and/or subjective) is present in resected CRC patients prior to commencing chemotherapy treatment or at a similar point in time in the surgery only patients.

Related objectives are to compare the "chemotherapy" patient group with the "surgery-only" patient group regarding:

1.1 The incidence of OCI.

1.2 The most commonly affected cognitive domains

1.3 The relationships between demographic, clinical and psychosocial factors and objectively measured cognitive functioning

1.4 The relationship between perceived cognitive function (as measured by self-assessment questionnaires) and objectively measured cognitive function

after surgery and before the start of chemotherapy (or at a similar point in time for the "surgery only" participants).

Research question 2: What is the nature and trajectory of CRCI in patients with resectable CRC who do or do not receive adjuvant chemotherapy treatment?

Aim 2: To investigate the nature, course and extent of cognitive impairment (both objective and subjective) in patients with resected CRC who go on to have systemic chemotherapy treatment compared to those who do not have any further treatment.
Related objectives are to:

2.1 Explore the extent and nature of both OCI and SCI pre-, mid- and post-chemotherapy treatment in resected CRC patients undergoing chemotherapy (Qualitative and Quantitative components).

2.2 Explore the extent and nature of both OCI and SCI in resected CRC patients who require no further treatment at similar points in time to those undergoing chemotherapy treatments

2.3 Explore the relationships between cognitive function (objective and subjective) and psychosocial outcomes in resected CRC patients in both the chemotherapy and "surgery-only" patient groups.

2.4. Examine the relationship between patients' self-reported cognitive functions and their objectively assessed cognitive functions

Research question 3: Is OCI in patients with CRC associated with lesser HRQoL?

Aim 3: To explore whether OCI, if present in patients with resected CRC is related to HRQoL? If so, what cognitive domains are related to what aspects of HRQoL?

Research question 4: **Are patients with CRC aware of CRCI? How do those patients who perceive themselves to have CRCI (before, during and after chemotherapy treatment) experience such impairments?**

Aim 4: To explore the perceived cognitive changes experienced by patients with resected CRC before, during and after adjuvant chemotherapy treatment.

Related objectives are to:

4.1 Explore whether patients with CRC are aware of CRCI prior to the start of chemotherapy treatment and whether they are aware of having experienced any cognitive difficulties since diagnosis (Qualitative component).

4.2 Explore the type and extent of individual experiences of CRCI and its perceived effects prior to, during and post chemotherapy treatment (Qualitative component).

6.5 Structure of subsequent chapters

Chapter 7 will describe the methodology used in this thesis, followed by the analyses, which will address each of the aims described above (Chapters 8 to 10 inclusive). A discussion of the findings is included immediately following each set of analyses and a general discussion will integrate the findings and discuss the implications (Chapter 11).

Chapter 7: Methodology

7.1 Introduction

This chapter presents the methodology adopted in this thesis, including the study design, measures and an overview of the statistical strategy adopted for data analysis of each study. It begins by providing an outline of the different types of mixed method designs available, the method chosen for this PhD and why. It then goes on to discuss recruitment strategy and procedures and the measures utilised in each component study, followed by a brief overview of the planned analyses strategy.

7.2 Mixed methods approaches

7.2.1 Rationale for a mixed methods approach:

Mixed methods approaches are increasingly used in health-related research, such as cardiology (Curry, Nembhard, & Bradley, 2009), paediatric oncology nursing (Wilkins & Woodgate, 2008), mental health services (Creswell & Zhang, 2009; Palinkas, Horwitz, Chamberlain, Hurlburt, & Landsverk, 2011) and disabilities (Mertens, 2014). Advocates of this approach discuss the potential to generate unique insights into multifaceted phenomena (Cresswell & Clark, 2011) such as health care. Other researchers (who have explored the use of mixed methods research in health services) consider these types of designs to be more comprehensive (O'Cathain, Murphy, & Nicholl, 2007). The different methods (i.e. qualitative and quantitative) are often used to address different questions or aspects of the overall research question so that the study is more comprehensive (O'Cathain, Murphy, & Nicholl, 2007).

Whilst both quantitative and qualitative approaches have each been used in "cancer and cognition" studies they are rarely found together. One example where both methods were used is Downie and colleagues (2006) study with breast cancer patients. They used a neuropsychological assessment alongside a semi-structured interview and self-report measures of fatigue and menopausal symptoms to examine the relationship between experience with symptoms and cognitive performance. However, they did not specifically examine the experience of living with cognitive impairment.

Quantitative research in the context of "cancer and cognition" is often used to gather information and examine relationships among variables that yield numeric data and can be analysed statistically. This also allows for efficient data collection procedures, creates the possibility of replication and generalisation of results, which facilitates the comparison of groups, and can provide insight into a breadth of experiences (NIH Office of Behavioral and Social Sciences, 2018). Whereas, one of the major strengths of qualitative research is its focus on the contexts and meaning of human lives and experiences for the purpose of inductive or theory-development driven research (NIH Office of Behavioral and Social Sciences, 2018).

Where the quantitative studies' use of validated measures and statistical approaches minimise researcher bias, they generally do not offer an in depth subjective understanding of the phenomenon, which qualitative approaches may offer (Lewis & Ritchie, 2003). The integration of quantitative and qualitative data therefore minimizes the weaknesses and maximizes the strengths of each type of data (NIH Office of Behavioral and Social Sciences, 2018). Triangulation is also a benefit of using a mixed methods approach as it enables the researcher to compare the quantitative and

qualitative results and examine similarities and differences (Curry, Nembhard, & Bradley, 2009).

This thesis uses a mixed method concurrent approach in order to obtain a more in depth picture and understanding of CRCI in a solid tumour population. Research to date has shown that there is rarely any correlation between subjective and objective CRCI (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012). The integration of two methods of data collection and interpretation will allow for the development of a more comprehensive understanding of the issue and examination of experiences along with the assessed outcomes (Plano Clark, 2010).

7.2.2 Design

As mentioned, since 1996, there has been a growing interest in mixed methods approaches in health-related research (Plano Clark, 2010). Johnson and colleagues (2007) found 19 definitions of mixed methods research with varying levels of specificity. An examination of all of these led to Johnson and colleagues' (2007) general definition of mixed methods research as:

The type of research in which a researcher or team of researchers combines elements of qualitative and quantitative research approaches (e.g., use of qualitative and quantitative viewpoints, data collection, analysis, inference techniques) for the broad purposes of breadth and depth of understanding and corroboration (P.123).

Essentially, it involves the intentional collection and integration of both quantitative and qualitative data (Creswell, Klassen, Plano Clark, and Smith, 2011). There is no gold standard formula for designing a mixed methods study. There are numerous possibilities, such as the convergent parallel design, the explanatory sequential design,

the exploratory sequential design, the embedded design, the transformative design and the multiphase design (Creswell & Plano Clark, 2011), as briefly outlined below.

Taking each in turn:

The convergent (or parallel or concurrent) designs: This involves the merger of concurrent quantitative and qualitative data and a comparison of the two sets of data and results. The qualitative and quantitative components may be of equal status or one could be dominant.

The sequential (explanatory or exploratory) designs: are two-phase studies where one dataset builds on the results of the other.

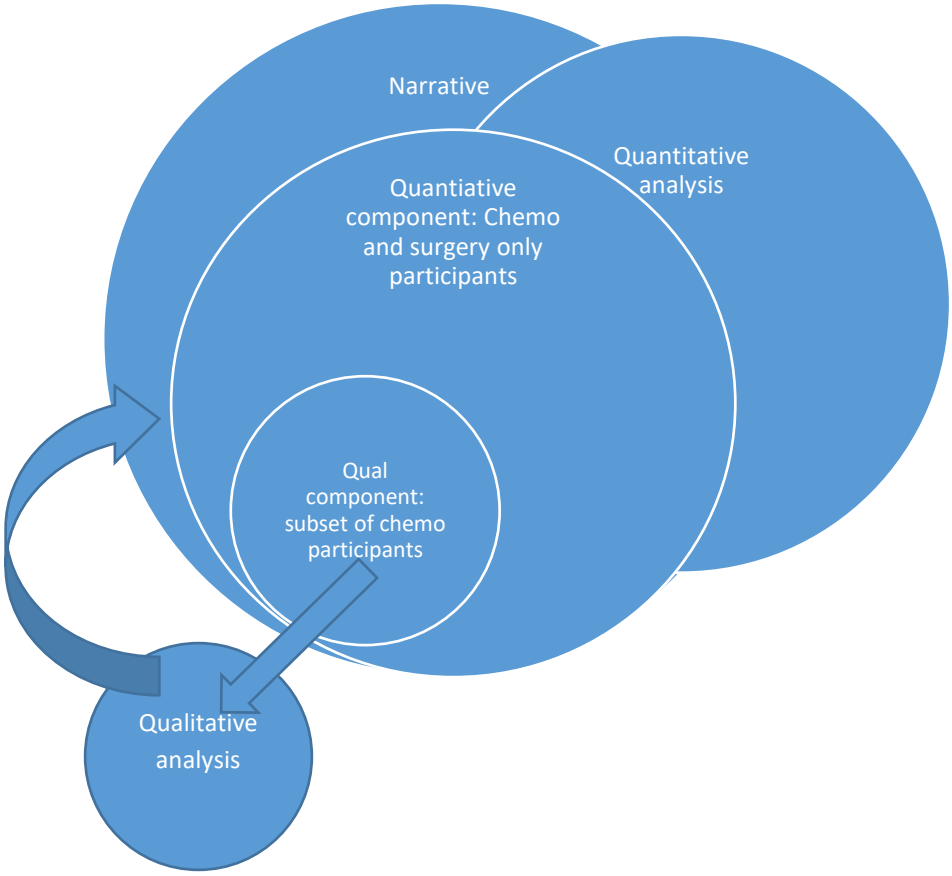
Embedded (or nested) designs: use quantitative and qualitative approaches in tandem where one is embedded in the other to provide new insights or more refined thinking. They may be a variation of a convergent or sequential design.

Multiphase designs: emerge from multiple projects conducted over time and linked together by a common purpose. They commonly involve convergent and sequential elements (Creswell & Plano Clark, 2011).

This thesis follows a mixed methods concurrent longitudinal framework (Creswell & Plano Clark, 2011) (as shown in Figure 7.1), where the results of the qualitative component and quantitative component will be integrated in the general discussion (Creswell & Plano Clark, 2011) to provide further insights into the individual experience of CRCI. The data collection for the qualitative component took place concurrently with the quantitative assessments and quantifiable self-report questionnaires. The purpose of this mixed-methods approach was to develop a more complete understanding of

CRCI; to develop a complementary picture, defined by Greene and colleagues (1989) as the use of quantitative and qualitative methods to *"measure overlapping but also different facets of a phenomenon, yielding an enriched, elaborated understanding of that phenomenon."* The qualitative component within this thesis was to provide a fuller picture and deeper understanding (Johnson, Onwuegbuzie & Turner, 2007) of CRCI; to examine individual experiences over time (Plano Clark, 2010).

Figure 7.1: Pictorial representation of the concurrent research design used in this thesis

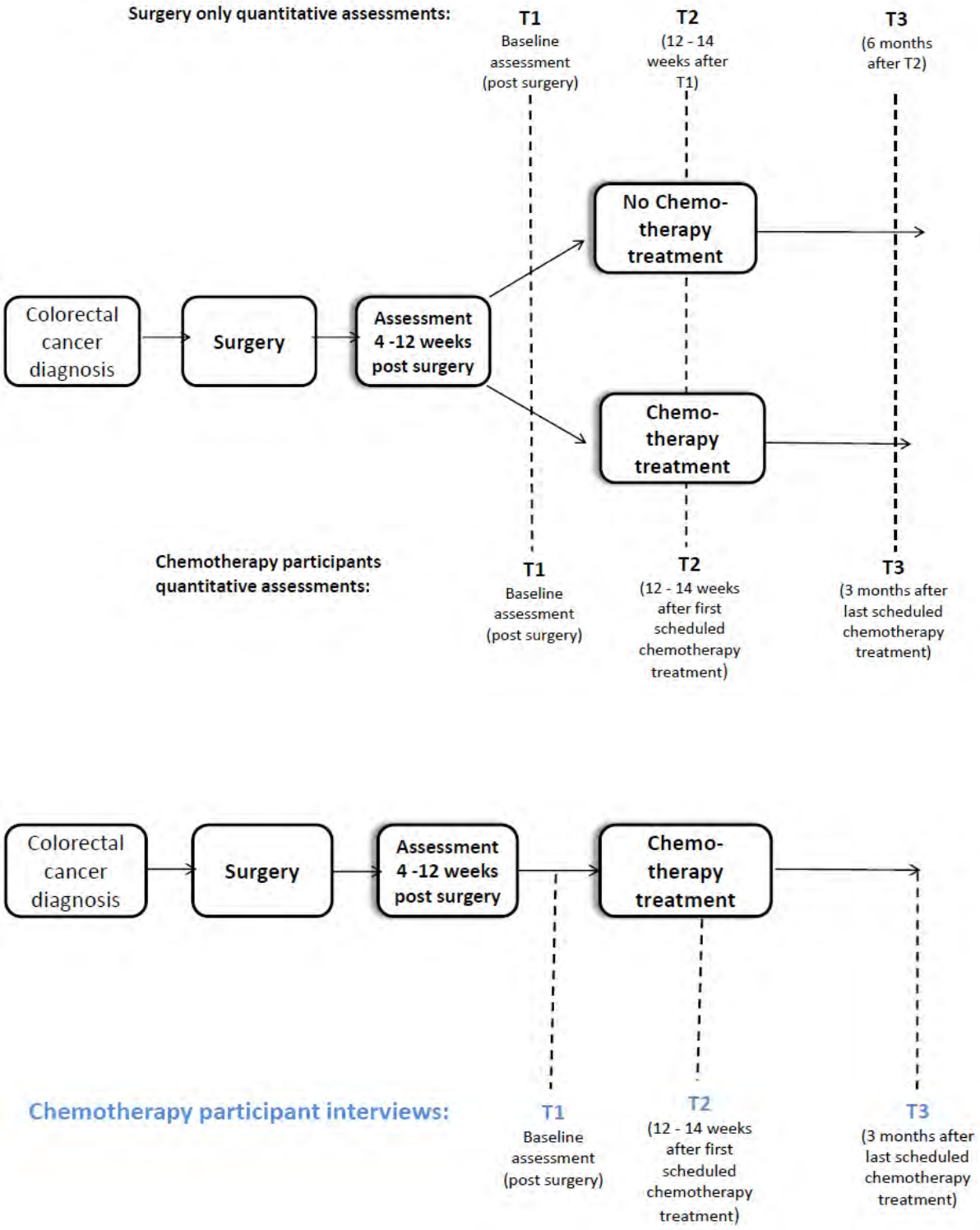


The quantitative and qualitative approaches to data collection and analysis in this thesis were as follows:

Quantitative study component:

As can be seen in Figure 7.2, a longitudinal comparative study was employed. This involved collecting data using self-report questionnaires and neuropsychological (NP) assessments at 3 time points over a 9 month period, from a consecutive sample of resected (i.e. they had had surgery) CRC patients at a number of consenting NHS Trusts across London. Some participants required adjuvant chemotherapy treatment following surgery (the "chemotherapy group") and others did not require any further systemic treatment (the "surgery only" patients). The "surgery only" participant assessments were administered to patients at similar points in time as for those participants undergoing chemotherapy, as indicated below. Full participant details are presented in Chapter 8.

Figure 7.2: Pictorial representation of the concurrent data collection for the quantitative and qualitative studies



As discussed in Chapter 2, adjuvant chemotherapy treatment for patients with a resectable CRC diagnosis starts once the patient has recovered from surgery, usually between 3 to 12 weeks later. The drugs are then administered either every two weeks (for intravenous drugs) or every three weeks (for oral drugs) for between 1 and 5 days followed by a break of two or three weeks. This constitutes one chemotherapy cycle and a complete treatment course usually takes up to a total of 6 months (Appendix B). Assessments were mapped to the chemotherapy timetable as far as was possible for the "chemotherapy group" and at similar points in time for the participants in the "surgery only" group, as follows:

T1: (After surgery, before chemotherapy treatment) this baseline assessment captured patients experiences approximately 3 to 12 weeks after surgery;

T2: (Mid chemotherapy treatment (i.e. after the first 3 or 6 cycles depending on the prescribed chemotherapy protocol). (Please see Appendix B for full details of all chemotherapy regimens). This assessment captured patient's experiences at approximately the middle of the chemotherapy treatment course or approximately 3 months after T1 for the "surgery only group";

T3: Three months post the last scheduled chemotherapy treatment (i.e. approximately 6 months after T2).

The use of NP assessments and questionnaires at these three time points enabled the collection of quantifiable data that were analysed using statistical tests as detailed in Chapters 8 and 9.

Qualitative study component:

In tandem with the quantitative assessments, interview data was collected from a subset of the chemotherapy patient group at each of T1, T2 and T3 satisfying the same inclusion/exclusion criteria as those who were eligible for the quantitative study. It was the intention of this study to capture the in-depth experiences (pre-, mid- and post-chemotherapy treatment) of CRC patients' perceived cognitive impairment, its trajectory, and its impact on the individual.

None of the reviewed interview/focus group studies to date (whether longitudinal or cross sectional) have focused on or included adults with CRC (Chapter 4, Table 4.1). The majority of the studies (14 out of 20) reviewed in Chapter 4 have been in female breast cancer survivors (Becker et al, 2015; Boykoff et al., 2009; Cappiello et al, 2007; Cheung et al, 2012; Downie et al, 2006; Kanaskie & Loeb, 2015; Munir et al., 2010 & 2011; Myers, 2012; Player et al, 2015; Raffa & Martin, 2010; Rust & Davies, 2013; Shilling & Jenkins 2007; Von Ah et al, 2013). Twelve of the studies focused on patients who had already completed treatment (Boykoff et al., 2009; Cappiello et al, 2007; Cheung et al, 2012; Kanaskie & Loeb, 2015; Munir et al., 2010 & 2011; Myers, 2012; Raffa & Martin, 2010; Rust & Davies, 2013; Shilling & Jenkins 2007; Skoogh et al, 2012; Von Ah et al, 2013). This study therefore adds to the longitudinal literature by interviewing cancer patients with a different solid tumour (involving both men and women) pre-, mid- and post chemotherapy treatment.

This mixed methods approach provided a valuable all-encompassing strategy that overcame the limitations of using just quantitative or qualitative measures on their own. The methodological limitations of previous research were also addressed as:

1. The longitudinal design enabled an examination of changes in cognitive function and psycho-social outcomes over time;
2. The pre-chemotherapy treatment baseline enabled an examination of the impact of the chemotherapy on patients' experiences and cognitive function as all patients had been through the shock of the diagnosis and curative surgery.

7.3 Ethical approval

Full ethical approvals for both the qualitative and quantitative studies were obtained from the NHS Health Research Authority – NRES Committee South-West Cornwall & Plymouth (REC reference number: 13/SW/0201) in August 2013 and June 2015 (see Appendix H for approval letters). Relevant approvals were also gained from the Research & Development (R&D) departments at University College London Hospitals NHS Foundation Trust (UCLH), Barts and the London NHS Trust (Barts), Imperial NHS Trust (Imperial), Royal Free London NHS Foundation Trust (Royal Free) and West Middlesex University Hospital NHS Trust (West Mid) (later it became the Chelsea and Westminster Hospital and West Middlesex University Hospital NHS Trust) (each a 'Participating Trust').

7.4 Study participants and sampling procedures

7.4.1 Participants

A consecutive series of outpatients (satisfying the inclusion criteria) attending medical oncology clinics under the care of the CRC team at each of the Participating Trust hospital sites were invited to take part in both the qualitative and quantitative study. 98 patients were recruited from eight hospital sites across five Participating Trusts (63

chemotherapy patients and 35 “surgery only” patients) for participation in the quanitative study and 24 of the chemotherapy patients invited to participate also agreed to take part in the quantitative study. Full participant details can be found in Tables 8.2, 9.2 and 10.1 in Chapters 8, 9 and 10 respectively.

7.4.2 Inclusion and exclusion criteria

Specific inclusion/exclusion criteria were set for participation in the study.

Inclusion criteria:

- Aged between 18 years and 65 years (the upper age limit was removed on 1 January 2015 following the Feasibility Trial) (please see Section 7.6 and Appendix J)
- Diagnosed with resectable (i.e. suitable for surgery) CRC to be followed by adjuvant chemotherapy treatment or no further systemic cancer treatment.
- Fluent in spoken and written English language, sufficient to complete self-report questionnaires and neuropsychological assessments.

Exclusion criteria:

- Prior exposure to chemotherapy
- Significant psychiatric or medical comorbidities which could affect ability to participate
- History of stroke or other brain trauma.

7.4.3 Recruitment Strategy

7.4.3.1 Identification of eligible participants for both the quantitative and qualitative studies.

Between 1 April 2014 and May 2017, eligible participants were initially identified at the weekly CRC multi-disciplinary team (MDT) meetings held by each Participating Trust. The researcher kept careful track of each new eligible patient and post –operative patient discussed at the MDT with the help of the Colorectal Nurse Specialists (CNS) at each hospital site. The appropriate CNS would then provide the researcher with the date and time of all relevant outpatient appointments in order to enable the researcher to attend the appropriate clinic at the right time and recruit to the study. In order to minimise sample attrition and its impact on the current study, the researchers responsible for data collection attended all clinics to recruit the patients in person; and maintained rapport with all participants throughout the 9-month data collection period. All patients scheduled to have adjuvant chemotherapy treatment and satisfying the inclusion/exclusion criteria were invited to take part in **both** the quanitative study and qualitative study, as more particularly described below. Eligible patients who did not wish to take part in one or other of the studies were given the opportunity to participate in the other study should they have wished to do so.

Chemotherapy patients: During the course of the post-surgery follow-up appointment, the oncology team mentioned both the qualitative and quantitative studies to the patient before making an introduction to the researcher who then provided the patient with the appropriate informational documents for them to take away and read (Appendix I). Those patients who provided telephone numbers were contacted at least

48 hours after the introduction. They were invited to participate in the study, either at the applicable chemotherapy clinic or at home prior to the commencement of chemotherapy treatment.

The longitudinal qualitative study was open to all of the chemotherapy participants from June 2015 (when there was a change in the study design, from cross sectional to longitudinal) until a sufficient number of participants had been recruited and consented into the study by the cut off date for recruitment (pleases see section 7.5.2 for the sample size calculation). Consequently, only those participants who were interviewed for the first time after April 2015 were able to continue in the longitudinal qualitiative study and their data was the only data analysed for that study. (Please see Appendix H for the change to the design and approval letter from ethics).

Surgery only patients: A consecutive sample of CRC "surgery only" patients were recruited in the same way as the chemotherapy patients. These eligible patients were introduced to the researcher by either the surgeons or CNSs at the outpatient surgical follow-up appointment. Patients were given appropriate informational documents and those who provided telephone numbers were contacted at least 48 hours later and invited to participate in the quantitative study at home or place convenient to the patient.

Please refer to the published paper in Appendix J '*Chemotherapy-related cognitive changes in colorectal cancer patients: a feasibility trial'* (Dwek, Rixon, Hurt & Newman, 2016) ("Feasibility Trial" paper) for an account of the procedural hurdles that were encountered at the beginning of the study with a subset of the included participants and how these were resolved {e.g. removal of upper age limit of 65 years}.

7.4.3.2 T1

As mentioned in Section 7.4.3.1, a patient who had been approached in clinic and had taken any of the patient information sheets (Appendix I), was telephoned a few days later and asked if they wished to participate. Appointments were made with those who agreed to take part. The researcher then attended the patient's home or they met at the hospital as agreed on the telephone. The patient completed the appropriate consent form(s) (Appendix I), which was/were counter signed by the researcher prior to the administration of assessments, questionnaires and/or interview (as applicable).

7.4.3.3 T2

The researcher contacted patients who completed T1, ten to twelve weeks later. If the patient was unreachable via the telephone (after leaving 2 further voice mail messages), the researcher sent out a letter to the home address asking if the patient would be willing to continue in the study and if so, to contact the researcher. Once a mutually convenient time, date and place had been agreed with the patient the researcher attended the appointment and administered the assessments, questionnaires and/or interview, as appropriate.

7.4.3.4 T3

The same process outlined in relation to T2 was carried out again approximately 3 months after the last scheduled chemotherapy date or 6 months after T2 in the case of the "surgery only" participants.

7.5 Sample size calculation

7.5.1 Quantitative sample size

A meta-analysis of chemotherapy and cognitive function (Jansen et al, 2005) estimated mean effect sizes in a range of cognitive domains. The effect sizes ranged from d= -0.11 to -0.51. A sample size calculation was performed using GPower 3.1 (Faul, Erdfelder, Buchner, and Lang, 2009). Taking into consideration the resources constraints of this PhD study the sample size was calculated with the aim of detecting an effect size, with 80% power and a significance level of 0.05 at T3. (Please see the published Protocol at Appendix K (Dwek, Rixon, Hurt, Simons and Newman, 2015) for a full account of the sample size calculation). Although a minimum sample size of 120 participants was indicated, given the time and resource constraints of undertaking this PhD, it was agreed with the study team that recruitment would be brought to a close in sufficient time to write up this thesis. It was therefore anticipated that a subset of the target number of participants would be analysed for this thesis.

7.5.2 Qualitative sample size

The approach to sample size in quantitative research, where larger numbers are generally more desirable, is not applicable to qualitative research, where the sample size reflects the depth and richness of information that describes a phenomenon (O'Reilly & Parker, 2013). The recruitment sample for this study was not fixed although it was estimated that an approximate sample of 20 chemotherapy patients (ideally 10 male and 10 female) would be sufficient for exploring awareness and experiences of CRCI over the three time points (producing 60 interviews). This was based on Morse (1994)'s recommendation that qualitative explorations of experiences require a

minimum of six participants and a review of previous interview studies in the "cancer and cognition" literature. For example, Downie and colleagues (2006), assessed and interviewed 21 breast cancer patients at one point in time in a mixed method design; and Player and colleagues (2014) interviewed nine breast cancer patients.

Fugard and Potts' (2015) tool for estimating a useful sample size for thematic analysis also produced a suggested sample of 19 or 20. This was calculated as follows:

(a) the expected population theme prevalence of the least prevalent theme, derived either from prior knowledge or based on the prevalence of the rarest themes considered worth uncovering (was set at 30%). It was estimated that 50 % of people who could say something relevant about a theme would do so, providing an adjusted prevalence of 15% (0.3 x 0.5 = 0.15).

(b) the number of desired instances of the theme (was set at 2); and

(c) the power of the study (set at 80% to mirror the quantitative sample calculation).

Using Fugard and Potts (2015) Table 1 for adjusted prevalence of 15%, 2 instances and 80% power led to the suggestion that approximately 19 participants would be required for the qualitative interviews, although slightly less would be acceptable as each participant will be interviewed three times (Fugard & Potts, 2015).

7.6 Feasibility Trial

During the first 9 months of recruitment (i.e between 1 April 2014 and 31 December 2014 (the "Trial Period")) 42 consecutive patients satisfying the eligibility criteria were invited to take part in the study in order to examine the feasilibity of the Protocol and to determine if the quantitative study could be implemented as designed or whether any

alterations were necessary (the "Feasibility Trial"). (Please refer to Appendix J for a full account of the Feasibility Trial). Of the 42 eligible patients identified by the researcher (across 3 London NHS Trusts) and invited to participate, 23 agreed and were consented into the quantitative study. At the end of the Trial Period 18 patients had completed T1 and 8 had completed T2 of the quanitative study and their data are incorporated into the results reported in Chapters 8 and 9.

All adjustments made to the design of the study following the Feasibility Trial (i.e from January 2015 onwards), were as follows:

- the removal of the upper age limit for eligibile participants (the inclusion/exclusion criteria remained the same in all other respects);
- the removal of the pre-screening test; and
- a change in the type of analysis conducted on the longitudinal quanitative data (as discussed in Chapter 9) from ANCOVA's to multi-level modelling.

The design of the quantitative study remained the same in all other respects. A full account of the Feasibility Trial can be found in Appendix J.

7.7 Participation rates

Of the patients that declined to take part in the Feasibility Trial, 4 of the eligible 'surgery only' patients approached by the researcher said that they had completed treatment and did not want to keep being reminded of their diagnosis. They also felt that they had 'nothing to offer' the study; 1 patient agreed to take part but on the scheduled date simply refused without any explanation and 1 patient failed the MOCA so could not continue into the study. For the eligible patients who were scheduled to have chemotherapy treatment, 2 failed the MOCA although one of them did not enjoy doing it

anyway and only wanted to be interviewed, 1 patient had severe dyslexia and was unable to do any of the assessments, a further 3 patients only wanted to do an interview study and the rest just said that they were simply not interested in taking part. The reasons given for refusal to participate were very similar to those provided to Mandleblatt and colleagues (2014), which included "not interested" (133 out of 310 patients approached provided this reason), "too busy" (82/310), "too sick" (14/310), "live too far away" (65/310).

However, due to the number of hospital sites involved and the discrepancies that regularly arose between pre and post-surgical staging of CRC it was not possible to obtain an accurate estimation of the total number of eligible patients with a diagnosis of resectable CRC attending each of the hospitals. In addition, as a number of members of the supervision team were involved in participant identification and recruitment (following the Feasibilitly Trial) and due to the introduction of new data protection laws, it was not possible to obtain a complete list of all those who refused to participate. Please see Chapter 8 Section 8.4.1 and Chapter 9 Section 9.7.1 for full descriptions of the participant participation rates for each of the quantitative and qualitative studies.

7.8 Measures

Detailed demographic and clinical information were gathered for each participant at T1 using a self-report form.

Demographic details included:

- Age
- Gender
- Ethnicity

- Marital status: married/in civil partnership, in relationship, single, divorced/separated, widowed
- Educational level: Primary, secondary, tertiary, undergraduate degree, master's degree, doctorate degree
- Employment status: Employed, self-employed, seeking job, housewife/husband, student, retired, long-term sick leave, unable to work.

Clinical information was also collected through electronic hospital records regarding co-morbidities, surgery type, hospitalization days, CRC staging and pain, anti-depressant and anti-sickness medication (See Appendix L for clinical details form used by the researcher to collect clinical data from hospital records).

7.8.1 Pre-screening test

At T1 (during the Trial Period), consented participants over the age of 65 were asked to complete the Montreal Cognitive Assessment (MoCA) version 3 as a pre screening test in order to exclude those with mild cognitive impairment (MCI) from taking part in the study (so as not to skew the the results by including those with pre-existing cognitive conditions). A raw score of less than 26 indicated MCI and precluded entry into the study. The MoCA is a brief screening instrument that evaluates multiple cognitive domains including short-term memory, visuospatial abilities, executive function and attention in 10 minutes. It has demonstrated sensitivity in detecting MCI (90%) and good specificity at 87% (Nasreddine, Phillips, Bédirian, Charbonneau, Whitehead, et al 2005).

However, after the Trial Period (i.e from 1 January 2015 onwards) this measure was discarded on the basis that it was too sensitive. It was found to be excluding patients

with mild cognitive problems who may still have shown cognitive impairment over time had they undergone the full battery of tests, as well as those who wished to continue in the study (Appendix J).

The data in relation to the potential participants that failed the MoCA is not reported in this thesis as there was not enough to be adequately analysised quantitatively and consequently it was not considered relevant once the test had been abandoned.

7.8.2 Quantitative study measures:

A wide range of measures were used to assess cognitive function and psychosocial outcomes. The following criteria were considered when selecting measures:

(a) To obtain as comprehensive as possible assessment battery for the time available

(b) The three core measures as recommended by the ICCTF (Wefel et al, 2011),

(c) The applicability of the measure to the patient group (e.g. the Functional Assessment of Cancer Therapy-Colorectal (FACT C) quality of life measure which contains items specifically related to CRC),

(d) Favourable reliability and validity reported in previous studies (reported where available), and

(e) Availability of measures.

A description of all of the measures included in the questionnaire booklets (the "Battery") is presented in this Section 7.8.2 and summarised in Table 7.1 along with the

domains assessed. The Battery took approximately 2 hours and 30 minutes to complete at T1 and 1 hour and 30 minutes at each of T2 and T3.

7.8.2.1 NP measures

All participants underwent a detailed NP assessment as described below (See Table 7.1). The Battery included the three core measures recommended by the ICCTF (Wefel et al, 2011), namely:

- The Trail Making Test (Part A and B)(TMT A & B) (Reitan & Woolfson, 1985; Reitan, 1992);
- Hopkins Verbal Learning Test – Revised (HVLT-R) (Brandt & Benedict, 2001); and
- The Controlled Oral Word Association Test (COWA) (Ruff, Light, Parker & Levin, 1996.).

These were supplemented with the Digit Span subtest of the Wechsler Adult Intelligence Scales – Third Edition, (WAIS - III Digit Span) (Wechsler, D, 1981); The Symbol Digit Modalities Test (SDMT) (Smith, 1968; Smith, 1982); Grooved Pegboard Test (GP) (Klove, 1963; Matthews & Klove, 1964) and The Benton Visual Retention Test (BVRT) (Sivan, 1992). All measures were standardised, validated and taken from published test batteries with population norms.

The Battery was ordered in such a way as to alternate and distribute the more difficult (cognitively challenging) tasks with the less difficult ones and to avoid the administration of any language and verbal memory tests during the 20–25 minute period prior to the administration of the HVLT-R recall and recognition tests. At T2 and

T3 alternate forms of the HVLTR, BVRT and TMT were used, with the aim of reducing participant practice effects.

As discussed in Chapter 2, there are often overlaps in the cognitive domains assessed by each test. The tests used in the quantitative study were therefore classified into overarching domains adapted from Strauss, Sherman and Spreen (2006) and the ICCTF (Wefel et al, 2011). These overarching domains include tests that largely assess some aspect of a similar cognitive function as illustrated in Table 7.1 and described below.

Table 7.1: Table detailing the tests included in the Battery: Neuropsychological tests grouped by principal cognitive domains, self-reported cognition, mood, and fatigue and quality of life measures

NP measures				
Domain	**Description**	**Test/measure**	**Abbreviation**	**Reference**
Attention and visual-motor ability	The ability to selectively concentrate on one aspect of the environment, while ignoring other things	Trail Making Test A	TMTA	Reitan and Wolfson, 1985; Tombaugh, 2004.
		Symbol Digit Modalities Test	SDMT	Smith, A., 1982.
		Digit Span subtest from the WAIS-III – forwards and backwards	DS	Wechsler, D 1997
Domain	**Description**	**Test/measure**	**Abbreviation**	**Reference**
Concentration	The ability to concentrate mental powers on an object	Symbol Digit Modalities Test	SDMT	Smith, A., 1982.
Executive Function	Cognitive abilities that control and regulate	Trail Making Test B	TMT B	Reitan and Wolfson, 1985;

	other abilities and behaviours			Tombaugh, 2004
		The Controlled Oral Word Association of the Multilingual Aphasia Examination	COWA	Benton, Hamsher & Sivan, 1989
Motor Function	The ability to perform body motor movements (movement of limbs) with precision, coordination, or strength	Grooved Pegboard	GP	Lafayette Instrument, 1989; Klove, 1963; Matthews & Klove, 1964.
Processing Speed	The ability to automatically and fluently perform relatively easy or overlearned cognitive tasks		TMT	Reitan and Wolfson, 1985; Tombaugh, 2004
Working Memory	The ability to actively monitor, temporarily store, and manipulate information or behaviours		TMT SDMT	Reitan and Wolfson, 1985; Tombaugh, 2004; Smith, A., 1982.
Verbal Memory	The ability to retain linguistic information for a designated time period and typically presented orally	Hopkins Verbal Learning Test-Revised	HVLT-R	Benedict, Schretlen, et al, 1998; Brandt and Benedict, 2001
Visual Memory	The ability to create an eidetic image of past visual experiences	Benton Visual Retention Test	BVRT	Benton, & Sivan, 1992

Reaction Time	The ability to react and/or make decisions quickly in response to simple stimuli		TMT GP	Reitan and Wolfson, 1985; Tombaugh, 2004
Measure of subjective cognition				
	Description	**Test/measure**	**Abbreviation**	**Reference**
Participants own perception of mental capabilities	4 scales - perceived cognitive impairments (20 items); impact on QoL (4 items); Comments from others (4 items); perceived cognitive abilities (9 items)	Functional Assessment of Cancer Therapy Cognitive Scale	FACT-Cog Version 3	Wagner et al 2009
Psychosocial measures				
	Description	**Test/measure**	**Abbreviation**	**Reference**
Anxiety and Depression		Hospital and Depression Scale	HADS	Zigmond and Snaith, 1983
Fatigue	A 20 item measure - general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue	FACIT Fatigue Version 4	Yellen et al, 1997
Health Related Quality of Life	4 domains - Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. Considered appropriate for use with patients with any form of cancer. Combined with FACT C specifically for CRC	Functional Assessment of Cancer Therapy General and Colorectal Symptom Index	FACT-G & C (Version 4)	Cella et al 1993

Premorbid Intelligence measure				
		Test/measure	**Abbreviation**	**Reference**
IQ		Wechsler Abbreviated Scale of Intelligence Second edition – Vocabulary and Matrix Reasoning - only at T1.	WASI	Wechsler, 1999

7.8.2.1.1 Measures of attention

Symbol Digit Modalities Test (SDMT)

Description

The SDMT (Smith, 2002) assesses divided attention, visual scanning, tracking (Shum, MacFarland and Bain, 1990) and motor skills. It has demonstrated sensitivity in detecting the presence of brain damage, as well as changes in cognitive functioning over time and in response to treatment (Smith, 2002).

A paper and pencil test that comprises rows of 110 blank squares each with an assigned symbol. Above the rows there is a coding key which consists of nine numbers (from 1-9), each paired with an abstract symbol. The participant is required to use the key in order to match each symbol with a corresponding number and write these down as quickly as possible, consecutively in the order presented. The sequence of symbols is random (Strauss, Sherman, & Spreen 2006). Participants are asked to perform a practice trial on the first 10 symbols and are then given 90 seconds to complete the test.

The test is administered twice. In the first trial responses are written down by the participant (SDMT Written) and in the second they are given orally and written down by the administrator (SDMT Oral). This allows drawing comparisons between visual-motor and oral responses (Lezak, 1995; Strauss, Sherman and Spreen, 2006).

Scoring

A written and oral score is calculated by totalling the number of correct answers for each section in order to provide two differing indices of functioning, which assess attention, scanning abilities, and motor skills (Lezak, 2004). A higher score on each section indicates better performance.

Psychometric properties

The test-retest reliability of the SDMT has been shown to be high (0.91) (Hinton-Bayre Geffen, Geffen, McFarland, & Frijs, 1999).

Trail Making Test: Forms A and B (TMT)

Description

The TMT (Reitan & Wolfson, 1985) is a two-part paper and pencil measure of attention, psychomotor speed and aspects of executive function and tests spatial organisation, visual pursuits, recall, and recognition. Part A (TMT A) requires the participant to connect 25 encircled randomly arranged numbers in ascending order without lifting the pencil from the paper in order to test visuo-scanning, numero-sequencing, and visuo-motor speed. When completing Part B (TMT B) the participant is required to connect 25 randomly arranged letters and numbers in alternating order (1-A, 2-B, 3-C ..) as quickly

as possible. TMT B tests cognitive demands including visuo-motor, visuo-spatial abilities and mental flexibility.

The participant first completes short practice exercises for Parts A and B in order to ensure familiarity with the test and comprehension of the test instructions. Both parts of the test are timed. The TMT-B subtest is terminated if the respondent takes over 5 minutes to complete.

Scoring

Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment. Part B is more difficult than Part A; it takes longer to complete and may indicate difficulties in divided attention, executive functioning and cognitive flexibility along with conceptual motor tracking (Bremmer, Wert, Durica, & Weaver, 1997). Both scores (TMT-A and TMT-B) are reported in this study.

Psychometric properties

The test-retest reliability of the TMT varies with age-range and population (Strauss, Spreen & Sherman, 2006). Dikmen and colleagues (1999) examined 384 healthy individuals and who were retested 11 months after the first test and reported reliability coefficients as 0.79 for Part A and 0.89 for Part B. The inter-rater reliability has been reported as 0.94 for TMT A and 0.90 for TMT B (Fals-Stewart, 1992).

The Digit Span subtest of the Wechsler Adult Intelligence Scales – Third Edition, (WAIS - III Digit Span) (Wechsler, D, 1981)

Description

The Digit Span measure of the WAIS III Scale consists of two mental activity tests involving auditory attention and short-term memory retention capacity. For each test, the administrator reads out random number sequences, which increase in length. There are two trials for each span length.

The 'Digit Span Forward' test is a measure of focused attention where the participant is asked to repeat the random numbers to the administrator in the exact order given, continuing until the participant fails a pair of sequences or repeats the highest sequence correctly. The 'Digit Span Backward' test demands more effort from working memory. The participant repeats the number pairs in exactly the reverse order until the participant fails a pair of sequences or repeats the highest sequence correctly.

Scoring

To score, no digits may be omitted or be in the wrong order. The maximum total digit forward score is 16 and the maximum total digit backward score is 14. The final score is obtained by adding the total forward score to the total backward score (for a maximum score of 30). The lower the score the more impaired the participant.

7.8.2.1.2 Measure of executive function

Controlled Oral Word Association Test (COWA)

Description

The COWA of the Multilingual Aphasia Examination (Benton, Hamsher, & Sivan, 1989) is a test of executive functioning, verbal association and fluency (Benton, Sivan, Hamsher, Varney, & Spreen, 1994). Each participant is administered three trials of a phonemic fluency task that measures the spontaneous production of words within a restricted timeframe (Strauss, Sherman & Spreen, 2006). The participant is asked to produce as many words as possible, beginning with each of the letters 'C', 'F' and 'L' excluding proper nouns (e.g. Bob, Boston) and repetitions of the same word with different endings (e.g. big, bigger and biggest). Participants are allocated sixty seconds for each letter (C, F, and L). The researcher records a list of all the words named by the participant. All errors, including repetitions and intrusions, are recorded along with correct words in the order in which they were generated.

Scoring

The total score is the sum of all admissible words for all three letters. A higher score indicates better performance.

Psychometric properties

The COWA-CFL has been shown to have moderate to high internal reliability (r=0.83) (Ruff et al, 1996).

7.8.2.1.3 Measures of motor functioning and dexterity

Grooved Pegboard (GP) (Klove, 1963; Matthews & Klove, 1964)

Description

The Grooved Pegboard task (Matthews & Klove, 1964) is a manual dexterity test measuring visuo-motor coordination. It has been useful in detecting motor dysfunction in cancer patients (Wieneke & Dienst, 1995).

The test consists of a small metal board containing a 5x5 set of randomly positioned slots and 25 metal pegs that each has a ridge along one side. Participants are required to rotate the pegs in order match the groove of the peg with the groove of the hole for insertion, as quickly as possible consecutively across and down the grid (right to left for the left hand and vice versa) (See Figure 7.3). The participant continues until all pegs have been placed. The participant is required to complete two trials, one with the dominant hand and then the second with the non-dominant. A maximum of 5 minutes are allowed for test completion, after which the test is terminated.

Figure 7.3: Grooved Pegboard

(Source: www.lafayetteeevaluation.com)

Scoring

The score is computed for each hand and is the time taken to place the pegs. Some researchers also record the number of pegs dropped and the number of pegs not inserted. These two scores may be considered for clinical use as such errors are rarely seen in neurologically intact individuals, but they are less useful for population research purposes (Heaton, Miller, Taylor, & Grant, 2004; Strauss, Sherman and Spreen, 2006). In the present study, time taken to complete was the only score utilized. A higher score on each hand indicates poorer performance.

Psychometric properties

With retest intervals ranging from four to twenty-four months, the reliability coefficients of the GP are marginal/high (0.67 to 0.86) in normal populations aged 15 years and older (Strauss, Sherman, and Spreen, 2006).

7.8.2.1.4 Measures of memory

Hopkins Verbal Learning Test - Revised (HVLT-R) (Benedict, Schretlen, et al, 1998; Brandt and Benedict, 2001)

Description

The HVLT-R assesses verbal short-term learning and memory performance. The test includes three learning trials (Trials 1-3), a delayed recall (25 minute delay) (Trail 4), and a yes/no recognition trial. Six distinct forms of the HVLT-R are available, minimizing practice effects on repeated administrations. Form 1 was used at T1, Form 2 at T2 and Form 3 at T3.

Each form of the HVLT-R consists of a list of 12 nouns, with four items drawn from each of three semantic categories. A list is read to the participant who then attempts to recall as many words as possible in any order. The administrator records each response verbatim including intrusions and repetitions. This task is repeated two more times. After an interval of 20 to 25 minutes, a delayed recall trial is administered. Again, responses are recorded verbatim. Finally, a list of 24 randomly ordered words that consist of the 12 target words and 12 non-target foils is read. The participant is asked to identify as many target words as possible with a "yes" response and to respond to the non-target words with a "no" response.

Scoring

The number of correct words recalled are counted as correct for each trial up to a maximum score of 12. The total recall score is the sum of the Trials 1 to 3. The delayed recall score is the number correct on Trial 4. The percentage retention score is calculated as Trial 4 divided by the best of Trials 2 and 3 and multiplied by 100; and the recognition discrimination index is the number of true positives minus the number of false positives on the last trial administered.

Psychometric properties

The HVLT-R is reportedly useful in screening for dementia (Hogervorst, Combrinck, Lapuerta, et al, 2002; Shapiro, Benedict, Schretlen, & Brandt, 1999; Carey, Woods, Gonzalez, et al, 2004), although the authors of the test reported reliability coefficients as follows: 0.74 for Total Recall; 0.66 for delayed recall; 0.39 for % retention and .40 for recognition discrimination index. Forty older adults had completed different forms of the test on 2 occasions with a mean test retest interval of 6 weeks.

The Benton Visual Retention Test (BVRT) (Sivan, 1992)

Description

The BVRT is a measure of visual perception, visual memory and visuo-constructive ability. There are three near-equivalent forms (Forms C, D, and E) of the BVRT. Each of the three test forms consist of 10 designs presented one-by-one. Form C was used at T1, Form D at T2 and Form E at T3, which allowed for retesting while minimizing practice effects. Administration A (of the four possible methods) was used throughout. The participant viewed each design for 10 seconds before reproducing it from memory. The test was not timed and the results were scored by form, shape, pattern and arrangement on the paper.

Scoring

There are two scores for describing a participant's performance. The Number Correct Score which is a measure of the participant's overall level of performance; and the Number Error Score which provides information about the frequency of specific types of errors made by the participant.

Number Correct Score: The participant's reproduction of each design is judged on an all or none basis. If the reproduction contains no errors, it is scored as correct and awarded 1 point. If the reproduction contains any errors, it receives 0 points. The range of possible scores for any single form of the test (10 designs) is 0 to 10 points.

Number Error Score: In any less than perfect reproduction the number of errors is recorded and each error is classified and recorded by type. The specific types of errors are grouped into six major categories: Omissions, Distortions, Perseverations, Rotations,

Misplacements and Size Errors. Within these are 56 specific error types. An incorrect reproduction may contain as many as four specific errors.

Psychometric properties

The test-retest reliability of the BVRT is 0.85, and alternate form reliabilities range from 0.79 to 0.84 (Benton, 1992). Correlation between immediate and delayed memory recall (Administration A and D, respectively) range from 0.40 to 0.83, depending on the combinations of forms used. Total errors on the test have been shown to increase with age, especially after 70 (Emilien, Durlach, Antoniadis, Van der Linden, & Maloteaux, 2004).

7.8.2.2 Self-reported cognitive assessments

Functional Assessment of Cancer Therapy-Cognitive scale (FACT-Cog, Version 3)

Subjective cognition was measured using the Functional Assessment of Cancer Therapy-Cognitive scale (FACT-Cog, Version 3) (Wagner et al, 2009). It is a validated self-report measure of cognitive function, which aims to evaluate the "real-world" impact of CRCI. It evaluates mental acuity, attention and concentration, memory, verbal fluency, functional interference, deficits observed by others; change from previous functioning, and impact on quality of life. Items developed for the FACT-Cog were based on interviews and focus groups with oncology patients and providers (Wagner, Sweet, Cella & Doninger, 2003); they included behavioural examples of cognitive dysfunction, and responses are based on frequency of occurrence.

In all 'FACT' assessments, the participant responded on a 5-point scale from "not at all" to "very much" as to the extent to which they had been affected by the item in the prior 7 days.

Scoring

The FACT-Cog contains 37 items, with subscales created by the developers consisting of 1) patients' perceived cognitive impairments, 2) perceived cognitive abilities, 3) noticeability or comments from others, and 4) impact of cognitive changes on quality of life (Webster, Cella, Yost, 2003). A global or summary score is obtained by summing all the item scores. The total scores for each of the FACT Cog subscales have the following ranges:

Perceived Cognitive Impairment (PCI): 0-72

Perecieved Cognitive Abilities (PCA): 0-28

Impact of PCI on quality of life (CogQoL): 0-16

Comments from Others (Oth): 0-16

FACT Cog Total: 0-132

with higher scores denoting better function and less cognitive symptoms. It was administered to all participants' at all three time points.

Psychometric properties

This measure has demonstrated high internal consistency (Cheung, Maung Shwe, Chan, 2012).

7.8.2.3 Psychosocial measures

Psychosocial self-report questionnaires assessing mood and quality of life were also included in the quantitative component of the study. As discussed in Chapter 2 some of these measures, such as depression and anxiety are known to have the potential to influence cognitive functioning and hence were selected to assess their relationship to cognition (Lezak. Howieson, Bigler, & Tranel, 2012).

Measures of Mood: Anxiety and depression:

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983)

Description

Anxiety and depression were measured at each time point using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), developed specifically for the measurement of depression and anxiety in physically ill populations. Participants were asked to reflect upon the past 7 days and to rate 14-items on a 4-point Likert scale (seven items measured anxiety and seven measured depression). The scores for each subscale were summed together to obtain a measure of the amount of anxiety and depression experienced in the week prior to test administration.

Scoring

The scores can range from 0-21. Separate scores for depressive and anxious symptomology were calculated with scores ≤ 7 = no depression/anxiety; 8-10 = doubtful cases; ≥ 11 = definite depression/anxiety (Zigmond & Snaith, 1983).

Psychometric properties

The HADS measure usually takes approximately five minutes to complete and has been widely used in research with breast cancer patients (e.g. Hermelink, Untch, Lux et al., 2007; Weis, Poppelreuter, & Bartsch, 2009). The subscale scores of depression and anxiety have been validated in cancer patients. For example, principal components analysis in a sample of 568 cancer patients revealed a 2 factor solution corresponding to anxiety and depression and high internal consistency (anxiety subscale, $\alpha = 0.93$; depression subscale, $\alpha = 0.90$) (Moorey, Greer, Watson, et al, 1991).

Fatigue

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F, version 4) (Yellen et al, 1997)

Description

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F, version 4) FACIT-F is a commonly used measure of cancer-related fatigue in clinical trials (Cella et al, 1993; Yellen et al, 1997; Wu & McSweeney, 2001; Passik, Kirsh, Donaghy et al, 2002). It is a 13-item self-report subscale of the FACT-G (see below) and is a well-validated quality of life instrument. The items include physical and functional consequences of fatigue (Yellen et al, 1997). It usually takes no more than 5 minutes to complete.

Scoring

Participants are asked to rate the intensity of fatigue and its related symptoms experienced in the past week on a 5-point Likert scale ranging from 0 = 'not at all' to 4 =

'very much'. The total score ranges between 0 and 52, with higher scores denoting less fatigue. It was administered to all participants' at all three time points.

Psychometric properties

This measure has demonstrated excellent internal consistency in a study of 1,011 cancer patients ($\alpha = 0.93$) (Lai, Cella, Chang, Bode, & Heinemann, 2003).

Health Related Quality of Life measure:

The Functional Assessment of Cancer Therapy - General (FACT-G, Version 4) and FACT C

Description

FACT-G is a 27-item self-administered questionnaire used to measure four quality of life domains (Cella et al, 1993): physical (PW), emotional (EW), family/social (SW) and functional well-being (FW) in the previous 7 days. Participants also completed the 9-item FACT-C subscale (CCS) that evaluates symptoms related specifically to CRC including energy, pain, weight, diarrhoea, nausea, swelling or cramps in the stomach area, appetite, ability to enjoy life, and overall quality of life. All the items are based on a 5-point Likert scale except for the one investigating the presence of stoma (yes/no). These scales provide reliable measures in patients with CRC and have been extensively validated (Ward, Hahn, Mo et al, 1999; Cella et al, 1993).

Scoring

Items are summed to give scores for each domain and can also be summed to provide an overall quality of life score in CRC participants.

Psychometric properties

Concurrent validity of the FACT-G has been provided with the Functional Living Index–Cancer (r = 0.80) (Schipper, Clinch, McMurray, & Levitt, 1984) and the Quality of Life Index (r = 0.74) (Ferrans, 1990) in a sample of 854 adult participants with 15 different types of cancer. Internal consistency has been satisfactory for the FACT-G (α = 0.89), as well as individual dimensions (α = 0.65 to 0.82) (Cella et al., 1993). Ward and colleagues (1999) reported higher internal consistency for FACT-C (0.91) than for FACT-G (0.88) as measured from 2 separate samples (n= 60 and n=63). Similarly, Yost and colleagues (2005) reported internal consistency separately for three different samples (observational, preliminary and clinical trial sample). Overall, Cronbach's alpha was reported between 0.87-0.92 for the FACT-C total and a low 0.59-0.76 for CCS.

7.8.2.4 Measure of IQ – only at T1

Sub-scales from the Wechsler Abbreviated Scale of Intelligence – second edition (WASI – II)

Description

The WASI-II is used to measure general intellectual function in individuals between the ages of 6 and 90 years. The WASI-II is comprised of four subtests, which require approximately 30 minutes to complete. However, where time is a constraint only two subtests are needed to estimate general cognitive functioning in less than 15 minutes – namely Vocabulary and Matrix Reasoning.

To reduce patient burden, this study utilized the shorter recommended administration. Methods to calculate an estimated full-scale IQ from a limited number of sub-tests have

been established in the literature (Jeyakumar, Warriner, Raval, & Ahmad, 2004). This method of reducing the number of subscales rather than items per subscale was considered a more reliable technique to reduce test burden without compromising the overall assessment (Jeyakumar et al, 2004).

The vocabulary subtest involves the administrator asking the participant to define words that are presented visually and orally (E.g. – Please could you me what shirt mean?). The matrix reasoning subtest assesses the participant's fluid intelligence, broad visual intelligence, classification and spatial ability, knowledge of part-whole relationships, simultaneous processing and perceptual organisation (Groth-Marnat, 2003; Kaufman & Lichtenberger, 1999; Sattler, 2008)

Scoring

The total raw score for each subtest is calculated by summing the item scores. The raw scores are then converted to T scores based on age and provided in the test manual. The Full Scale IQ-2 is calculated by summing the T scores for vocabulary and matrix reasoning and then by reference to the composite score conversion table provided in the manual.

7.8.3 Qualitative study measures

Semi structured interviews were used at each time point. The topic guides and interview schedules (See Appendix M) were developed by the researcher in collaboration with the supervisory team as detailed in Chapter 10, Section 10.2.5.

Table 7.2: Semi-structured interview topic guides at each time point

	T1 (before chemotherapy treatment after surgery)	**T2 (Mid chemotherapy treatment)**	**T3 (3 months after last scheduled chemotherapy treatment)**
Aware of side effects? Aware of CRCI?	Information received about side effects. Have you heard about CRCI?	n/a	n/a
Side effects experienced	Now	Changes	Continuing?
Experience of cognitive changes	Have you been aware of any changes in the way your mind/thoughts worked since diagnosis or surgery?	Have you been aware of any changes in the way your mind/thoughts worked since you started chemotherapy treatment?	Continuing since end of treatment?
Tiredness	Do you have any problems with sleeping	Do you have any problems with sleeping	Do you have any problems with sleeping
Feelings about changes	Do the changes bother you or interfere with your everyday life in anyway?	Do the changes bother you or interfere with your everyday life in anyway?	Do the changes bother you or interfere with your everyday life in anyway?
Effect on social life	How is your social life?	How is your social life?	How is your social life?
Is there anything else you would like to share about your experience?	Is there anything else you would like to share about your experience?	Is there anything else you would like to share about your experience?	Is there anything else you would like to share about your experience?

7.9 Data analyses

The following is a brief overview of the analyses that were carried out for each study included in this thesis. Full descriptions can be found in the following Chapters 8, 9 and 10.

7.9.1 Quantitative analysis

All of the data collected from the NP measures and self-report questionnaires were entered into SPSS and all analyses were conducted using IBM SPSS (Statistical Package for the Social Sciences) version 25.

Once all of the data (for all time points) had been entered on SPSS it was cleaned and checked for missing values. Preliminary analyses were conducted to check assumptions of normality. This process is fully described in the following Chapter 8. An alpha level of .01 was used for all analyses, unless otherwise stated. Effect sizes statistics are reported where relevant as detailed in Chapter 8.

Multiple imputation procedures were then conducted for data missing at item and scale level rather than ANCOVA's as was originally discussed in the Protocol (Appendix K) for the reasons outlined in Chapter 9. Preliminary analyses compared baseline scores of OCI, SCI, anxiety, depression, fatigue and HRQoL across the 2 participant groups. Multilevel modelling was used to assess change in cognitive functioning and psychosocial outcomes over the nine-month study period; and correlational analyses were used to explore all potential relationships between important outcomes. Please see Chapters 8 and 9 for a full account of the rationale and analysis strategy employed in relation to each research question.

7.9.2 Qualitative analysis

All interviews were conducted and transcribed verbatim by the researcher. A two-stage process of analysis was then applied to the data. First, inductive thematic analysis was conducted for each interview. This is a method of identifying, analysing, and reporting patterns (themes) within data (Braun & Clarke, 2006). This was then followed by further analyses of the data inspired by Saladans (2003) in order to examine the changes that emerged over time. The rationale and analytical steps are fully described in Chapter 10.

7.10 Summary

This chapter has described the design and recruitment strategies involved in this research as well as the measures used for each of the quantitative and qualitative studies. A detailed account of the analysis used and the results obtained in the quantitative study are presented in the following two chapters.

Chapter 8: BASELINE ANALYSIS AND RESULTS

Cognitive function prior to adjuvant chemotherapy treatment in patients with CRC

8.1 Introduction

This chapter presents the analysis strategy and results for Research Question One: "*What is the nature and extent of cognitive impairment in patients with resectable colorectal cancer (CRC) prior to adjuvant chemotherapy treatment?"* together with the related objectives as detailed in Chapter 6. Following an account of the analysis strategy, an examination of data assumptions are presented before the description of participant demographic, clinical, neuropsychological and psychosocial characteristics along with an examination of the potential differences between the surgical and chemotherapy groups at baseline.

8.2 Preliminary statistical analysis

8.2.1 Data screening

Data for all time points were screened to ensure that all variables fell within possible ranges, that there were no errors in data entry or missing values. All manual errors and/or values that were out of range were crosschecked using the raw data and corrected where necessary. The types of missing data that were identified included NP raw scores and individual items and entire sub-scales in questionnaires.

8.2.2 Missing value analysis

Missing value analysis was performed at item and scale level. The overall amount of data that was missing at T1 was 1.7%. Some clinical information (including total

number of chemotherapy cycles administered, variations in chemotherapy treatment administered and anti-sickness drugs administered) was not available for all participants (Appendix N). These items were therefore not considered in the analysis. In demographic characteristics, five items (0.43%) were missing out of 1176.

Mean item replacement was undertaken when calculating scale scores on the Hospital Anxiety and Depression Scale (HADS) for cases that had ≤ 50% of items missing before conducting scale imputation, as suggested by Graham (2009). In cases where more than 50% of items were missing the scale score was considered missing and missingness was treated at scale level. The Functional Assessment of Cancer Therapy–Cognitive Function (FACT Cog), Functional Assessment of Cancer Therapy -General and Colorectal (FACT G & C) and Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT Fatigue)(together the "FACT battery") have scoring manuals that are each supplemented by SPSS syntax which addresses missing data prior to scoring the subscales. For the present study, the official scoring syntax was used as per the scoring manuals.

When participants missed an entire time point or a whole questionnaire at a given time point, missing data were not replaced. Only fully completed sub-tests of the NP measures at any time point were used in the analyses. There were no cases where data was considered not applicable. If someone chose not to complete a subtest it was considered missing. For example, if a participant was unable or refused to do the Grooved Pegboard (GP) with one of his/her hands due to arthritis or some other pain the measure was considered missing.

For missing data at the scale level and item level (where scales were not viable), multiple imputation (MI) was conducted using MCMC procedures within the SPSS MULTIPLE IMPUTATION procedure (m=10). Data from all time points was used to predict the missing data, but the three time points were imputed separately only for participants who provided data at that time point. The resultant 10 datasets were individually analysed using the regular statistical procedures. Rubin's rules for combining multiple imputations (Rubin, 1987; Schafer & Olsen 1998) were then utilised to combine the results from the 10 datasets. In analyses including only variables where <10% data was missing, a single imputation was analysed.

8.2.3 Data assumptions

8.2.3.1 Normality

Although it has been argued that parametric tests tend to be robust to moderate violations of assumptions in relatively large samples (i.e. over 30)(Field, 2009; Tabachnick & Fidell, 2007) a number of steps were taken to check the normality of data for all dependent variables (DVs). The significance ($p < .001$) as suggested by Tabachnik & Fidell, 2007) of the Shapiro Wilk test was considered, as shown in Appendix O. A significant result indicates non-normal distribution. It was significant for most NP measures, HADS anxiety and depression, FACT-C physical wellbeing (PWB), emotional wellbeing (EWB) and social wellbeing (SWB) subscales, FACIT fatigue and all of the FACT Cog subscales at all time points as shown in Appendix O. The distribution of the variables was also examined visually by exploring the data using histograms and Q-Q plots. It is usual for measures such as depression and fatigue not to be normally distributed in a normal population. It is expected that the majority of people are not

depressed or fatigued in the general population, although as discussed in Chapter 2 Section 2.4.3, in the context of cancer patients a larger proportion may be feeling fatigued and/or depressed.

Although data that is non-normally distributed may be transformed (using mathematic formulas to attain a more normal data distribution) when conducting statistical analysis only the NP measures were transformed, in this study. Unless stated otherwise, non-parametric tests were used where the data was not normally distributed.

8.2.3.2 Outliers

Boxplots and standardised z scores greater than ±3.29 (Tabachnick & Fidell, 2007) revealed a number of outliers on the NP tests (in particular TMT B, HVLT-R retention and GP). Outliers are observations that lie an abnormal distance from other observations. An outlier may be due to variability in the measurement or it may indicate experimental error, which can cause serious problems in statistical analyses. Researchers disagree on whether outliers should be removed from the analysis. Unless they are erroneous data entries, outliers may contain valuable information and can represent the inherent variability of the variable in question (Orr, Sackett, & DuBois, 1991). In addition, removing cases that have random outlying scores may greatly reduce the sample size. Therefore, outliers were retained in order to maximise sample size and because it was believed that in this study, they would provide valuable information regarding the relationships studied.

8.2.3.3 Floor and ceiling effects

Floor and ceiling effects in all measures were assessed. A floor effect occurs when the majority of the participants score near the bottom of the scale. Whereas a ceiling effect occurs when most of the participants score at the top of the scale. Such effects indicate that the measure does not have the sensitivity or range of scores to differentiate the group of participants well. It therefore limits the utility of the scale. For example, in a longitudinal study a questionnaire may be unable to detect further deterioration or improvement in a group of participants if a high proportion of the group scored at the scale minimum or maximum (respectively).

In the present study, there were no median values the same as the minimum or maximum values of any NP measure. On the questionnaire measures, however there was one subscale on the FACT Cog, which asked participants to report on what others had said to them about their cognition ('Comments from Others' FACT Cog (Oth)), where 68 participants (83%) said that they had never been told by other people that they were having any cognitive difficulties. On all of the other measures less than 25% of the participants scored at the minimum or maximum so floor and ceiling effects were not considered to be substantial.

8.2.3.4 Scale reliability

All scales and subscales of the psychosocial questionnaires used in the study showed good internal reliability based on Cronbach's alpha scores (Table 8.1) ranging from 0.376 to 0.977, Cronbach's alpha of > .70 are generally considered optimal (Clark & Watson, 1995).

Table 8.1 Internal reliability of all scales at each time point

Scales & Subscales	No of Items	Cronbach alpha		
		T1	**T2**	**T3**
HADS				
HADS Anxiety	7	.840	.881	.895
HADS Depression	7	.720	.711	.766
FACT C				
PWB	7	.800	.842	.828
SWB	7	.784	.791	.801
EWB	6	.727	.789	.792
FWB	7	.815	.864	.879
CCS	7	.632	.638	.744
	9[1]	.410[2]	.376	.692
FACT Cog				
PCI	18	.977[3]	.951	.958
Oths	4	.767	.912	.764
PCA	7	.918	.900	.928
QoL	4	.916	.921	.923
FACIT Fatigue	13	.923	.931	.952

Key: FACT C CCS[1] = the extra 2 items are in relation to a stoma which not all patients had fitted
FACT C CCS[2] = the extra 2 items only applied to a small number of patients
PCI[3] = Scales with a large number of items may cause an inflated Cronbach's alpha;
FACT C subscales: PWB: Physical wellbeing; SWB: Social wellbeing; EWB: Emotional wellbeing; FWB: functional wellbeing; CCS: Additional colorectal concerns; FACT Cog subscales: PCI: Perceived cognitive impairments; Oths: Comments from others; PCA: Perceived cognitive abilities; QoL: Perceived Impact on quality of life.

Although the FACT C CCS scale has a poor alpha coefficient when the additional 2 items relating to the stoma are added, the scale was still used in this study. The reason being that the items of concern are very different from the rest of the items and only apply to a small number of participants.

8.2.3.5 Level of statistical significance

For all preliminary and main analyses the level of statistical significance was set at $p<0.01$. This significance level was considered most appropriate in light of the large number of tests performed and the risk of obtaining a false-positive result i.e. rejecting the null hypothesis when it is in fact true (Type 1 error).

8.3 Statistical analysis strategy for Research Question One

8.3.1 Demographic and clinical characteristics of the sample

Differences in socio-demographic characteristics between participant groups (IV: (chemotherapy and "surgery only") were analysed using independent sample t tests for continuous variables (DVs: anxiety, depression, fatigue, and subjective cognitive function) and Chi-square ($\chi 2$) tests for independence for categorical variables (e.g. gender, English as a first language and type of surgery). The Fisher's exact probability test was reported where cell counts were lower than 5 and for 2x2 analysis. Cramer's V (φc) (.10= small, .30= medium, .50= large) and Cohen's d (0.2= small, 0.5= medium, 0.8= large) effect size measures were reported for $\chi 2$ tests and t-tests respectively. Means and standard deviations for continuous variables and frequencies with percentages for categorical variables are presented where appropriate.

8.3.2 Cognitive impairment at T1

As an initial step, analyses were conducted on the post-surgery pre-chemotherapy baseline data (T1) to identify

1.1 Prevalence of OCI prior to systemic treatment in each group;

1.2 The most commonly affected domains of cognitive functioning in each group; and

1.3 Differences between the participant groups on the following DVs: anxiety, depression, fatigue and self-reported cognitive function.

8.3.2.1 NP data scoring

To judge the nature of performance on a test relative to the normative data, the raw score was converted to a standardised score for each test (except for the Benton Visual Retention Test (BVRT) and Digit Span as described below). Following the procedure of the ICCTF (Wefel et al, 2011), raw scores on the NP tests were converted into z scores (mean=0, SD=1) using published normative data adjusted for age, education, and gender as shown in Appendix P. The z score is expressed in terms of standard deviation units from the mean of the general population. Such conversion allows the researcher to determine the participants' relative standing compared with the normative group, it also allows for a direct comparison of scores across different tests.

In relation to the Digit Span forward and backward tests, the raw scores were used to establish impairment, in accordance with Lezak's advice that it '*makes more sense to deal with the data in raw score form than to convert them*' (Lezak 2004, p 404) for this test. The procedure used is outlined in Appendix P. Raw scores were also used for

establishing impairment on the BVRT in accordance with the guidelines provided in the manual also detailed in Appendix P.

8.3.2.2 Criteria used for establishing cognitive impairment

After evaluating each participant's test performance in order to determine if there was OCI, one out of the two following criteria had to be met:

1) z scores of ≤−1.5 SD below the normative mean score for two or more NP tests (1.5 SD criteria); or
2) z scores of ≤−2.0 SD below the normative mean score for just one NP test (2 SD criteria)

as recommended by the ICCTF (Wefel, 2011).

It is important to bear in mind that cognitively intact individuals are likely to vary in their performance on any cognitive test battery and may score in the impaired range by chance on 1 to 2 tests in any given cognitive test battery (Taylor and Heaton, 2001, Lezak, et al, 2012). In addition, the probability that individuals will have deviant test scores rises as the number of tests in the battery is increased (Ingraham & Aitken, 1996). Therefore, when using multiple measures in test batteries additional factors such as the risk of overestimating the extent of cognitive impairment needs to be taken into account. Ingraham and Aitken, (1996) suggest that a mathematical formula based on binominal theory should be used to calculate the probability of finding impairment in the normal population based on the number of tests utilized, and the established cut-off criteria for cognitive impairment employed (i.e. 1.5 and 2SD). Although this approach assumes independence between the tests, they justify the formula even when the tests are not independent as long as the user is aware and exercises caution, as the estimates

provided of the percentage of the population exhibiting impairment may be reported as being higher than expected. (I.e. they acknowledge that the binomial approach can overestimate the required percentages, due to the additional variance, correlated scores may add).

The present study included seven measures each with a number of subscales that produced 15 scores in total. As the size of the test battery could influence the number of abnormal test results obtained, the equations of Ingraham and Aiken (Ingraham & Aiken, 1996) were used (in accordance with the recommendations of the ICCTF (Wefel et al, 2011) to determine whether the frequency of observed OCI exceeded expectation based on use of multiple measures. In order to determine if the proportion of participants found to be impaired was higher than the expected value (for each criteria) a one-sample proportions test for the total sample was undertaken.

8.3.3 Relationships between NP measures and psychosocial outcomes

Bivariate correlational analysis (Pearson's correlations for parametric data and Spearman's rho for non-parametric data) was used to assess the relationships (if any) between the NP test scores and psychosocial outcomes.

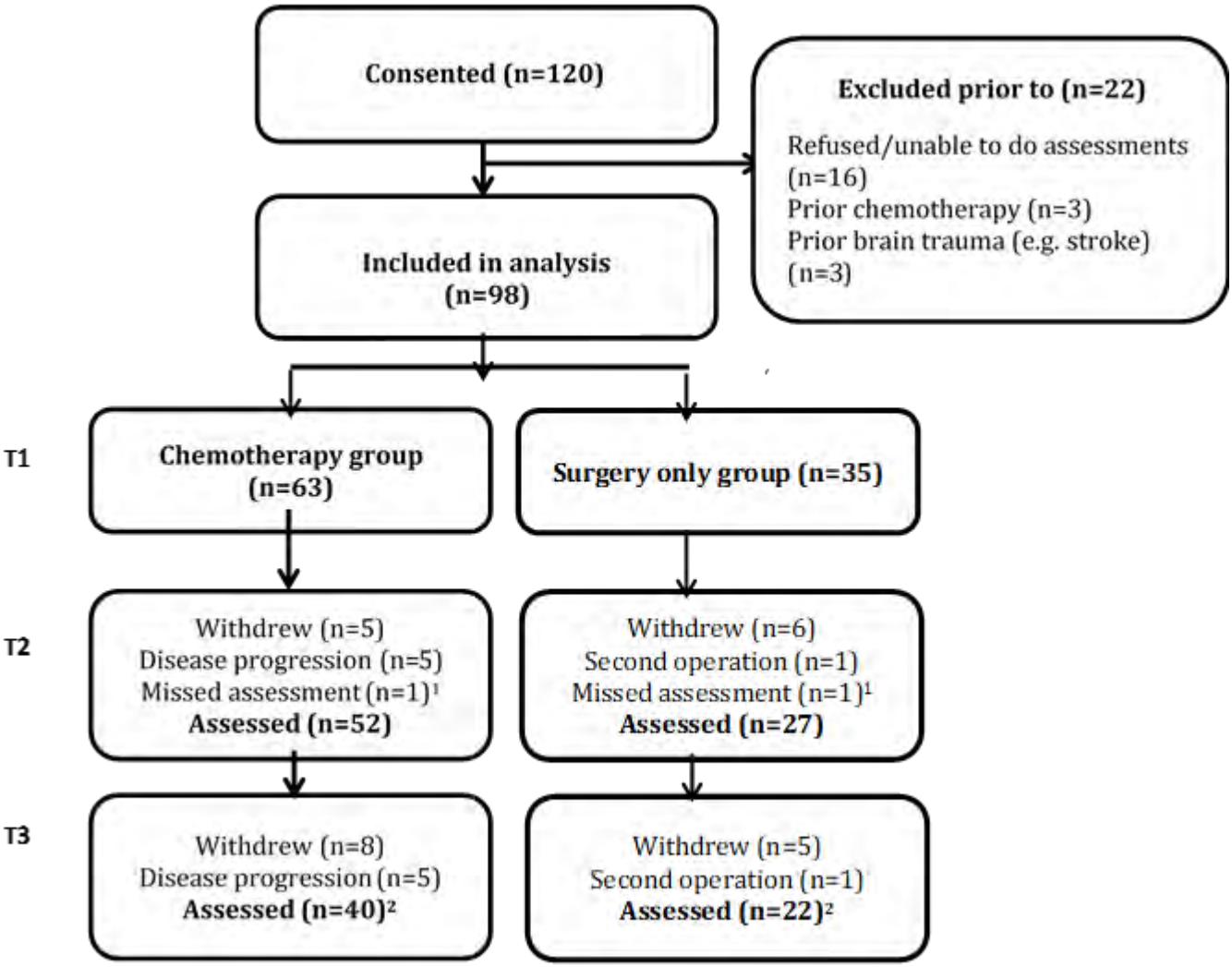
8.4 PRE-CHEMOTHERAPY TREATMENT RESULTS

Research Question One: What is the nature and extent of cognitive impairment in resected CRC patients prior to chemotherapy treatment?

8.4.1 Participation rates

One hundred and twenty patients meeting the study inclusion criteria provided written consent to take part in the quantitative study. However, of the 120 consenting patients, 6 (5%) were ineligible based on the inclusion/exclusion criteria and 16 (13.33%) withdrew from the study prior to the first assessment as illustrated in Figure 8.1 Due to ethical reasons in relation to accessing the patient records of individuals who did not consent, examining differences in key demographic and clinical characteristics between participants and non-participants was not possible. The final sample in the quantitative analyses at T1 consisted of 98 participants: 63 chemotherapy participants and 35 "surgery only" participants (Figures 8.1 & 8.2).

Figure 8.1. Flow diagram of participation rates for the longitudinal quantitative study



[1] = one participant was temporarily unavailable to complete T2
[2] = this number includes the participant who did not complete T2 but returned to complete T3

8.4.2 Demographic and clinical characteristics of the sample

Table 8.2 summarises the demographic characteristics for the two participant groups (i.e. the chemotherapy group and "surgery only" group) after surgery at (T1). Demographic and clinical information was reported for all participants with available data in those variables (n= 98).

Table 8.2: Demographic and medical characteristics for all participants at T1

Characteristic	**CT group** (n=63)	**Surgery only group** (n=35)	**Test Statistic**	**df**	**Significance**	**Effect size**
Mean age in years (SD)	61.78 (10.123)	65.49 (12.189)	t=1.574	96	.119	Cohens d = -.30
Age range in years	31-80	25-84				
Mean FSIQ score (SD)	103.76 (19.172) (n=62)	102.00 (20.978) (n=31)	t=-.404	91	.274	Cohens d = .08
Education						
• < 12 years	17	10	Fishers exact test		1.00	V=.017
• > 12 years	46	25				
Gender						
• Male	29 (46%)	20 (57%)	Fishers exact test		.399	V=.106
• Female	34 (54%)	15 (43%)				
Marital Status						
• Single[1]	25	18	χ^2=.829	1	.363	V=.113
• Married[2]	38	17				
Occupational Status						
• Employed[3]	25	14	Fishers exact test		.833	V=.028
• Not employed[4]	36	21				
• Student[6]	2	0				
Nationality						
• UK[5]	54	24	Fishers exact test		.066	V=.204
• Other	9	11				
Native English Speaker						
• Yes	51	25	Fishers exact test		.318	V=.109
• No	12	10				
Tumour stage [7]						
• Stage I	2	9	χ^2=44.195	4	.000	V=0.672
• Stage II	14	24				

Characteristic	CT group (n=63)	Surgery only group (n=35)	Test Statistic	df	Significance	Effect size
• Stage III	43	2				
• Stage IV	4	0				
Tumour site[7]						
• Colon	44	24	χ^2=1.185	2	.110	V=0.553
• Rectal	12	9				
• Colon & rectal	7	2				
Type of surgery						
• Keyhole	37	24	χ^2=.425	1	.514	V=-.088
• Open	25	11				
Stoma						
• Yes	18	9	Fishers exact test		.817	V=0.31
• No	45	26				
Comorbidities						
• None	17	12	t=-1.063	96	.290	Cohens d = .24
• 1 or 2	31	17				
• 3 or 4	15	6				
Mean (SD) number of days from surgery to T1 assessment	47.76 (16.11)	52.74 (23.22)	t=-1.248	96	.005	Cohens d = -.21

Key: CT: Chemotherapy group**; [1]** Includes divorced and widowed participants; [2]Includes defacto couples; [3]Employed includes full and part time; [4]Not employed includes unemployed, retired & homemaker; [5] UK includes English, Welsh, Scottish, Northern Irish, British; [6]Students were counted as being employed in the analysis; [7]Tests not run for these variables because of the low cell counts. V= Cramer's V

As can be seen in Table 8.2 there were no significant group differences found for gender, marital status, English as a first language or nationality. The overall mean age for the whole sample was 63.10 years (SD 11.26) (range: 25-84) with 49 (50%) males and 49 (50%) females in the total sample. The mean age for the chemotherapy group was slightly younger at 61.78 compared to a mean age of 65.49 years in the "surgery only" group. There were also proportionally less males in the chemotherapy group (46%)

than the "surgery only" group (57%) and more than half of the participants in the chemotherapy group were married or in a relationship (60.3%) (Figure 8.2) and the majority were unemployed in both groups (57% and 60% respectively).

Figure 8.2: Participants demographic characteristics at the first assessment

Chemotherapy patients	**Surgery only patients**
	
N = 63	**N=35**
Age: 31 - 80	Age: 25 - 84
M= 61.8 ; SD = 1.28	M= 65.5 ; SD = 2.18
Male: 29 (46%); Female: 34 (54%)	Male: 20 (57%); Female: 15 (43%)

There was no significant difference in years in education or IQ scores for the two groups (Table 8.2). The level of education of the study sample was initially classified into seven sub-groups but due to the small proportion in many categories (e.g. primary, secondary school, degree, masters and doctorate) groups were combined into a dichotomous variable (≤12 years and > 12 years, as this was how the norms used were split), with most of the study sample having been in education more than 12 years.

Sixty three percent of the participants had keyhole surgery but the groups did not differ significantly in terms of the type of surgery or type of cancer (i.e. rectal, bowel or both).

Although as expected, the cancer diagnosis was more advanced in the chemotherapy group with 74.6% having stage 3 or above compared to 5.71% in the "surgery only" group. Just over half of the individuals in the chemotherapy group (54%) were scheduled to have 12 chemotherapy cycles (i.e. FOLFOX/5FU), and the rest were scheduled to have 8 cycles. 73% of the chemotherapy group had at least one comorbidity. However, there were no significant differences between the groups in the number of co-morbidities reported by participants, t (96) = 1.13 p= .290; or in time from surgery to the first assessment t (96) = 1.248 p= .005.

8.4.3 Research Objective 1.1: Prevalence of cognitive impairment prior to systemic treatment in each group

There was cognitive impairment in both groups after surgery and prior to the start of the chemotherapy treatment (T1) as shown in Table 8.3.

Table 8.3: The number and percentage of participants found to be cognitively impaired at T1 according to the ICCTF criteria:

	1.5 SD criteria					2 SD criteria				
	No (%) impaired	**χ^2**	**df**	**Signifi-cance**	**Effect size (V)**	**No (%) impaired**	**χ^2**	**df**	**Signifi-cance**	**Effect size (V)**
CT (n=63)	33 (52.38%)	1.003	1	.317	.101	29 (46.03%)	1.757	1	.185	.131
Surgery only (n=35)	22 (62.86%)					21 (60%)				
Total sample (n=98)	55 (56.1%)					50 (51%)				

Key: CT: Chemotherapy patient group

There was no statistically significant difference between the groups in terms of impairment (Table 8.3) at T1 (irrespective of the criteria):

- 1.5 SD criteria: χ^2 (1, n=98) =1.003, p=.317

- 2 SD criteria: χ^2 (1, n=98) =1.757, p=.185.

52.38% of the chemotherapy patient group and 62.86% of the sample "surgery only" patient group showed impairment on the ICCTF's 1.5 SD criteria. Whereas a smaller proportion of participants in each group (46.03% and 60% respectively) exhibited impairment on the ICCTF's 2SD criteria.

These findings appear to show that there is no association between type of treatment and cognitive impairment, as measured in this study sample.

Based on the number of test scores and the impairment criteria used in the present study, the estimation provided by Ingraham and Aiken (1996) suggests that approximately 30% of the sample can be expected to exhibit impairment on at least two tests using an impairment criterion of 1.5SD and 34% of the sample can be expected to exhibit impairment on at least one test using an impairment criterion of 2SD.

A chi square goodness of fit test indicates that there was a statistically significant difference in the proportion of impaired participants identified in the whole sample (56.1%) as compared with Aiken's 30%, (when using the 1.5 SD criterion), χ^2 (1, n=98) =31.845, p=.00.

There was also a statistically significant difference in the proportion of impaired participants identified in the whole sample (51%) as compared with Aiken's 34%, (when using the 2 SD impairment criterion), χ^2 (1, n=98) = 12.652, p=.00.

So, although there is no statistically significant difference between the groups (i.e. both groups are similar in terms of impairment); as whole, the entire sample is significantly

impaired at T1 compared to what would be expected in a normal population matched for age, gender and education.

8.4.4 Research objective 1.2: The most commonly affected domains of cognitive functioning in each group.

As can be seen in Table 8.4 the most commonly affected cognitive domain(s) for the whole sample were executive function, motor function and verbal memory. The "surgery only" group were proportionally more impaired than the chemotherapy group at T1 on both tests of executive function and on the verbal memory recall and recognition tests (HVLR – recall and recognition) on both criteria of impairment. Also, 26.98% and 25.71% in the chemotherapy and "surgery only" groups respectively were found to be impaired on the Digit Span backwards when using the 1.5 SD criteria.

When using 2 SD criteria, no one in the "surgery only" group and very few in the chemotherapy group were found to be impaired in attention as measured by Digit Span or visual memory as measured by the BVRT correct score.

Table 8.4. The number and percentage of participants in each group found to have cognitive impairment at T1 on each of the NP measures

Domain	NP measure	Total number (%) of participants[1] who scored 1.5 SD below normative mean on each measure		Total number (%) of participants[1] who scored 2 SD below normative mean on each measure	
		CT (n=63)	Surgery only (n=35)	CT (n=63)	Surgery only (n=35)
Attention and visual-motor ability	TMT A	3 (4.76)	5 (14.29)	2 (3.17)	5 (14.29)
	DS forward	4 (6.35)	3 (8.57)	0	0
	DS backward	17 (26.98)	9 (25.71)	2 (3.17)	0
Concentration	SDMT written	4 (6.35)	1 (2.86)	4 (6.35)	0
	SDMT oral	6 (9.52)	5 (14.29)	5 (7.94)	2 (5.71)
Executive Function	TMT B	8 (12.70)	5 (14.29)	7 (11.11)	5 (14.29)
	COWA	12 (19.04)	10 (28.57)	5 (7.94)	5 (14.29)
Motor Function	GP dom	14 (22.22)	5 (14.29)	11 (17.46)	4 (11.43)
	GP non dom	16 (25.40)	14 (40)	14 (22.22)	10 (28.57)
Verbal Memory	HVLT R recall	13 (20.63)	13 (37.14)	9 (14.29)	6 (17.14)
	HVLT R delay	14 (22.22)	11 (31.43)	9 (14.29)	4 (11.43)
	HVLT R retention	13 (20.63)	6 (17.14)	10 (15.87)	5 (14.29)
	HVLT R recognition	9 (14.29)	7 (20)	4 (6.35)	4 (11.43)
Visual Memory	BVRT - Correct	4 (6.35)	1 (2.86)	1 (1.59)	0
	BVRT - Error	9 (14.29)	3 (8.57)	6 (8.06)	2 (5.71)

Key: Participants[1]: these numbers came from pooled imputed dataset, they have been rounded down if below .5 and up if above. TMT A/B: Trail Making Test; DS forward/backward: Digit Span forward/backward; SDMT written/oral: Symbol Digit Modalities Test written/oral; COWA: Controlled Oral Word Association Test: GP dom hand: Grooved Pegboard dominant hand; GP non dom Grooved Pegboard non dominant hand; HVLT R: Hopkins Verbal Learning Test -Revised; BVRT: Benton Visual Retention Test.

As can be seen in Table 8.5 there were no statistically significant differences between the groups in relation to the mean z scores on all of the NP measures. However, both

groups show more deficits across all tests at baseline (i.e. after surgery and pre-chemotherapy treatment/3-8 week's post-surgery) than would be expected by chance.

Table 8.5 Mean z scores and standard deviations at T1 on each of the NP measures in each participant group

Domain	NP measure	CT (n=63)	Surgery only (n=35)	t	df	Signifi-cance	Effect size
		Mean z score (SD)	Mean z score (SD)				
Attention and visual-motor ability	**TMT A**	.2969 (3.27)	.0166 (1.44)	.480	96	.631	.19
	DS forward[1]	9.95 (2.47)	9.54 (2.43)	.791	96	.429	.17
	DS backward[1]	6.48 (2.62)	6.31 (2.207)	.309	96	.757	.08
Concentra-tion	**SDMT written**	.2212 (1.20)	.0646 (.87)	.724	96	.469	.18
	SDMT oral	.1841 (.122)	-.2029 (.98)	1.632	96	.103	.39
Executive Function	**TMT B**	.2479 (1.92)	-.0644 (2.79)	.631	96	.515	.11
	COWA	-.3369 (1.27)	-.3488 (1.46)	.042	96	.966	.01
Motor Function	**GP dom**	-1.2012 (3.64)	-.6459 (1.42)	-.864	96	.387	-.39
	GP non dom	-1.2618 (3)	-1.3252 (1.73)	.115	96	.909	.04
Verbal Memory	**HVLT R recall**	-.7179 (1.14)	-.9356 (1.10)	.915	96	.360	.20
	HVLT R delay	-.7369 (1.43)	-.7698 (1.15)	.117	96	.907	.03
	HVLT R retention	-.5638 (1.95)	-.4048 (1.24)	-.435	96	.664	-.13
	HVLT R recognition	-.3065 (1.13)	-.4628 (1.39)	.602	96	.547	.11
Visual Memory	**BVRT – Correct[1]**	6.22 (1.84)	6.56 (1.46)	-.894	96	.372	-.23
	BVRT – Error[1]	5.68 (3.71)	5.85 (2.56)	-.231	96	.817	-.07

Key: [1]the mean raw scores are reported for this measure; CT: chemotherapy patient group; TMT A/B: Trail Making Test; DS forward/backward: Digit Span forward/backward; SDMT written/oral: Symbol Digit Modalities Test written/oral; COWA: Controlled Oral Word Association Test: GP dom hand: Grooved Pegboard dominant hand; GP non dom Grooved Pegboard non dominant hand; HVLT R: Hopkins Verbal Learning Test -Revised; BVRT: Benton Visual Retention Test.

8.4.5 Research objective 1.3: The relationships between demographic, clinical and psychosocial factors and objectively measured cognitive functioning

Anxiety

An independent samples t –test was conducted to compare the anxiety scores for the "chemotherapy" group and "surgery only" group. It showed that the two participant groups did not significantly differ on levels of anxiety (M= 5.8, SD = 3.93) for chemotherapy participants and (M=6, SD =3.94) for "surgery only" participants at T1; t (96) = .238, p = .813. The magnitude of the difference in the means was very small (eta squared = .05)

A similar proportion of participants in each group reported feelings of definite anxiety: Eight (12.70%) in the chemotherapy group and four (11.43%) in the "surgery only" group (scored > 11 on the anxiety subscale (i.e. definite anxiety)). A larger proportion of participants in both groups: 12 (19%) in the chemotherapy group and eight (22.90%) in the "surgery only" group scored in the 'doubtful case' range (Zigmond & Snaith, 1983).

Depression

An independent samples t –test also showed that the two participant groups did not significantly differ on levels of depression (M= 4.1, SD = 4.17) for "chemotherapy" participants and (M=4.1, SD = 4.11) for "surgery only" participants at T1; t (96) = -0.86, p = .932. The magnitude of the difference in the means was also very small (eta squared = .02)

Fewer participants (than had reported experiencing anxiety) in each group scored more than 11 (i.e. definite depression) or between 8 & 10 (i.e. doubtful depression): with two

(3.17 %) and 6 (9.52%) participants respectively in the chemotherapy group and one (2.86 %) and three (8.57%) in the "surgery only" group.

Table 8.6 Means and standard deviations for fatigue, mood and HRQoL

Measures and subscales	CT (n=63)		Surgery only (n=35)		T- stat	p	df	Effect size
	Mean	SD	Mean	SD				
FACIT Fatigue (0-52)	36.89	10.65	36.50	11.06	-.169	.866	95	0.04
HADS Anxiety (0-14)	5.80	3.94	6	3.93	.238	.813	96	-0.05
HADS Depression (0-14)	4.17	3.03	4.11	3.11	-.086	.932	96	0.02
FACT C Global score (0-136)	105.9	17.29	102.58	14.36	-.965	.334	96	0.23
PWB (0-28)	22.04	4.87	21.56	5.62	-.440	.660	96	0.09
SWB (0-28)	24.53	4.96	23.21	3.76	-1.366	.172	96	0.35
EWB (0-24)	19.14	4.20	19.32	3.83	.213	.813	96	-0.05
FWB (0-28)	19.64	5.53	17.63	6.12	-1.656	.101	96	0.33
CCS (0-28)	20.55	4.99	20.55	4.69	-.043	.098	96	0.00

Key: CT: Chemotherapy; HADS: Hospital Anxiety and Depression Scale; FACT C subscales: PWB: Physical Well Being; SWB: Social Well Being; EWB: Emotional Well Being; FWB: Functional Well Being; CCS: Colorectal Cancer Specific Items.

Fatigue

As mentioned in Chapter 7, higher scores on the FACIT Fatigue scale indicate less fatigue. A score of < 37 was used to define significant fatigue in two studies that used this scale for patients with breast cancer (Wratten et al, 2004; Lange et al, 2014). The use of this score to define significant fatigue was based on the work of Cleeland and colleagues (1999). Therefore on that basis 41.2% of the entire sample (24 (38.09%)) patients in the chemotherapy group and 16 (47%) in the "surgery only" group) in this study reported having experienced clinically significant symptoms of fatigue. The mean

score was just over 36 for participants in both participant groups. There were no statistically significant differences between the "chemotherapy" and "surgery only" groups in levels of fatigue (p=.866).

HRQoL

There were no statistically significant differences between the chemotherapy and "surgery only" groups in relation to any of the FACT C quality of life subscales.

As mentioned in Chapter 7, higher scores on each of the FACT C subscales indicate better quality of life. A comparison of normative mean scores found in the general U.S. adult population sample (Brucker et al, 2005) (see Appendix Q) showed that this sample of participants had comparable scores to the general U.S. adult population sample. Very small differences in PWB (chemotherapy M=22.04; "surgery only" M=21.56; US general population M=22.7), EWB (chemotherapy M=19.14; "surgery only" M=19.32; US general population M=19.9) and FWB (chemotherapy M=19.64; "surgery only" M=17.63; US general population M=18.5) were noted in relation to both groups. However there was a meaningful difference (i.e., > 2 points) on the SWB subscale between the general U.S. adult population norms (M = 19.1) and the chemotherapy group (M=24.53) and the "surgery only" group (M=23.21). This suggests that both participant groups in this study diagnosed with CRC (whether or not scheduled for adjuvant chemotherapy treatment) are actually comparable to those in the general US population in respect of physical, emotional, and functional wellbeing at T1 but not social well being which is actually better in this study. It may be that the participants in this study received more social support than that reported in the general US population,

which could be explained by the social support need caused by a serious illness that recently required surgery.

Table 8.7: Table of correlations between each NP measure and mood, fatigue, HRQoL and perceived cognitive impairment

		Digit Span		SDMT		TMT		HVLT –R				BVRT		GP		COWA
		For Ward	Back-ward	Written	Oral	A	B	Recall	Delay	Reten	Rdi	Correct	Error	Dom	Non Dom	
HADS	Anxi-ety	0.083	-0.139	-0.017	0.014	-0.174	-0.099	0.004	-0.144	**-0.224**	-0.020	0.004	0.072	-0.031	0.096	0.126
	Dep	0.092	-0.139	0.015	0.013	-0.098	-0.098	-0.003	-0.090	-0.145	0.087	0.025	0.005	-0.081	-0.084	0.152
FACIT Fatigue		0.012	0.032	-0.016	-0.030	0.048	0.073	-0.073	-0.069	-0.031	-0.098	-0.065	0.100	0.042	-0.055	-0.085
FACT C	PWB	0.057	0.109	0.149	0.038	0.069	0.105	0.084	0.108	0.045	-0.106	0.004	0.108	0.033	0.030	0.061
	SWB	-0.062	0.016	0.027	0.097	0.121	0.167	0.088	0.048	-0.120	-0.112	0.041	-0.046	0.185	0.107	-0.042
	EWB	-0.063	0.154	0.039	0.081	**0.254**	0.184	-0.086	0.033	0.105	-0.136	-0.030	-0.086	0.165	0.076	-0.146
	FWB	0.045	0.132	0.070	0.167	0.190	0.087	0.035	0.055	-0.031	-0.020	0.026	-0.056	0.188	0.088	-0.098
	CCS	-0.189	-0.059	-0.033	0.034	-0.047	0.113	-0.043	-0.085	-0.099	**-0.227**	0.000	-0.052	0.122	0.010	-0.186
	Total Score	-0.030	0.101	0.055	0.151	0.165	0.189	0.053	0.060	-0.046	-0.142	0.020	-0.017	0.173	0.074	-0.138
FACT Cog	PCI	-0.079	-0.014	-0.053	-0.116	-0.097	-0.129	-0.086	-0.075	-0.036	-0.065	-0.150	0.140	0.066	0.015	-0.077
	PCA	0.018	-0.003	0.047	0.036	-0.086	-0.054	0.052	0.001	-0.031	0.025	-0.064	0.088	-0.054	-0.117	0.000
	Oths	-0.053	0.109	0.004	-0.041	-0.056	-0.097	0.113	-0.001	-0.020	0.018	-0.134	0.083	-0.008	0.028	-0.047
	QoL	-0.017	-0.017	0.091	0.000	0.042	0.150	0.019	0.075	0.163	-0.030	**-0.287**	**0.225**	0.134	0.056	-0.088

Key: RED = significant at .01; Blue = significant at .05; HADS Dep= depression subscale; FACT C subscales: PWB: Physical Well-being; SWB: Social Well-being; EWB: Emotional Well-being; FWB: Functional Well-being; CCS: Colorectal Cancer Subscale; FACT C total = PWB + SWB + EWB + FWB +CCS; FACT Cog subscales: PCI: Perceived Cognitive Impairment; Oths: Comments from Others; PCA: Perceived Cognitive Ability; QoL: Impact on quality of life.

Relationship between psychosocial outcomes and objective cognitive function

The relationship between anxiety, depression, fatigue, quality of life and subjective cognitive impairment was investigated using Spearman Rho correlation coefficient, after having carried out preliminary analyses to ensure no violation of the assumptions of normality, linearity and homoscedasticity.

Weak correlations were found between verbal memory (as measured by the HVLT-R) and anxiety and verbal memory and perceived colorectal cancer symptoms/concerns (FACT C CCS) (Table 8.7). There was also a weak positive correlation between attention (as measured by the TMTA) and perceived emotional wellbeing (FACT C EWB).

There was a weak-moderate negative and a weak positive correlation between visual memory (as measured by the BVRT correct and error) and perceived cognitive impairment impact on quality of life (FACT Cog QoL) rho =-0.287, $p<0.01$, and rho= .225, $p<0.05$ respectively; with lower perceived QoL associated with less correct and also more visual memory inaccuracies.

8.4.6 Perceived Cognitive Impairment

There were no statistically significant differences between the groups on any of the FACT Cog subscales: perceived cognitive abilities (PCA); perceived cognitive impairment (PCI); impact on quality of life (QoL) or comments from others (Oth). The mean scores for the Fact Cog subscales found in each group are presented in Table 8.8. As discussed in Chapter 7, the higher the score the less percieved cognitive impairments.

Table 8.8: Table of means and standard deviations for perceived cognitive impairment in each group

FACT Cog subscales	**CT (n=63)**		**Surgery only (n=35)**		**T- stat**	**p**	**df**	**Effect size**
	Mean	**SD**	**Mean**	**SD**				
PCI (0-72)	57.37	13.10	57.79	12.48	.160	.873	96	-.03
PCA (0-28)	20.82	6.44	20.37	7.14	-.320	.749	96	.07
QoL (0-16)	11.95	4.39	11.34	4.28	-.664	.520	96	.14
Others (0-16)	14.90	2.04	15.52	1.08	1.945	.098	95.77	-.58

Key: CT: Chemotherapy; FACT Cog subscales: PCI: Perceived Cognitive Impairment; PCA: Perceived Cognitive Ability; QoL: Impact on Quality of Life; Others: Comments from others

Anxiety, depression and fatigue were all significantly moderately associated with the FACT-Cog PCI subscale (rho = -0.261, -.308 and .548 respectively) (Table 8.9) and also with FACT Cog QoL.

FACT Cog QoL was significantly moderately associated with PWB, EWB, FWD, CCS and total FACT Cog QoL.

Table 8.9: Table of correlations between each perceived cognition (FACT Cog) and mood, fatigue and HRQoL in the whole sample

Spearman r correlations	FACT Cog PCI	FACT Cog Oth	FACT Cog PCA	FACT Cog QoL
HADS Anxiety	**-.261**	-.140	**-.252**	**-.411**
HADS Depression	**-.308**	**-.283**	-.184	**-.362**
FACIT Fatigue	**.548**	**.204**	**.423**	**.415**
FACT C - PWB	**.416**	.196	**.241**	**.418**
FACT C - SWB	.115	.119	**.218**	.141
FACT C - EWB	**.206**	.099	**.225**	**.431**
FACT C - FWB	**.201**	.126	.198	**.326**
FACT C CCS	**.203**	.174	**.217**	**.255**
FACT C Total	**.271**	.172	**.293**	**.421**

Key: Red = significant at .01 (2 tailed); Blue = significant at .05 (2 tailed)
Interpretation should be r < |0.30| is no to minimal association, |0.30| ≤ r ≤ |0.60| is moderate association, and r > |0.70| is strong association
CT: Chemotherapy; FACT Cog subscales: PCI: Perceived Cognitive Impairment; PCA: Perceived Cognitive Ability; QoL: Impact on Quality of Life; Others: Comments from others; HADS: Hospital Anxiety and Depression Scale; FACT C subscales: PWB: Physical Well-being; SWB: Social Well-being; EWB: Emotional Well-being; FWB: Functional Well-being; CCS: Colorectal Cancer Subscale;

8.4.7 Research objective 1.4: The relationship between perceived cognitive function (as measured by self-assessment questionnaire FACT Cog) and objectively measured cognitive function.

As can be seen in Table 8.7 there were no significant relationships between the PCI, PCA or comments from Others subscales of the FACT Cog and any of the NP measures.

8.5 Discussion

This chapter described the demographic, clinical, and psychosocial characteristics of the study sample at T1 (after surgery and prior to the start of adjuvant chemotherapy treatment). It then went on to examine the nature and extent of OCI in the sample as well as in each of the groups. It also examined whether there was a relationship between OCI and SCI, anxiety, depression, fatigue and quality of life.

8.5.1 Participant characteristics

The study sample was split almost equally between males and females with an age range of 25 to 84 years. More than half of the participants were not working at the time of diagnosis. Clinically, the majority of participants were Stage 2 and 3 patients; with a larger proportion of the sample requiring adjuvant chemotherapy treatment. This could partly be explained by the difficulties experienced in recruiting "surgery only" patients to the study, as detailed in Dwek and colleagues (2016) feasibility study carried out as part of this thesis (Appendix J).

This study sample was similar to other CRC studies regarding the demographic and clinical characteristics of the sample such as Cruzado and colleagues (2014) who assessed 81 patients pre-chemotherapy treatment with Stage 2 and 3 CRC, between the ages of 38 and 85; 62% of which were male.

8.5.2 Cognition

In this study, we found that using the ICCTF'S criteria of a z score of:

- ≤1.5 SD below the normative mean on at least 2 NP tests; and
- ≤2 SD below the mean on at least 1 NP test (Wefel et al, 2011)

56.1% and 51% respectively of the participants were found to have cognitive impairment, which was 26.1% and 17% above the expected level of impairment. These data also indicate a higher incidence than the 37% and 43% observed by Cruzado and colleagues (2014) and Vardy and colleagues (2015) respectively, in a similar size sample of patients with CRC and with those documented in breast cancer patients at a similar point in time (i.e. before the start of chemotherapy treatment) (17to 33 %) (Ahles et al., 2008; Bender et al., 2006; Hermelink et al., 2007; Hurria et al., 2006; Mar Fan et al., 2005; Paraska & Bender, 2003; Quesnel, Savard, & Ivers, 2009; Verncombe et al, 2009; Wefel et al, 2004; Wefel et al, 2011). Such differences may have been attributable to the NP measures used in the different studies. For example, neither Cruzado (2014) nor Vardy (2015) measured motor speed, which accounted for a lot of the impairment found in this study even at baseline; both used fewer pencil and paper tests than this study.

Data from this study suggests that when examining mean pre-chemotherapy treatment performance across multiple measures and domains of cognitive functioning, patients with CRC who are scheduled for chemotherapy treatment do not differ from those that are not required to have any further systemic treatment. Therefore, based on this analysis it is reasonable to conclude that there are no pre-chemotherapy treatment differences in NP performance between the patients in the chemotherapy group and those in the "surgery only" group included in this study.

Consistent with other studies, this study found that executive function, motor function and verbal memory were the most commonly involved domains (Argyriou et al, 2011; Janelsins et al, 2011; Jim et al, 2009). Although it is unclear whether lower than expected pretreatment cognitive performance is due to adverse effect of the cancer

itself or to other unidentified factors, these results underscore the importance of designing studies with a pre-systemic chemotherapy treatment baseline evaluation (Cruzado et al, 2014).

There were no self-reported differences in cognition between the groups. There was only one statistically significant ($p<0.01$) association found between NP performance (in the domain of visual memory) and self-reported cognitive symptoms as measured by the FACT Cog CCS. (See Chapter 10 for patients' in depth perspectives on cognitive impairments.)

8.5.3 Mood

12% and 3% of the total sample exhibited anxious and depressive symptoms respectively, which is similar to what would be expected from a healthy population (Chapter 2). Anxiety was significantly ($p<0.05$) related to verbal memory (HVLR Retention). Whereas there was no significant correlation between any of the NP measures and depression which is often the case in the "cancer and cognition" studies (van Dam et al, 1998; Schagen et al, 1999; Brezden et al, 2000; Ahles et al, 2002; Tchen et al, 2003; Castellon et al, 2004; Bender et al, 2005; Jenkins et al, 2006; Mar Fan et al, 2005; Wefel et al, 2004; Wieneke et al, 1995; Cimprich et al, 2005; Cull et al, 1996; Eberhardt, et al, 2006). Although consistent with many other studies in the literature anxiety and depression were statistically significantly related to percieved cognitive impairment (as measured by the FACT Cog PCI).

8.5.4 Fatigue

Fatigue was self-reported by 42.85% of the whole sample; which was less than the 52% early-stage CRC patients (also the chemotherapy group and non chemotherapy group)

that reported fatigue in Vardy and colleagues study (Vardy 2014) (although it must be noted that a different cut off was used to define significant fatigue). The mean scores were very similar to those that Vardy and colleagues (2014) found in her study of patients with CRC. There was no significant difference between the groups in this study. Fatigue was significantly moderately associated with percieved cognitive impairment for the whole sample.

8.6 Summary

Researchers examining CRCI have emphasized the importance of using longitudinal designs that include pre-treatment NP assessments. However, in order to interpret longitudinal change, it is critical to understand whether cognitive performance is lower than expected prior to the initiation of treatment (Ahles et al, 2008). Data from the current study shows that over 50% of the patients diagnosed with and operated for CRC, compared to normative data based on age, gender and education, had cognitive impairment mainly epitomised by impaired verbal memory, motor function and executive function before any adjuvant chemotherapy treatment, which is significantly higher than what would be expected considering healthy population norms.
CRC patients about to receive chemotherapy and those who were not to receive any further systemic treatment reported similar levels of depression, anxiety, fatigue and subjective cognitive function at pre-chemotherapy treatment baseline.

Overall, the findings suggest that the present sample of people with CRC is comparable to previous studies in the literature, in relation to pre-chemotherapy measures of subjective cognitive function; mood, fatigue and HRQoL; but slightly higher in relation

to the OCI observed. The next chapter will address the second and third aims of the study by examining cognitive changes (if any) over time.

Chapter 9: LONGITUDINAL ANALYSIS AND RESULTS

Longitudinal analysis of cognitive performance in resected patients with CRC comparing those who receive chemotherapy treatment with those who do not.

9.1 Introduction

This chapter begins by discussing the methodological challenges associated with the longitudinal assessment of cognitive functioning and the different techniques commonly used to assess change in cognitive functioning. It then presents the strategy that is applied to the longitudinal quantitative analysis in this thesis before detailing the results found for:

Research Question 2: ***What is the nature and trajectory of CRCI in resected CRC patients who do or do not receive adjuvant chemotherapy treatment?*** And

Research Question 3: ***Is OCI in patients with CRC associated with lesser HRQoL?***

9.2 Cognitive functioning in the normal adult population

As discussed in Chapter 2, cognition may be affected by many factors even in the absence of cancer and/or its associated treatments. Cognitive domains such as memory, processing speed and executive function all tend to show age related decline (Deary et al, 2009). Research has shown that such declines in cognitive functioning can begin as early as ones thirties or even sooner (Park and Reuter-Lorenz, 2009). It may also be related to smoking, diet and alcohol intake (Chapter 2).

Cognitive functioning and changes in cognitive functioning can influence many different areas of an individual's life such as the ability to work, maintain meaningful relationships, self-care and overall wellbeing. Assessing the extent (if any) of impairments in cognitive functioning during the course of cancer treatment and shortly afterwards is very important given the effect that impairments may have on an individual's ability to live, make decisions (including those relating to health care) and sustain independent and fulfilling lives. A decline in cognitive functions following a diagnosis of cancer and systemic treatment may have wide spread implications for cancer survivors' quality of life (Mehnert et al, 2007).

9.3 Longitudinal assessment of cognitive functioning

Longitudinal cognitive assessments involve examining the same set of individuals on more than one occasion, using the same or psychometrically matched equivalent measures. As discussed in Chapters 3 and 4, the length of time between these consecutive assessments varies greatly across the 'cancer and cognition' studies and relates to resources (e.g. funding, time constraints); the disease itself (e.g. life expectancy, recurrence, extent of side effects) and to the research question (i.e. researchers may be exploring short term and/or long term effects, such as "Is cognitive impairment present 3, 6, 12 or 24 months post systemic treatment?").

9.4 Methodological considerations

Practice effects are characteristic of almost all NP tests when repeated during serial assessments (Bartels et al, 2010; Goldberg et al, 2015). They refer to improvements in test scores, which may result from several different factors. Practice effects could be attributed to familiarity with and exposure to instruments, items and what the testing

procedure involves (e.g., that letters and numbers alternate in TMT B) and some knowledge of the sequence of a task (e.g., that multiple trials of a word list in the HVLT-R will be administered) (Goldberg et al, 2015). Prior exposure and familiarity may also lead to a reduction in test anxiety, which could improve performance.

The period between the assessments can also be a contributing factor to the extent of practice effects. The shorter the duration between assessments the more likely the test-taker is to remember the test and the strategy applied when being reassessed. Evidence shows that practice effects may persist for as long as two years after the initial assessment (Lezak et al, 2012). The presence of practice effects makes it difficult to establish a distinction between a 'real change' and change due to prior exposure to the test being administered (or how much of any change observed is attributable to each).

It is for this reason that the ICCTF recommended the use of tests where alternate forms are available (such as HVLT-R) (Wefel et al, 2011). The alternate forms could help reduce the presence of any practice effects that may occur due to familiarity with the original test. Although the ICCTF acknowledges that the use of alternate forms will not necessarily eliminate all confounding due to practice effects (Wefel et al, 2011); alternate forms of tests such as the recommended HVLT-R were studied in the context of serial testing (which consisted of four testing sessions separated by a 14 +/– 3- day interval) and there was no significant evidence of residual practice effects found (Benedict & Zgaljardic, 1998). When using an alternate form, it is essential to check if the reliability and validity of the measure has been assessed in comparison to the original form, in order to ensure that it assesses the same function. Alternate forms must be the same style, have an equivalent number of items, type of content and method of administration as the original measure (Groth- Marnat, 2009). It is important to note

that alternate forms are not available for all NP tests and consequently researchers often have to repeat the same measure at different time points and manage practice effects via procedural design.

As mentioned, the use of alternate test versions may not entirely eliminate the problems of repeated testing (Lezak et al, 2012). Some task familiarity effects may be due to procedural learning. Whilst the content of a test is changed in an alternate form, the examinee may have still learned the style and format of the test. For example, with the TMT B whilst the numbers and letters may appear in a different position on the page the principle of alternating between the two remains the same. This is so that the two test forms are comparable. Thus making it relatively easy for the test-taker to replicate the strategy previously applied, given that the 'novelty' of the test may be lost upon reassessment, due to familiarisation with the test and its execution (Groth-Marnat, 2009). Whilst practice effects may be considered an interference when interpreting test results, they could also reflect some level of cognitive ability. The ability to learn and remember a strategy previously applied, and to re-apply it upon re-assessment is in itself indicative of some cognitive skills.

Fatigue effects also need to be taken into consideration when designing a study that will involve repeated testing. Fatigue effects refer to a decrease in performance over the course of a study particularly if the task is too long, boring or difficult. However, they can be minimised by arranging the order in which assessments are presented as was done in this study (Chapter 7, Section 7.7.1).

Another challenge often associated with repeated testing is that of the statistical phenomenon known as 'regression to the mean'. If a variable is extreme on its first

measurement, it will tend to be closer to the mean or average on its second (i.e. on a repeated measure) thus showing a relatively larger change compared to those with a moderate score at the first assessment (Barnett, Van Der Pols and Dobson, 2005). This can make a natural variation in repeated data look like a real change, and can therefore affect the true magnitude of change observed (Barnett, Van Der Pols and Dobson, 2005). If there is regression to the mean and it is not taken into account, an improved (or worse) test score could be interpreted as an improvement (or decline) in the underlying cognitive domain when there has not actually been such an improvement (or decline). One way to deal with this issue is by using residualised change scores, as these scores control for baseline variance (as described below) (Levine et al, 2007).

9.5 Measurement of change in cognitive functioning over time

In order to assess whether there is a decline or improvement in cognitive function over time the researcher needs to be able to reliably quantify the difference between the assessment scores at each time point, while controlling for the influence of confounding factors that may be responsible for the observed change. There are several ways to detect a statistically significant change in cognitive functioning over time but each technique has advantages and disadvantages.

The ICCTF (Wefel et al, 2011) recommends several of ways of analysing longitudinal data. Taking each of the recommendations in turn:

1. The use of a pre-specified Reliable Change Index (RCI) to determine change in cognitive function (Jacobsen & Truax, 1991; Chelune, Naugle, Lüders, Sedlak, Awad, 1993; Temkin, Heaton, Grant, Dikmen, 1999). RCI scores, are derived by calculating the difference between (for example) the T2 (mid-chemotherapy

treatment/3 months post T1) and T3 (post-chemotherapy treatment/6 months post T2) scores, and dividing this value by the standard error of the difference of the test scores, to obtain a standardized score (See Figure 9.1). A modified version of the RCI, RCI_{PE} has been developed in order to control for practice-induced effects (Chelune et al, 1993). Calculating the RCI_{PE} involves calculating the difference between the discrepancy of test scores (T2 and T3) and the discrepancy of the mean from the control group (M2 and M3), divided by the standard error of the difference (See formula below).

Figure 9.1:

Formula used to calculate the Reliable Change Index (RCI) and RCI_{PE}

$$RCI = (T_2 - T_1) \div S_{diff}$$

$$RCI_{PE} = (T_2 - T_1) - (M_2 - M_1) \div SED$$

T_2= time two scores
T_1= time one scores
M_1= control group mean at time one
M_2= control group mean at time two
S_{diff}= Standard Error of difference between two test scores
SED= Standard Error of the Difference

* Formula adopted from Jacobson and Truax, (1991) and Duff, (2012)

2. The use of residualised change scores. This approach utilizes a regression equation by regressing T3 scores onto T2 scores resulting in a standardized change score (derived from the two scores of each participant). These residualised change scores are adjusted for baseline variance by removing the correlation between the two scores (Prochaska, Velicer, Nigg, Prochaska, 2008)

and might be more sensitive to changes in cognitive function over time (Temkin et al, 1999; Reynolds, Gatz, Pedersen, 2002; Ouimet et al,. 2009).

3. Longitudinal modelling techniques. ICCTF suggested that growth curve, growth-mixture modelling, or linear mixed-effects models could also be applied to assess effects at group and individual levels simultaneously (Wefel et al, 2011). Growth models (also known as random coefficients models, multilevel models, and mixed effect models) are well suited for the purpose of studying change at the group as well as the individual level (Hesser, 2015) particularly when there are more than 2 time points (Hesser, 2015).

As mentioned, each of these methods have advantages and disadvantages. Whilst the RCI method is one of the ICCTF's recommended approaches (Wefel et al, 2011) it is not without its methodological challenges. The RCI_{PE} method assumes that the change in an individual test score equals the mean score of the normative group; this assumes that the degree of change in the measure over time is equal across different groups (i.e. chemotherapy patients and "surgery only" patients) which is what is being investigated here. Given that the level of cognitive functioning in patients with cancer may not be the same as the normative group, the assumption that the degree of change due to practice effects over time will be the same, could lead to an incorrect estimation of change.

The recommended multilevel modelling (MLM) technique controlling for baseline differences was used in this study rather than ANCOVAs as stated in the Protocol. Although this technique meant that an examination of changes from T1 would be forfeited the research team was of the opinion that this technique would produce a better analysis of group differences at subsequent time points. MLM allows the researcher to model the relationship between repeated measures (unlike regular

ANOVA) and accounts for all available data without dropping cases (again unlike ANOVA or any change indice). MLM can be used as an alternative to ANCOVA, where scores on the dependent variable are adjusted for covariates (e.g. individual differences) before testing treatment differences (as was done in this study). With ANCOVA's, subject's data must be excluded if they are missing a single data point. So potentially too much data would have been lost in this study. In addition MLM has less stringent assumptions, it can be used if the assumption of constant variances (homogeneity of variance, or homoscedasticity), constant covariances (compound symmetry), or constant variances of differences scores (sphericity) are violated.

9.6 Analyses strategy

This section details the statistical strategy applied to assess the aims and objectives of Research Question 2: *What is the nature and trajectory of CRCI in resected CRC patients who do or do not receive adjuvant chemotherapy treatment?* And then

Research Question 3: *Is OCI in patients with CRC associated with lesser HRQoL?*

9.6.1 Measures utilised at each assessment time point

As described in Chapter 7, the complete test battery used at T1 was re-administered to each participant at T2 and T3. To control for practice effects, alternate versions of the NP tests were used where available (TMT (2 versions), HVLT-R (Forms 1, 2 & 3) and BVRT (Forms C, D& E)). All of the other NP tests were re-administered using the original test used at T1 (DS, SDMT and Grooved pegboard). The IQ test (WAIS-III) was the only measure that was not re-administered at follow-up. Intelligence as a construct has been reported as being stable over time, with tests producing similar scores upon reassessment (Moffitt, Caspi, Harkness, Silva, 1993; Canivez and Watkins, 2001). (In the

short timeframe of this study there was no expectation of change in IQ. Nevertheless it did provide a good measure of overall cognitive ability that could be controlled for in other tests such as the BVRT where it was used as a control variable for calculating the normative score as required in the manual (Benton, 1991)). The entire test administration procedure including the order of assessments and the test-taking environment were consistent with those at T1 (see Chapter 7 for details).

9.6.2 Scoring procedures used for all measures included in the test battery

All NP tests at T2 and T3 were scored using the same scoring procedures as were used at T1 (Chapter 8, Section 8.3.2) i.e. all NP raw scores (other than for the Digit Span and BVRT measures) were converted to z scores (mean=0, SD=1) using published normative data adjusted for age, education, and gender as shown in Appendix P. The normative data used at T1 was also used at T2 and T3 (Appendix P) but was adjusted wherever a participant's age changed such that they crossed into a different boundary. All self-report questionnaires were also scored using the same procedures as at T1 (Chapter 8).

9.6.3 Preliminary data analysis

All T2 and T3 data was entered on IBM SPSS (version 25) and screened in accordance with the procedures outlined in Chapter 8, Section 8.2 for T1 data. Missing value analysis was also performed at item and scale level in accordance with the procedures outlined in Chapter 8, Section 8.2.2. for all T2 and T3 data. For missing data at the scale level and item level (where scales were not viable) multiple imputation (MI) was conducted using MCMC procedures within the SPSS Multiple Imputation procedure (m=10) as described in Chapter 8.

9.6.4 Cognitive impairment at second and third assessment

As an initial step, analyses were conducted on each of T2 and T3 data to identify

1.1 Prevalence of OCI; and

1.2 The most commonly affected domains of cognitive functioning

in each patient group at each time point.

The ICCTF specifically encourages the reporting of data on the frequency of impairment for each test (Wefel et al, 2011).

The ICCTF's recommended criteria (Wefel, 2011) was used to establish cognitive impairment at T2 and T3, following the same procedures as at T1 (Chapter 8). The frequencies of impairment for each NP test were then calculated to see which domains were the most affected.

9.6.5 Differences between the participants who remained in the study and those that withdrew after the first assessment.

An analysis was conducted to assess whether there were any differences between patients that participated in T2 and T3 and those that did not. T-tests and Pearson's chi square tests were performed to compare demographic and clinical characteristics and overall OCI of patients who had only completed T1 assessment and those that completed T2 and T3.

T tests were also performed to compare the means scores for anxiety, depression and fatigue of patients who had only completed T1 assessment and those that completed T2 and T3.

9.6.6 Multilevel modelling (MLM)

MLM was used to assess change in cognitive functioning over the 9-month study period for each NP outcome variable (Marques and Hamilton, 2014). The use of MLM is increasing in psychological research and was the method of choice in this thesis for the following reasons. It

a) allows the hierarchical structure of the data to be considered, by accounting for the non- independence of scores given on the same test/questionnaire by the same participant at multiple time points, i.e. data points are more similar within individuals over time than they are between individuals (Cartwright, Traviss and Blance, 2012); and
b) is able to include all collected data points despite missing data, which if excluded listwise can cause biases and reduce power.

The application of MLM approaches are increasingly being recommended in designs where the data has been collected from individuals on more than one occasion, as multilevel models imply that scores are clustered within each individual (Queńe and Van den Bergh, 2004). Heck and colleagues (2014) recommendations for dealing with repeated measures data using SPSS software were used to guide the analysis within this study. In preliminary steps to prepare the data for analysis, the data was restructured by the three administration time points to recognize its hierarchical nature of the different assessments within individuals. This resulted in a vertical arrangement of the data points for all participants at T1, T2 and T3 for each variable, with covariates (baseline measures) repeated for each time point. This stacking of the data resulted in a single variable for each important outcome.

Each NP score was used as the dependent variable (DV) in the main MLM analysis, with the baseline scores and participants' years of education, age and gender used as covariates, where they had not already been taken account of in the z scores. A first-order ante-dependence covariance structure (COVTYPE (AD1)) was chosen to represent the relationship between the repeated measures.

The main effect of time (a difference in scores between two assessments (T2 & T3)), main effect of group (a difference between the groups irrespective of time-points) and the time x group interaction (difference in the pattern of means between the 2 groups across time points or change in the means of the groups across time) were assessed using adjusted mean scores (estimated marginal means in SPSS).

9.6.7 Relationships between OCI and SCI

A point-biserial correlation was run to examine whether there was a relationship between deficit/no deficit OCI and SCI (as measured by FACT Cog) after first checking that the following assumptions were not violated:

- There were no outliers for any of the FACT Cog subscales or for each category of the OCI deficits.
- The FACT Cog subscales were approximately normally distributed for each category of the NP variables.
- The FACT Cog subscales have equal variances for each category of the NP variables.

9.6.8 Research Question 3: An examination of the relationship between OCI and HRQoL

A point-biserial correlation was run to examine whether there was a relationship between deficit/no deficit on each of the NP measures and HRQoL (as measured by FACT C) at T2 and at T3.

9.6.9 Level of statistical significance

For all preliminary and main analyses the level of statistical significance was set at $p<0.01$ (Chapter 8, Section 8.2.3.6).

9.7 LONGITUDINAL RESULTS

Research question 2: **What is the nature and trajectory of CRCI in patients with resectable CRC who do or do not receive adjuvant chemotherapy treatment?**

Aim 2: To investigate the nature, course and extent of cognitive impairment (both objective and subjective) in patients with resected CRC who go on to have systemic chemotherapy treatment compared to those who do not have any further treatment.

9.7.1 Participant demographic and clinical characteristics at follow up assessments

11 (17.46%) participants from the chemotherapy group and 8 (22.86%) from the "surgery only" group did not complete any of the mid-chemotherapy/3 months post T1 (T2) assessments. At 3 months after the end of treatment/6 months post T2 (T3) one of the "surgery only" participants and one of the chemotherapy participants that had missed T2, returned to complete T3. Excluding those that had returned by T3, a further

10 chemotherapy participants and 6 "surgery only" participants had dropped out. Reasons provided for non-participation are outlined in Table 9.1.

Table 9.1: Reasons for study participant exclusions and refusals at T2 and T3

	T2 (Mid CT/3 months post T1)		**T3 (3 months post CT/6 months post T2)**	
	CT	**Surgery only**	**CT[1]**	**Surgery only[1]**
Could not make contact	-	1	3	1
Health reasons (recurrence of cancer, a change to treatment, too unwell to participate, in hospital with other issues)	5	-	8	1
Other temporary commitments (travel, work)	1	2	-	3
Declined to participate again	5	5	10	6
Operation (e.g. stoma reversal)				1
Deceased	-	-	2	-
Total number of participants (cumulative rate of attrition)	**52 (17.46%)**	**27 (22.86%)**	**40 (36.51%)**	**22 (37.14%)**

Key: CT: chemotherapy; [1]This figure also includes T2 losses. Note. Attrition rates calculated from baseline value (T1).

Two of the chemotherapy participants' cancer metastasized (i.e. spread to other organs) during chemotherapy and they passed away before T3. Most participants (in both groups) simply withdrew from the study at T2 and T3 without providing a reason for withdrawal and by T3 there were 4 participants who were simply not contactable and did not return the researchers telephone calls when a message had been left for them.

Table 9.2 summarises the demographic characteristics for the two participant groups after surgery at each time point. Demographic and clinical information was reported for all participants with available data in those variables.

Table 9.2: Demographic and medical characteristics for all participants at each assessment

	T1		**T2**		**T3**	
Characteristic	**CT** (n=63)	**Surgery only** (n=35)	**CT** (n=52)	**Surgery only** (n=27)	**CT** (n=40)	**Surgery only** (n=22)
Mean age in years (SD)	61.78 (10.123)	65.49 (12.189)	61.19 (9.730)	65.52 (12.744)	62 (9.816)	69.52 (8.222)
Age range in years	31-80	25-84	31-80	26-82	32-81	54-84
Education						
• Less than 12 years	17	10	16	7	11	6
• More than 12 years	46	25	36	20	29	16
Gender						
• Male	29 (46%)	20 (57%)	25 (48%)	17 (63%)	23 (57.5%)	13 (59%)
• Female	34 (54%)	15 (43%)	27(52%)	10 (37%)	17(42.5%)	9(41%)
Marital Status						
• Single[1]	25 (40%)	18 (51%)	21(40%)	13 (48%)	15 (38%)	11(50%)
• Married[2]	38 (60%)	17(49%)	31(60%)	14(52%)	25 (62%)	11 (50%)

	T1		T2		T3	
Characteristic	**CT** (n=63)	**Surgery only** (n=35)	**CT** (n=52)	**Surgery only** (n=27)	**CT** (n=40)	**Surgery only** (n=22)
Occupational Status						
• Employed[3]	25	14	21	10	16	7
• Not employed[4]	36	21	29	17	22	15
• Student	2	0	2	0	2	0
Nationality						
• UK[5]	54	24	46	20	34	18
• Other	9	11	6	7	6	4
Native English Speaker						
• Yes	51	25	43	23	32	19
• No	12	10	9	4	8	3
Tumour stage						
• Stage I	2	9	2	8	2	7
• Stage II	14	24	11	17	10	14
• Stage III	43	2	36	2	27	1
• Stage IV	4	0	2	0	1	0

Differences between those participants that continued in the study and those that withdrew after T1

There were no statistically significant differences ($p<0.01$) between those participants who withdrew from the study at T2 and those who had completed T1 in terms of age, gender, nationality, English as a first language, marital status, number of reported

comorbidities, education or IQ. There were proportionately more male participants in both groups at T2 and T3 than there were at T1, suggesting that more females than males withdrew from the study as time progressed although this was not statistically significant at ($p<.01$) (Fishers Exact test = 0.02).

There were also no statistically significant differences ($p<0.01$) between those participants who withdrew from the study at T3 and those who had completed T1 in terms of age, gender, nationality, English as a first language, marital status, number of reported comorbidities, education or IQ. Neither were there any statistically significant differences between those participants who withdrew from the study at T2 or at T3 and those who completed T1 assessments in terms of anxiety, depression or fatigue.

9.7.2 The extent of OCI at T2 and at T3 in each patient group

As shown in Table 9.3, at T2 there were no statistically significant differences between the groups in the proportion who were found to have cognitive impairment:

- 1.5 SD criteria: χ^2 (1, n=79) = 1.241, p= V =.125;
- 2 SD criteria: χ^2 (1, n=79) = 0.885, p=.347, V =.106;

Although a smaller proportion of chemotherapy patients (61.54% and 57.69% depending on the criteria used) were found to be cognitively impaired at T2 compared to "surgery only" patients (74.07% and 70.37%).

Table 9.3: The number and percentage of participants found to be cognitively impaired according to the ICCTF's criteria at T2

T2	1.5 SD criteria					2 SD criteria				
	No (%) impaired	**χ^2**	**df**	**Signifi-cance**	**Effect size (V)**	**No (%) impaired**	**χ^2**	**df**	**Signifi-cance**	**Effect size (V)**
CT (n=52)	32 (61.54%)	1.241	1	.265	.125	31 (57.69%)	.885	1	.347	.106
Surgery only (n=27)	20 (74.07%)					19 (70.37%)				
Total sample (n=79)	52 (65.82%)					50 (63.29%)				

Key: CT: Chemotherapy

There was also no statistically significant difference between the groups in the proportion of participants who were found to be impaired at T3 (Table 9.4):

- 1.5 SD criteria: χ^2 (1, n=62) = 1.564, p=.211, V =.159;
- 2 SD criteria: χ^2 (1, n=62) = 2.078, p=.149, V =.183

Table 9.4: The number and percentage of participants found to be cognitively impaired according to the ICCTF's criteria at T3

T3	1.5 SD criteria					2 SD criteria				
	No (%) impaired	**χ^2**	**df**	**Signifi-cance**	**Effect size (V)**	**No (%) impaired**	**χ^2**	**df**	**Signifi-cance**	**Effect size (V)**
CT (n=40)	17 (42.5%)	1.564	1	.211	.159	16 (40%)	2.078	1	.149	.183
Surgery only (n=22)	13 (59.09%)					13 (59.09%)				
Total sample (n=62)	30 (46.40%)					29 (46.81%)				

Key: CT: Chemotherapy

However, as can be seen in Tables 9.3 and 9.4, the overall percentage of participants that were found to be impaired (on both ICCTF criteria) in each group was greater at T2 than at T3. This suggests that cognitive function improves 3 months after chemotherapy for a subset of chemotherapy patients and at a similar point in time in relation to "surgery only" patients.

9.7.3 Nature of OCI at T2 and at T3 in each patient group

The frequency of impairments for each NP test at T2 and T3 can be seen in Tables 9.5 and 9.6.

The most commonly affected cognitive domains in both the chemotherapy patient group and "surgery only" patient group at T2 (when using either ICCTF criteria) (Table 9.5) were:

- verbal memory (as measured by the HVLT-R),
- visual memory (as measured by BVRT error),
- motor function (as measured by the GP), and
- executive function (as measured by the TMTB).

In the chemotherapy patient group the frequency of impairments in verbal memory ranged from 13 to 23% across the subscales. In the "surgery only" patients' impairments in verbal memory ranged from 25.9% to 40% across the subscales.

The pattern was similar at T3 (Table 9.6). After chemotherapy treatment the most affected domains were:

- verbal memory (as measured by the HVLT-R),
- motor function (as measured by the GP).

The frequency of impairment in motor function as measured by the GP non dominant hand test was 32.5% in the chemotherapy patient group and 30% in the surgery only patient group.

Whilst verbal memory was still affected at T3 in both groups, it was proportionally less affected than at T2.

At T3 there was proportionately more impairment found in executive function on both the COWA (15%) and TMT B (12.5%) in the chemotherapy group when the 1.5SD criteria was used to define OCI.

Attention, concentration and visual memory were the least affected domains in both groups (irrespective of criteria used).

Table 9.5. The number of participants in each group found to have cognitive impairment at T2 on each of the NP measures

Domain	NP measure	1.5 SD criteria		2 SD criteria	
		Number (%) of CHEMOTHERAPY patients[1] impaired on measure	Number (%) of Surgery only patients[1] impaired on measure	Number (%) of CHEMOTHERAPY patients[1] impaired on measure	Number (%) of Surgery only patients[1] impaired on measure
Attention and visual-motor ability	TMT A	9 (17.3)	6 (22.2)	6 (11.5)	2 (7.4)
	DS forward	1 (1.9)	3 (11.1)	0 (0)	0 (0)
	DS backward	10 (19.2)	7 (25.9)	4 (7.7)	1 (3.7)
Concentration	SDMT written	4 (7.7)	4 (14.8)	2 (3.8)	2 (7.4)
	SDMT oral	5 (9.6)	3 (11.1)	2 (3.8)	2 (7.4)
Executive Function	TMT B	13 (25)	7 (25.9)	10 (19.2)	5 (18.5)
	COWA	7 (13.5)	0 (0)	5 (9.6)	0 (0)
Motor Function	GP dom	15 (28.8)	7 (25.9)	12 (23.1)	7 (25.9)
	GP non dom	18 (34.6)	5 (18.5)	14 (26.9)	4 (14.8)
Verbal Memory	HVLT R recall	11 (21.2)	7 (25.9)	5 (9.6)	4 (14.8)
	HVLT R delay	12 (23.1)	11 (40.7)	6 (11.5)	6 (22.2)
	HVLT R retention	11 (21.2)	7 (25.9)	6 (11.5)	5 (18.5)
	HVLT R recognition	7 (13.5)	9 (33.3)	4 (7.7)	5 (18.5)
Visual Memory	BVRT - Correct	13 (25)	6 (22.2)	2 (3.8)	1(3.7)
	BVRT - Error	10 (19.2)	7 (25.9)	9 (17.3)	6 (22.2)

Table 9.6. The number of participants in each group found to have cognitive impairment at T3 on each of the NP measures

Domain	NP measure	1.5 SD criteria		2 SD criteria	
		Number (%) of Chemotherapy patients[1] impaired on measure	Number (%) of Surgery only patients[1] impaired on measure	Number (%) of Chemotherapy patients[1] impaired on measure	Number (%) of Surgery only patients[1] impaired on measure
Attention and visual-motor ability	TMT A	0 (0)	0	0	0
	DS forward	3 (7.5)	0	0	0
	DS backward	4 (10)	4 (18.2)	0	0
Concentration	SDMT written	1 (2.5)	0	0	0
	SDMT oral	1 (2.5)	1 (4.5)	0	1 (4.5)
Executive Function	TMT B	5 (12.5)	1 (4.5)	3 (7.5)	1 (4.5)
	COWA	6 (15)	1 (4.5)	3 (7.5)	1 (4.5)
Motor Function	GP dom	9 (22.5)	5 (22.7)	5 (12.5)	4 (18.2)
	GP non dom	13 (32.5)	7 (31.8)	12 (30)	6 (27.3)
Verbal Memory	HVLT R recall	5 (12.5)	7 (31.8)	3 (7.5)	2 (9.1)
	HVLT R delay	10 (25)	5 (22.7)	5 (12.5)	2 (9.1)
	HVLT R retention	7 (17.5)	3 (14.3)	3 (7.5)	2 (9.1)
	HVLT R recognition	3 (7.5)	2 (9.1)	3 (7.5)	2 (9.1)
Visual Memory	BVRT - Correct	0	2 (9.1)	0	1 (4.5)
	BVRT - Error	1 (2.5)	4 (18.2)	0	3 (14.3)

Key for Tables 9.5 & 9.6: Participants1 these numbers came from pooled imputed dataset, they have been rounded down if below .5 and up if above; TMT A/B: Trail Making Test; DS forward/backward: Digit Span forward/backward; SDMT written/oral: Symbol Digit Modalities Test written/oral; COWA: Controlled Oral Word Association Test: GP dom hand: Grooved Pegboard dominant hand; GP non dom Grooved Pegboard non dominant hand; HVLT R: Hopkins Verbal Learning Test -Revised; BVRT: Benton Visual Retention Test.

9.7.4 Changes in OCI over time

The following sections detail the results of the MLM analysis conducted to investigate changes in objectively measured cognitive functioning in CRC patients over time. The MLM results are presented separately for each cognitive domain: executive functioning, attention, motor function and memory.

Changes in executive function over time

The results of the MLM analysis in relation to executive functioning are detailed in Table 9.7. The only test of executive functioning that showed a significant difference between time-points was the TMT B, with a significant main effect for time ($F = 10.126$, $p = 0.002$). The mean difference across the two time points showed a gain in the scores (i.e. more time taken to complete the task, which is a **deterioration in performance**) from T2 to T3, demonstrating a worsening in performance upon re-assessment, with small effect sizes.

There was no significant difference on the COWA: The main effect of treatment group was not significant ($p > .01$) and neither was the main effect of time ($p > .01$) demonstrating no differences in the test performance of patient groups; irrespective of time or treatment. However, as can be seen in Table 9.7 the mean difference across the two time points showed a gain in the scores on the COWA (i.e. more words correctly recited) from T2 (to T3, suggesting an improvement in the scores upon re-assessment, although these were not statistically significant.

Furthermore, the time x group interaction did not reach significance on either the COWA or the TMT B, thus demonstrating i) no difference in the pattern of means

between the two groups at each time-point and ii) no differential change in the means of the groups across time.

Table 9.7: Results of the MLM analysis (main and interaction effects): Treatment differences over time in executive function as measured by the COWA and the TMT B

		T2		T3		Treatment		Time		Treatment x Time		Effect size	
		Mean[1] z scores	St Error	Mean z scores	St Error							T2	T3
COWA	**Surgery only**	0.151	0.133	0.241	0.189	F=0.605	P=0.438	F = 1.332	P= 0.251	F = 0.272	P= 0.603	-0.27	-0.04
	CT	-0.034	0.094	0.203	0.136								
TMTB	**Surgery only**	-1.111	0.476	0.739	0.366	F=0.278	P=0.599	F=10.126	**P=0.002**	F=2.211	P=0.140	0.32	-0.21
	CT	-0.323	0.337	0.368	0.270								

Key: COWA: Controlled Oral Word Association Test; TMT B: Trail Making Test B; CT: Chemotherapy; Mean[1] is the estitmated marginal mean of the z scores

Table 9.8: Results of the MLM analysis (main and interaction effects): Treatment differences over time in attention and concentration as measured by Digit Span, SDMT and TMT A

			T2		T3		Treatment		Time		Treatment x Time		Effect size	
			Mean z scores	St Error	Mean z scores	St Error							T2	T3
Attention	**DS For-ward**	**Surgery only**	10.0342[2]	0.339	10.397[2]	0.342	F=0.500	P=0.481	F=0.028	P=0.868	F=2.008	P=0.159	0.36	-0.13
		CT	10.660[2]	0.241	10.200[2]	0.241								
	DS Back-ward	**Surgery only**	6.687[2]	0.360	6.483[2]	0.415	F=0.593	P=0.443	F=0.019	P=0.892	F=0.567	P=0.453	0.01	0.29
		CT	6.704[2]	0.255	6.998[2]	0.294								
	TMTA	**Surgery only**	0.271[1]	0.185	1.028[1]	0.180	F=6.294	P=0.013	F=20.387	**P=0.000**	F=0.061	P=0.805	-0.46	-0.51
		CT	-0.164[1]	0.130	0.594[1]	0.132								
Concen-tration	**SDMT Written**	**Surgery only**	5.588[1]	0.396	5.812[1]	0.380	F=0.344	P=0.557	F=0.191	P=0.662	F=0.146	P=0.284	0.19	0.43
		CT	5.966[1]	0.271	6.570[1]	0.276								
	SDMT Oral	**Surgery only**	6.148[1]	0.690	5.527[1]	0.609	F=0.029	P=0.864	F=0.947	P=0.331	F=0.332	P=0.565	-0.06	-0.19
		CT	5.929[1]	0.480	4.979[1]	0.447								

Key: DS forward/backward: Digit Span forward/backward; TMT A: Trail Making Test A; SDMT written/oral: Symbol Digit Modalities Test written/oral; CT: Chemotherapy; Mean[1] is the estitmated marginal mean of the z scores; [2] this is the mean raw score

Changes in attention and concentration over time

The results of the MLM analysis in relation to attention and concentration (as measured by Digit Span forwards and backwards, TMT A and SDMT) are detailed in Table 9.8. With regard to the TMT A the main effect of time was significant for TMT A score ($F = 20.387$, $p < .001$) with T2 scores being lower than T3 scores (i.e. less time taken for completion at T2) demonstrating a **decline** in performance over time, although the magnitude of the difference in the means was moderate. The main effect of the treatment group and the time x treatment group interaction did not reach significance, thus demonstrating i) no difference in the pattern of means between the two groups at each time-point and ii) no differential change in the means of the groups across time.

Changes in motor function over time

With regard to the motor function as can be seen in the Table 9.9, the main effect of treatment was significant for the non-dominant hand in the Grooved Pegboard task ($F = 16.075$, $p < .001$) with the "surgery only" group mean scores being lower than the chemotherapy group mean scores (i.e. it took less time to complete the task). This demonstrates an **improvement** in performance with the non-dominant hand due to treatment. The magnitude of the difference in the means was moderate. The main effect of time and the time x treatment group interaction did not reach significance, thus demonstrating i) no difference in the pattern of means between the two groups at each time-point and ii) no differential change in the means of the groups across time

Table 9.9: Results of the MLM analysis (main and interaction effects): Treatment differences over time in motor function as measured by the Grooved Pegboard

		T2		T3		Treatment		Time		Treatment x Time		Effect size	
		Mean[1] z scores	St Error	Mean[1] z scores	St Error							T2	T3
GP dom	**Surgery only**	0.741	0.431	0.416	0.287	F=1.171	P=0.281	F=0.345	P=0.558	F=1.320	P=0.253	0.07	0.36
	CT	0.887	0.300	0.901	0.210								
GP non dom	**Surgery only**	0.281	0.375	0.303	0.486	F= 16.075	**P=0.000**	F= 0.604	P=0.439	F= 0.940	P=0.335	0.66	0.69
	CT	1.567	0.264	1.878	0.352								

Key: GP dom: Grooved Pegboard dominant hand; GP non dom: Grooved Pegboard non dominant hand; CT: Chemotherapy; Mean[1] is the estitmated marginal mean of the z scores

Changes in memory over time

The results of the MLM analysis in relation to changes in memory over time are presented in Table 9.10. There was one significant difference over time in verbal recognition ($p<.01$) but no significant differences over time in visual memory, between the chemotherapy participants and the "surgery only" participants.

The main effect of the treatment on verbal and also visual memory was non-significant (all $p>0.01$) showing no differences in the test performance of the two groups (irrespective of time). The time x treatment interaction term did not show any significant effects across any of the subscales of the HVLT-R or the BVRT.

The main effect of time on verbal memory: Recall ($p=0.030$), Delayed recall ($p=0.068$) and Retention ($p=0.467$) were non-significant showing no difference in most aspects of verbal memory over time. However, the main effect of time on delayed verbal recognition was significant ($p=0.004$). The mean difference across the two time points showed a **decline** in the scores (i.e. fewer words correctly recognised after a 20-minute interval) from T2 to T3, with small effect sizes (Table 9.10).

Table 9.10: Results of the MLM analysis (main and interaction effects): Treatment differences over time in memory as measured by the HVLT–R (z scores) and BVRT (raw scores)

			T2		T3		Treatment		Time		Treatment x Time		Effect size	
			Mean z scores	St Error	Mean z scores	St Error							T2	T3
Verbal	**HVLT-R Recall**	**Surgery only**	-0.859	0.161	-0.472	-0.859	F=0.542	P=0.463	F=4.861	P=0.030	F=0.014	P=0.906	-0.13	-0.03
		CT	-0.963	0.113	-0.616	-0.963								
	HVLT-R Delay	**Surgery only**	-1.050	0.210	-0.466	0.222	F=0.000	P=0.994	F=3.389	P=0.068	F=1.658	P=0.200	0.22	-0.23
		CT	-0.809	0.146	-0.705	0.161								
	HVLT-R Retention	**Surgery only**	-0.773	0.303	-0.336	0.251	F=0.073	P=0.788	F=0.533	P=0.467	F=1.175	P=0.280	0.21	-0.17
		CT	-0.447	0.213	-0.532	0.182								
	HVLT-R Recog-nition	**Surgery only**	-0.883	0.214	-0.005	0.222	F=0.152	P=0.697	F=8.375	**P=0.004**	F=3.075	P=0.082	0.37	-0.25
		CT	-0.478	0.150	-0.262	0.161								
Visual	**BVRT Correct**	**Surgery only**	5.588[1]	0.396	5.812[1]	0.380	F=2.632	P=0.105	F=2.458	P=0.117	F=0.332	P=0.565	0.19	0.42
		CT	5.966[1]	0.271	6.570[1]	0.276								
	BVRT Error	**Surgery only**	6.148[1]	0.690	5.527[1]	0.609	F=0.528	P=0.467	F=2.087	P=0.149	F=0.086	P=0.769	-0.06	-0.19
		CT	5.929[1]	0.480	4.979[1]	0.447								

Key: [1] = mean raw scores for BVRT; HVLT-R: Hopkins Verbal Learning Test Revised; BVRT: Benton Visual Retention Test; CT: Chemotherapy

9.7.5 Changes in perceived cognitive function over time

After controlling for baseline, the mean scores for FACT Cog subscales QoL and Others were relatively high as shown in the Table 9.11. As discussed in Chapter 7, a higher score on the FACT Cog indicates less perceived cognitive symptoms. These scores therefore suggest that neither the chemotherapy group nor the "surgery only" group perceived themselves as having experienced worse QoL due to poor cognition during the 9-month study period. These results are very similar to the results that Vardy and colleagues (2017) reported in their study that also examined perceived cognitive impairment (using the FACT Cog) in people with CRC who do and do not receive chemotherapy treatment.

Mean cognitive symptom scores were very similar in both groups. Means scores on the FACT Cog PCI and PCA subscales were worse at T3 than at T1 for both groups.

The results of the MLM analysis in relation to perceived cognitive functioning over time are presented in Table 9.11. There were no significant differences over time in any of the FACT Cog subscales between the chemotherapy participants and the "surgery only" participants.

The main effect of treatment on FACT Cog PCA (p=0.786), FACT Cog PCI (p=0.854), FACT Cog QoL (p=0.251) and FACT Cog Oths (p=0.077) were also non-significant showing no difference in perceived cognitive function over time. Similarly, the time x treatment interaction term did not show any significant effects across all subscales of the FACT Cog.

Table 9.11: Results of the MLM analysis (main and interaction effects): Treatment differences over time in perceived cognitive function as measured by the FACT Cog

FACT Cog	Participant group	Time 2		Time 3		Treatment		Time		Treatment x Time		Effect size	
		Estimated marginal mean	Std. Error	Estimated marginal mean	Std. Error							T2	T3
PCA (0-28)	Surgery only	20.931	1.113	19.097	1.160	F=.074	P=.786	F=.074	P=.786	F=1.214	P =.271	-0.30	0.08
	CT	19.191	0.793	19.504	0.840								
PCI (0-72)	Surgery only	56.113	1.874	53.361	2.050	F=.034	P=.854	F=.034	P=.854	F=.502	P=.478	-0.35	-0.10
	CT	52.763	1.338	52.397	1.482								
QOL (0-16)	Surgery only	13.479	0.667	13.454	0.737	F=.1.320	P=.251	F=.1.320	P=.251	F=.488	P=.485	-0.54	-0.30
	CT	11.604	0.475	12.422	0.534								
Others (0-16)	Surgery only	15.128	0.450	14.842	0.408	F= .004	P=.949	F= .004	P=.949	F=.125	P=.724	-0.20	-0.20
	CT	14.668	0.321	14.641	0.293								
Total score (0-132)	Surgery only	111.938	2.842	114.642	3.090	F=3.136	P= .077	F=3.136	P= .077	F=.264	P= .607	-0.81	-0.65
	CT	99.936	2.023	105.253	2.240								

Key: FACT Cog subscales: PCI: Perceived Cognitive Impairment; PCA: Perceived Cognitive Ability; QoL: Impact on Quality of Life; Others: Comments from others; CT: Chemotherapy

9.7.6 Psychosocial outcomes: Changes in fatigue, anxiety and depression over time

The results of the MLM analysis in relation to feelings of fatigue, anxiety and depression are presented in Table 9.15.

Fatigue:

As can be seen in Table 9.12, there was a significant main effect of time on fatigue (p=0.002), with a small effect size. The mean difference across the two time points showed an increase in scores from T2 to T3 demonstrating an **improvement** in feelings of fatigue at T3 (i.e less fatigue). The main effect of treatment on fatigue was not significant, showing no difference in the amount of fatigue between the two groups (irrespective of time). The time x treatment interaction did not show any significant effects.

As discussed in Chapter 8, a score of <37 indicates clinical fatigue on the FACIT Fatigue scale. Based on the estimated marginal means, the mean fatigue score as measured by the FACIT Fatigue scale for the chemotherapy patient group was 31.48, whereas the mean score for the surgery only group was 42.67. At T2 (i.e. mid chemotherapy treatment/3 months post T1) 65.38% of the chemotherapy participants reported feelings of clinical fatigue whereas only 18.32 % of the "surgery only" patient group were found to be clinically fatigued.

By T3 (3 months after the last chemotherapy treatment), the mean score for the chemotherapy participants improved to 38.06 and 35% reported feelings of clinical fatigue. However, the mean score for the "surgery only" group decreased to 39.99

(suggesting that they were on average more fatigued than at T2) and 25% of the group were found to be clinically fatigued.

Depression:

As can be seen in Table 9.12, there was a significant main effect of treatment on depression (p=0.001) with the "surgery only" group mean scores being lower than the chemotherapy group mean scores (i.e. there was less depression). This demonstrates an increase in depression due to treatment. The main effect of time and the time x treatment group interaction did not reach significance, thus demonstrating i) no difference in the pattern of means between the two groups at each time-point and ii) no differential change in the means of the groups across time.

The mean depression score for the chemotherapy participants mid-treatment (i.e. at T2) was 5.099 (i.e. no depression) and was only 2.701 for the "surgery only" group. However, this was the highest depression group mean score for the chemotherapy group across all time points and the lowest for the "surgery only" group. At T2, 5.76 % of the chemotherapy participants reported feelings of clinical depression (i.e. score ≥11) but none of the "surgery only" group did. At T3, this was 2.5% and zero respectively.

Table 9.12: Results of the MLM analysis (main and interaction effects): Treatment differences over time in fatigue, anxiety and depression and HRQoL

	Participant group	Time 2		Time 3		Treatment		Time		Treatment x Time		Effect Size	
		Mean	Std. Error	Mean	Std. Error							T2	T3
FACIT Fatigue (0-52)	Surgery only	42.674	1.673	39.994	2.407	F= .417	P=.518	F=9.715	**P=0.002**	F=6.719	P=0.010	-1.28	-0.17
	CT	31.483	1.192	38.061	1.753								
HADS Anxiety (0-14)	Surgery only	4.624	0.573	4.016	0.732	F=1.747	P=0.189	F=0.389	P=0.534	F=0.202	P=0.654	0.18	0.30
	CT	5.147	0.408	5.048	0.533								
HADS Dep-ression (0-14)	Surgery only	2.701	0.497	3.053	0.569	F=14.373	**P=0.001**	F=0.253	P=0.616	F=1.619	P=0.206	0.92	0.46
	CT	5.099	0.355	4.284	0.413								
FACT C PWB (0-28)	Surgery only	24.408	0.938	24.739	0.861	F=4.253	P=.039	F=14.950	**P=.000**	F=4.259	P=.039	-1.10	-0.55
	CT	19.027	0.671	22.536	0.617								
FACT C SWB (0-28)	Surgery only	23.051	0.694	24.395	0.808	F=3.001	P=.083	F= .680	P=.410	F=2.336	P=.126	0.06	-0.46
	CT	23.280	0.494	22.651	0.587								

FACT C EWB (0-24)	**Surgery only**	19.514	0.665	20.595	0.654	F=3.054	P=.081	F=.449	P=.503	F=1.830	P=.176	0.03	-0.47
	CT	19.621	0.475	19.175	0.471								
FACT C FWB (0-28)	**Surgery only**	22.775	1.016	22.690	1.242	F= 2.669	P=.102	F=2.795	P=.095	F=1.062	P=.303	-0.86	-0.44
	CT	18.242	0.722	20.156	0.899								
FACT C CCS (0-28)	**Surgery only**	22.421	0.822	21.697	0.994	F=.071	P=.789	F=2.828	P=.093	F=2.123	P=.145	-0.61	-0.07
	CT	19.810	0.585	21.366	0.723								
FACT C Total (0-136)	**Surgery only**	111.938	2.842	114.642	3.090	F= 5.941	P=.015	F=3.136	P= .077	F=.264	P= .607	-0.81	-0.65
	CT	99.936	2.023	105.253	2.240								

Key: HADS: Hospital Anxiety and Depression Scale; FACT C subscales: PWB: Physical wellbeing; SWB: Social wellbeing: EWB: Emotional wellbeing; FWB: Functional wellbeing; CCS: Colorectal symptoms; CT: Chemotherapy

Anxiety:

As can be seen in Table 9.12, there were no significant main effects of treatment or time on anxiety and the time x treatment group interaction did not reach significance, thus demonstrating i) no difference in the pattern of means between the two groups at each time-point; ii) no difference in the amount of anxiety between the two groups (irrespective of time and iii) no differential change in the means of the groups across time.

The mean anxiety scores in both groups remained roughly the same at each time point. At T2 13.46 % of the chemotherapy participants reported feelings of clinical anxiety (i.e. score ≥11) and 11.11% of the "surgery only" group. At T3, this was 15% and 9.09% respectively.

HRQoL:

As can be seen in Table 9.12, the mean scores for the chemotherapy patient group on the physical, functional, social and colorectal symptom wellbeing scales were better at T3 than at T2 (a higher score on each subscale represents a better quality of life). There was a significant main effect of time on PWB (p=0.000). The mean difference across the two time points showed an increase in scores from T2 to T3 demonstrating an **improvement** in feelings of physical well-being at T3 (i.e. better HRQoL). The main effect of treatment on HRQoL was not significant, showing no difference in the any of the wellbeing subscales between the two groups (irrespective of time). The time x treatment interaction did not show any significant effects.

9.7.7 Relationships between psychosocial outcomes and perceived cognitive function

The relationship between anxiety, depression, fatigue, quality of life and subjective cognitive function was investigated using Spearman Rho correlation coefficient, after having carried out preliminary analyses to ensure no violation of the assumptions of normality, linearity and homoscedasticity (Please see all Tables of correlations in Appendix R).

As can be seen in Appendix R, HRQoL in the whole participant sample was significantly related to FACT Cog PCA and PCI at T2 and T3. As FACT Cog PCI and PCA improved (i.e increased scores on each subscale) so did physical, emotional and functional wellbeing as measured by the FACT C. Depression, anxiety and fatigue were also significantly correlated with FACT Cog PCI and FACT Cog PCA at T2 and T3 for the whole sample.

When exploring the relationships within each patient group correlational analysis showed that at T2 fatigue was significantly correlated with FACT Cog PCI and PCA in each patient group. As the scores for fatigue increased so too did FACT Cog PCI and PCA scores. However, anxiety and depression were each significantly negatively correlated with PCA and PCI of the FACT Cog in the chemotherapy patient group but not in the "surgery only" group; such that as anxiety and also depression increased, the scores on the FACT Cog subscales decreased indicating more perceived cognitive symptoms.

At T3 depression and fatigue were significantly correlated with FACT Cog PCI and PCA in each patient group. However, anxiety was significantly negatively correlated with each of the FACT Cog subscales in the chemotherapy patient group but not in the

"surgery only" group; such that as anxiety increased the scores on the FACT Cog subscales decreased indicating more perceived cognitive symptoms.

9.7.8 Relationship between OCI and subjective cognitive function

There were no statistically significant relationships between any of the FACT Cog subscales and overall OCI for the sample as a whole at T2 (Table 9.13). However, at T3, there was a statistically significant negative relationship between those participants found to be impaired according to the ICCTF's 2 SD criteria and PCA (rho = -.440; $p<0.01$); and also, a statistically significant negative relationship between OCI and QoL (rho = -.328) (Table 9.13). This indicates that as the occurrence of OCI increases perceived cognitive abilities and perceived quality of life get worse (they decrease). It was not possible to explore the relationships between specific cognitive domains (i.e each NP measure) and each of the subjective domains (i.e each FACT Cog subscale) in each of the chemotherapy and "surgery only' patient groups as the samples were too small at T2 and T3.

Table 9.13: Table of point biserial correlations (Spearman's rho) for OCI (according to each of the ICCTF's criteria) and SCI (as measured by FACT Cog subscales) for the entire participant sample

T2				T3		
	OCI: 1.5 SD criteria	**OCI: 2 SD criteria**			**OCI: 1.5 SD criteria**	**OCI: 2 SD criteria**
PCI	-0.179	**-.258**		**PCI**	-0.178	**-.284**
PCA	0.002	-0.071		**PCA**	**-.290**	**-.440**
QoL	-0.098	-0.128		**QoL**	-0.233	**-.328**
Oth	0.078	0.042		**Oth**	-0.128	-0.104

Key: Blue=Correlation is significant at the 0.05 level (2-tailed). Red = Correlation is significant at the 0.01 level (2-tailed); FACT Cog subscales: PCI: Perceived Cognitive Impairment; PCA: Perceived Cognitive Ability; QoL: Impact on Quality of Life; Others: Comments from others.

When looking at each of the patient groups separately there were no significant relationships at T2 or T3 ($p<.01$) between overall OCI and any of the Fact Cog subscales (Table 9.13) when OCI was defined by the ICCTF's 1.5 SD criteria.

Table 9.14: Table of point biserial correlation coefficients (Spearman's rho) for OCI (according to the ICCTF's 1.5 SD criteria) and SCI (as measured by FACT Cog subscales) in each of chemotherapy and "surgery only" groups

T2				T3		
FACT Cog subscale	**CT**	**Surgery only**		**FACT Cog subscale**	**CT**	**Surgery only**
PCI	-0.104	**-.476***		**PCI**	-0.026	**-.518***
PCA	-0.119	-0.170		**PCA**	-0.142	-0.221
QoL	0.104	-0.092		**QoL**	-0.189	**-.483***
Oth	0.109	-0.331		**Oth**	-0.306	-0.216

Key: Blue=Correlation is significant at the 0.05 level (2-tailed). Red = Correlation is significant at the 0.01 level (2-tailed). FACT Cog subscales: PCI: Perceived Cognitive Impairment; PCA: Perceived Cognitive Ability; QoL: Impact on Quality of Life; Others: Comments from others; CT: Chemotherapy.

However, as can be seen in Table 9.15 there was a statistically significant negative relationship between OCI and FACT Cog PCI (rho = -.540) at T2and at T3 (rho=-.650) in the "surgery only" group but no statistically significant correlations in the chemotherapy group (Table 9.15). There was also a significant negative relationship between OCI and QoL at T3 in the "surgery only" group (rho = -.695)

Table 9.15: Table of point biserial correlation coefficients (Spearman's rho) for OCI (according to the ICCTF's 2 SD criteria) and SCI (as measured by FACT Cog subscales) in each of chemotherapy and "surgery only" groups

T2				T3		
FACT Cog subscale	**CT**	**Surgery only**		**FACT Cog subscale**	**CT**	**Surgery only**
PCI	-0.182	**-.540**		**PCI**	-0.114	**-.650**
PCA	-0.134	-0.238		**PCA**	-0.182	-0.053
QoL	0.073	-0.134		**QoL**	-0.306	**-.695**
Oth	0.043	**-.411**		**Oth**	**-.322**	**-.463**

Key: Blue=Correlation is significant at the 0.05 level (2-tailed). Red = Correlation is significant at the 0.01 level (2-tailed). FACT Cog subscales: PCI: Perceived Cognitive Impairment; PCA: Perceived Cognitive Ability; QoL: Impact on Quality of Life; Others: Comments from others; CT: Chemotherapy.

9.7.9 Research question 3: Is OCI associated with lesser HRQoL in patients with CRC?

Aim 3: To explore whether OCI in patients with CRC affects HRQoL? If so, which cognitive domains relate to what aspects of HRQoL?

At T2 there were no statistically significant correlations found between any of the cognitive domains and HRQoL (as measured by the FACT C) when using the ICCTF's 1.5 SD criteria. However, when OCI was defined by the 2 SD criteria, verbal memory (as measured by HVLT-R delay) was found to be negatively statistically significantly related to perceived emotional wellbeing scale (as measured by FACT C EWB) (rho = -.293) at T2 (Please see Appendix S for the table of correlations). In addition, attention (as measured by the Digit Span backwards) was found to be significantly correlated with FACT C perceived colorectal cancer symptoms (rho = .328) (Appendix S).

At T3, the only statistically significant correlations were found between:

- Motor function (as measured by PG dominant hand) and physical wellbeing (rho = -.334) (when OCI was defined by ICCTF 1.5 SD criteria); and
- Verbal memory (as measured by HVLT R delay) and social wellbeing (rho = -.344) (when OCI was defined by 2 SD criteria) (Appendix S).

It was not possible to examine the relationships between OCI and HRQoL in each of the participant groups as the samples were too small at T2 and T3.

9.8 Discussion

This chapter firstly examined the nature and extent of OCI mid chemotherapy treatment/3 months after the first assessments were carried out and again 3 months after the last scheduled treatment/6 months after the second assessment in the two patient groups before examining any changes over time. It then explored the relationships between cognitive function (objective and subjective) and psychosocial outcomes; and the relationship between subjective cognitive function and overall OCI. Lastly, it examined the relationship between OCI and HRQoL.

9.8.1 OCI

Overall, the results of this longitudinal study demonstrated that OCI continues to occur during and for at least 3 months after chemotherapy treatment/9 months after the first assessment in a subset of all patients with resected CRC. There was no significant difference in OCI between the participants that withdrew from the study after the first assessment, so there was no suggestion that the non-responders were poorer performers on the NP assessments. It was interesting to note that at each assessment

time point proportionately more "surgery only" patients were found to have OCI than chemotherapy patients (based on the ICCTF's criteria), although this was not a statistically significant finding.

OCI was most prevalent at T2 in each of the patient groups and for the sample as a whole. As discussed in Chapter 8, after surgery (and prior to chemotherapy treatment) a significantly higher proportion of participants in this study were found to have OCI compared to normative data based on age, gender and education. The proportion of participants found to have OCI was the highest at T2 and by T3 the proportion of participants found to have OCI was less than it had been at T1. These findings are similar to previous studies that found that OCI improves/resolves with time in a subset of patients diagnosed with breast cancer (including Mar Fan et al, 2005; Jenkins et al, 2006; Vardy et al, 2006; Jansen et al, 2008; Collins et al, 2009; Mehlsen et al, 2009; Quesnel et al ,2009; Vearncombe et al, 2009; Weiss et al, 2009; Ahles et al, 2010, Debess et al, 2010, Reid-Arndt et al, 2010; Wefel et al 2010; Hedayati et al, 2012; Cruzado et al, 2014). However, 3 months post chemotherapy treatment is not a very long time after treatment and further assessments are warranted over a longer period of time to ensure that there is a real improvement and that patients haven't simply developed temporary compensatory cognitive strategies as suggested by Ono and colleagues (2015). There were no statistically significant differences found between those participants who withdrew from the study and those that continued in terms of demographic, clinical or psychosocial characteristics.

Given the extent of the impairment in a subset of patients (most notably in verbal memory and motor function) in both groups, ongoing assessment of these domains is also warranted. However, it should be noted that it is unsurprising that motor function

was a commonly affected domain at T2 and T3 in the chemotherapy group as Oxaliplatin is believed to cause CIPN (Chapter 2) which often lasts for more than a year after the end of chemotherapy treatment; and many of the chemotherapy patients anecdotally complained of neuropathy in their fingers and toes. It is somewhat surprising therefore that it was also a commonly affected domain in the "surgery only" patient group at the second and third assessments. Although a number of the older participants may have been affected by other co-morbidities such as poor eyesight and/or arthritis, which would have affected performance on the Grooved Pegboard. As expected, the MLM analysis did show that an improvement in performance on the Grooved Pegboard (non-dominant hand) was due to treatment (moderate effect size). Although these results should also be interpreted with caution, as the norms used did not cover the older ages included in this study sample (they only went up to 70 years old).

It is also worth noting here that the ICCTF (Wefel et al, 2011) reports that memory, processing speed, and executive function seem to be most vulnerable to adverse effects of chemotherapy. However, as discussed in Chapter 3, this could partly be because memory is the most commonly assessed domain in the literature (Cheung, Tan and Chan, 2012). It could also be due to the researcher's choice of which domains to investigate. In this study, for instance the tests specifically recommended by the ICCTF were used to assess what the task force had found to be the most affected domains. Although the recommended tests were supplemented with a few others, the sample size in this study may not have been large enough to find any effects for attention and concentration (although the effect sizes were small).

The extent of OCI reported at each time point and the most commonly affected domains did vary according to the cut off used to define OCI. This is a common methodological problem in "cancer and cognition" studies (Chapter 2). Consequently, further studies with additional control groups would help to validate the results of the present study and enable a better understanding of the course and duration of OCI in this patient population.

The MLM showed that there appears to be very little change in cognitive function (neither objective nor subjective) over time. Although a main effect of time was significant for executive function (as measured by TMT B), attention (TMT A) and verbal memory (HVLT -R recognition) –performance in these 3 domains declined over time; but treatment made no difference. However, the effect sizes were small to moderate for all of the significant results.

9.8.2 Subjective cognitive function

Overall, cognitive symptom scores were similar in patients who received adjuvant chemotherapy for CRC and those who did not. The scores on the self-report measure were very similar to Vardy and colleagues (2017) study. However, it was not possible to examine whether the scores suggested significant SCI in the absence of any cut off criteria for the FACT Cog and/or a healthy control group. Consistent with other "cancer and cognition" studies (Schagen et al, 1999; Hermelink et al, 2007; Bender et al, 2008; Jansen et al, 2008; Schagen et al, 2008; Schilder et al, 2009: Klemp et al, 2017) this study does show that all of the psychosocial outcomes (depression, anxiety, fatigue and HRQoL) are significantly related to subjective cognitive function. The next chapter

examines the experience of cognitive changes in a sample of the chemotherapy participants in more depth through semi-structured interviews.

9.8.3 OCI and subjective cognitive function

There were no statistically significant relationships found between overall OCI and any of the subjective cognitive function subscales; or between OCI and anxiety, depression, fatigue or HRQoL.

9.8.4 OCI and HRQoL

In line with the findings of the systematic review in Chapter 5 (and Dwek et al, 2016) on the whole OCI did not appear to be related to poorer HRQoL during or after chemotherapy treatment or at similar points in time in this patient group.

9.9 Summary

Overall, the findings from these longitudinal analyses suggest that the present sample of patients with CRC is comparable to previous literature in relation to breast cancer patients. However, there do appear to be some slight differences that are particular to a diagnosis and the treatment of CRC such as the continued motor function impairments, which could possibly be related to the chemotherapy regimen used to treat patients with this particular cancer. Further larger studies are warranted to examine the effect on cognition of each of the CRC treatment protocols (which not only use different combinations of drugs but are also dispensed differently and for differing lengths of time).

Chapter 10: An exploration of the knowledge and perceived experiences of cognitive changes in patients diagnosed with CRC, prior to, during and several months following chemotherapy treatment: A Qualitative Study

10.1 Introduction

Chapters 8 and 9 described the findings from the quantitative component of this thesis examining CRCI in patients diagnosed with resectable CRC. To complement and expand the findings of the quantitative study an in-depth account of the impact of chemotherapy on perceived cognition was sought by conducting a qualitative study that elicited participants' narrative of their individual experiences prior to, over the time of and after their chemotherapy treatment.

The overall purpose of this qualitative study was to explore the knowledge and experiences of patients with resectable CRC concerning CRCI over time. Thus obtaining data describing patients' experiences and their interpretations, not the incidence, extent or severity as measured by quantitative tools (Mitchell & Turton, 2011). A longitudinal design was chosen, as it would provide the researcher with 'unfolding stories' as told by the patients over the course of their chemotherapy treatment and recovery rather than snapshots of expectations and/or experiences at a particular point in time. Thereby providing a more comprehensive level of information regarding individual experiences and perceptions (Saldaña, 2003) than has previously been the case. The rationale and purpose of this thesis' mixed methods approach is discussed in Chapter 6.

As detailed in Chapter 6, Section 6.4.2 the aims of this qualitative study were to:

1) Explore whether patients with CRC are aware of CRCI prior to the start of adjuvant chemotherapy treatment and whether they are aware of having experienced any cognitive difficulties since diagnosis.

2) Explore the type and extent of individual experiences of CRCI and its perceived effects prior to, during and post chemotherapy treatment.

10.2 Method

10.2.1 Ethical approval

As detailed in Chapter 7, final ethical approval for this mixed method thesis which includes this longitudinal qualitative study was granted by the NRES Committee London – South-West Cornwall & Plymouth (REC reference number: 13/SW/0201) in June 2015 (see Appendix H for approval letters). Relevant approvals were also gained from the Research & Development (R&D) departments at University College London Hospitals NHS Foundation Trust (UCLH), Barts Health NHS Trust (Barts) and Imperial College Healthcare NHS Trust (Imperial).

10.2.2 Design

This qualitative study utilised semi-structured interviews with participants who in the main also completed the quantitative study. Individual interviews were selected over focus groups because the purpose of this study was to gain individual in-depth accounts of the participants' experiences over time and it is likely that experiences of CRCI will be varied. A further practical reason against using a focus group approach was that the way in which patients were recruited to the study and the treatment trajectory would have made it impossible to arrange focus groups for patients who were at the same stage in the chemotherapy treatment cycle.

10.2.3 Participants and consent

Participants who were eligible for the quantitative study were eligible for participation in this study. The researcher recruited and consented the participants to this study in accordance with the procedures outlined in full in Chapter 7.

In tandem with the quantitative NP assessments and various questionnaires, interview data was collected from a subset (n=24) of the chemotherapy patients at the same three time points. Interviews lasted approximately 5 minutes at T1 and between 20 and 40 minutes at T2 and T3, allowing participants to share as much as they wished about their perceived experiences. It was the intention of this qualitative study to capture the patients' in-depth feelings and experiences of perceived cognitive impairment, its trajectory, and perceived impact on the patient over a period of 9 months covering pre-, mid- and post chemotherapy treatment.

Interested participants received an information sheet in relation to the qualitative study (Appendix I) when approached by the researcher and medical team at their post-surgery follow up appointment. Interviews were arranged at a time convenient to each of the participants and coincided with hospital appointments post-surgery and pre-chemotherapy treatment (T1), 3 months later (i.e. mid chemotherapy treatment) (T2) and again 6 months after the second interview (i.e. approx. 3 months post the last scheduled chemotherapy treatment) (T3). Written consent was obtained before the first interview (Appendix I). Participants were also reminded prior to each interview that they were to be audio-recorded, that all interviews would be confidential and transcribed verbatim, and that the transcripts would not include personally identifiable information.

10.2.4 Location of the interviews and safety protocol

Participants were offered a choice of location either at home or at the treating hospital at a time convenient for them. Interviews were conducted in quiet rooms/areas at home or at the treating hospital. The researcher carried a working mobile telephone with her at all times (in accordance with City University's lone worker policy) so that she could easily contact the supervisory team in the event of any safety concerns.

10.2.5 Topic guide

The researcher in collaboration with the supervisory team developed the interview schedules (See Appendix N). The interview schedules were designed to cover topics relating to the knowledge, experiences and future expectations of CRCI. The schedules were developed by firstly establishing the subjects to be covered following a review of the relevant literature (e.g. Downie et al., 2006; Mitchell & Turton, 2011) and further issues raised by participants at T1 and during informal conversations whilst carrying out the quantitative study. The subjects were discussed with the supervisory team, in terms of how questions should be phrased, prompts, and subject coverage. Two members of the supervisory team with experience in qualitative research then reviewed the interview schedules and made recommendations on practicality and the, wording, and length of each of the schedules.

A semi-structured interview style rather than open-ended questions was selected in order to narrow down the area being investigated, namely cognition and cognitive function. It was thought that a completely un-structured interview might elicit too much information on the side effects of chemotherapy generally and not necessarily cognitive experiences which was the theme more closely related to the research questions under

consideration. This approach allowed for key topics of interest to be explored and for new related themes to emerge (Ritchie & Lewis, 2003). The semi-structured schedules permitted some flexibility in the order that the questions were asked. A few general questions were also included to elicit conversation together with additional questions designed to probe for information related to cognition if it was not mentioned. Follow up questions were also used in order to obtain clarification and a deeper understanding where needed. All interviews were conducted and transcribed verbatim by the researcher.

10.2.6 Data analysis

Various approaches to data collection and analysis were reviewed and compared. Grounded theory (Glaser & Strauss, 2009) is concerned with generating theory for a particular phenomenon and often requires larger sample sizes to reach data saturation (O'Reilly & Parker, 2013). Since it was not the purpose of the present study to generate theory, grounded theory was deemed inappropriate. Interpretative Phenomenological Analysis (IPA) was not selected because it generally requires a small homogeneous sample (3-6 participants), which within the purpose of the present study was not deemed appropriate for exploring the range of participants' cognitive experiences (Smith et al., 2009). The present study used Thematic Analysis and content analysis. Thematic analysis has been successfully employed by other researchers in the area of "cancer and cognition", specifically in relation to the impact of CRCI on breast cancer patients' daily functioning (e.g. Cheung, Shwe, Tan, Fan, Ng, & Chan, 2012). It has therefore been shown to be suitable in a similar patient group. It is considered "*a flexible and useful research tool that can potentially provide a rich and detailed, yet complex, account of data*" (Braun & Clark, 2006, page 78). The specific approach in this

study was informed by previous literature and the quantitative study components of the thesis. It involved a two-step approach: an inductive thematic analysis was undertaken (Braun & Clark, 2006), followed by a content analysis inspired by Saladans (2003).

10.3 Step One: Inductive thematic analysis and results

10.3.1 Thematic analysis

As a first step, inductive thematic analysis was conducted for each interview in order to identify, analyse and report patterns within the data (Braun & Clark, 2006). An inductive rather than deductive mode of analysis was chosen, as this study is exploratory in nature and consequently data driven. The focus of the analysis was knowledge, perceptions and perceived experience of CRCI at each time point. It involved the six-step process described by Braun and Clarke (2006) (see below) and was conducted using paper-based methods and the computer software NVivo, version 11 for Windows by QSR International.

Familiarisation of the data was the first step undertaken in the analysis and involved transcribing the interviews, re-reading the transcripts and noting initial ideas. This enabled the initial identification of meaningful units of text relevant to the research topic. The second step involved systematically organising the entire data set (at each time point) into meaningful groups and developing initial codes. Collating similar codes together enabled the development of potential themes. The third step involved a systematic review of the coded data extracts to ensure that a name, definition and data to support each theme were identified. A second researcher from the supervisory team, experienced in qualitative data analysis, independently analysed a subsample (20%) of

the data in order to validate the coding. The researchers compared the naming of the themes and differences in opinion were resolved through discussion. The fourth step of the analysis involved reviewing and the fifth step led to defining and refining the specifics of each theme so that clear definitions of the themes were generated culminating in step six, which is the current report presented in this Section 10.3.

10.3.2 Results

The following section details selected verbatim extracts from the interview data to illustrate the themes and subthemes that emerged at each time point within an analytic narrative. This process acts as a reliability check to demonstrate how the data fits the initial analysis (Smith, 1996; Elliot, Fischer & Rennie, 1999).

10.3.2.1 Sample characteristics

Between April 2015 and May 2017, 24 participants who were scheduled to undergo adjuvant chemotherapy treatment and were eligible to take part in the quantitative study agreed to be interviewed for this study. As mentioned above everyone who was eligible to take part in the quantitative study was also invited to participate in the interview study. Two participants who did not wish to take part in the quantitative study consented to take part in this qualitative study.

In total, three participants withdrew from the study after T1. Two did not provide a reason for withdrawal and one participant was temporarily unavailable due to travel plans at T2 but continued in the study at T3. Five more withdrew after T2. Other than one participant whose cancer progressed necessitating additional chemotherapy treatment prior to T3, and another participant who unfortunately passed away, no reasons were provided for withdrawal although they all also withdrew from the

quantitative study. At T3, the final sample size included 17 participants, 15 of which completed all three-time points.

A total of 62 semi-structured interviews were conducted. As described in Chapter 7, Section 7.5.2, the approach to sample size in quantitative research, where larger numbers are generally more desirable, is not applicable to qualitative research, where the sample size reflects the depth and richness of information that describes a phenomenon (O'Reilly & Parker, 2013). (Please refer to Chapter 7 Section 7.5.2 for a full discussion of the sample size calculation). Therefore, this sample size was considered sufficient for the qualitative phase of this thesis (Castro et al., 2010).

Participants' ages ranged from 36 to 78 years, with a sample mean age of 63.17 years. There were a total of 15 male participants and 9 females. Participants' were mostly retired and educational status varied widely across individuals. The majority of the participants were Stage 3 CRC (Please refer to Chapter 1 for a full description of CRC staging); 18 participants were due to receive 12 cycles of intravenous chemotherapy whilst 6 were scheduled to receive 8 cycles of oral chemotherapy treatment; 15 of the 24 participants completed the scheduled course of treatment. One participant developed metastatic disease and went onto a second course of chemotherapy whereas the remaining participants stopped the treatment early due to severe adverse physical side effects. Basic demographic and clinical characteristics of the participants are presented in Table 10.1. Participant ID numbers were assigned to each participant to protect their identity.

Table 10.1: Participant demographics and clinical characteristics prior to the start of chemotherapy treatment (T1)

Characteristic	**Number of Participants (unless otherwise indicated:** n=24)
Age in years, mean (s.d)	63.17 (8.19)
FSIQ, mean (n =19)	102
Education	
• Less than 12 years	1
• More than 12 years	21
Gender	
• Male	15
• Female	9
Marital Status	
• Single/divorced/widowed	10
• Married/partnered	14
Occupational Status	
• Working	10
• Unemployed/Home maker	3
• Retired	10
• Student	1
Native English Speaker	
• Yes	19
• No	5
Tumour stage /TNM Stage	
• Stage I	0
• Stage II	6

Characteristic	**Number of Participants (unless otherwise indicated:** n=24)
• Stage III	16
• Stage IV	2
Tumour site	
• Colon	15
• Rectal	5
• Colon & Rectal	4
Stoma	
• No	17
• Reversible	6
• Permanent	1
Comorbidities	
• 0	5
• 1	7
• ≥ 2	12

10.3.2.2 Themes

Following the initial thematic analysis of the data, a number of codes were created and responses categorized into three main broad themes: 'participants' perceptions of the phenomenon of CRCI', 'participants' perceived experience of cognitive changes' and 'impact of cognitive changes' at each time point (as indicated in Table 10.2).

Table 10.2: Themes, subthemes, codes present across T1, T2 and T3

Themes	Subtheme	Codes	T1	T2	T3
Perceptions of CRCI	**Knowledge/ awareness of CRCI as a phenomenon**	Heard of it	✓	X	X
		May have heard of it	✓	X	X
	Concern	Concerned	✓	X	X
		Concern related to duration	✓	X	X
	Perceived causes of cognitive changes	Operation and/or anesthetic	✓	✓	X
		Just one of those things	✓	X	X
		Shock of diagnosis	✓	X	X
		Priming effect	X	✓	X
		Age related	X	✓	X
		Unexplainable/ something else	X	✓	X
Perceived experience of CRCI	**Affected cognitive domains**	Memory	✓	✓	✓
		Language	✓	✓	✓
		Concentration	✓	✓	✓
		Attention/ distraction	✓	✓	✓
		Dull/heavy head	X	✓	X
Impact of perceived experience of CRCI	**Changes to daily life**	Social activities restricted due to things other than CRCI	X	✓	X
		Modified social activities	X	X	✓
		Difficulties at work	X	X	✓

Themes	Subtheme	Codes	T1	T2	T3
	Emotional response/ attitudes towards noticeable changes	Not concerned	X	X	✓
		Frustrated	X	✓	X
		Dementia worry	X	X	✓

10.3.2.2.1 T1 (Post surgery, pre-chemotherapy treatment)

Theme 1: Perceptions of CRCI

This major theme emerged at T1 with three subthemes that highlight the fact that this is not a phenomenon usually associated with CRC and/or its treatment. The subthemes included the following: knowledge/awareness; concern and attributable causes of CRCI (Table 10.2).

i) Knowledge/awareness of the phenomenon of CRCI

The first subtheme "knowledge/awareness" relates to participants' general awareness of the existence of the phenomenon of CRCI. None of the participants recalled having received specific information from their medical teams about CRCI. The first mention of it was when they read the information sheets for this study. Nevertheless, when asked about it at T1, the majority of participants (18/24) said that they had never heard of CRCI. Unlike breast cancer patients, CRC patients appear (in the main) to be unaware of any potential cognitive impairments associated with CRC and/or its treatment. Only one participant mentioned having heard of it:

"Yes I did hear from a colleague who had a similar er diagnosis ……he in conversation mentioned … He mentioned that he had cognitive problems, and fatigue were his two…the two main things" (66 at T1).

Whereas two others thought that they may have heard of CRCI:

I have a friend… I…..She is 65 years old and she was having chemo and she was having radiotherapy and I think that she …she has been complaining that she forgot things that she lost her memory and all that….(44 at T1).

ii) Concern

Even though only a few participants had heard of CRCI, most said that they would be very concerned if it existed. Only one participant provided a reason for the concern, which was worry that such impairment would affect a return to work. 10 (approx. 42%) of the participants had been in employment up until their diagnosis and surgery for CRC).

"Ummm yeah…I would be… cause its…. I want to go back to work…. my memory has to has to be… pretty good because of what I do for a living…..I have to be on the ball …" (79 at T1).

A few participants were not at all concerned about the possibility of CRCI and four who felt that as long as it was only temporary then it did not matter if it occurred. For example:

"……., if it had a lasting effect I would be very concerned about it. Umm yes. But if it was a side effect during the treatment that went I would accept it as a side effect I think." (88 at T1).

iii) Causes of cognitive impairments

When participants were asked, what they thought might cause such cognitive impairments most did not have an answer. However, some people attributed possible causes to the operation itself and the effects of the associated medication:

> *The trauma of the operation. General stress about the condition, and possibly the anaesthetic (31 at T1).*
>
> *…that was the morphine (122 at T1).*

Whilst others believed it to be the result of the shock of the diagnosis:

> *Only to know that you have cancer and you are going to pass through to a lot of things is confusing and I think you have too much information in your head and too much thinking and worries that you get confused and sometimes you say oh I don't remember this, I forgot this, I don't remember that …so ….it's only because of that. I think it's confusing and too much pressure....(44 at T1).*

Theme 2: Participants experience of CRCI

This major theme emerged with several subthemes that elucidate the specific cognitive impairments experienced along with their consequences from pre- to three months post chemotherapy treatment. They included problems with memory, finding the right words, concentration, paying attention. A summary of this theme, its subthemes and the codes used in the analysis at each time point together with representative quotes are presented in Table 10.3.

Table 10.3: Perceived experiences of CRCI, subthemes, codes and selected quotes across T1, T2 and T3

Themes	Subtheme	Codes	Sample quotes		
			T1	**T2**	**T3**
Perceived experience of CRCI	**Affected cognitive domains**	Memory	"*Since I had the operation at the beginning of March, my memory is much worse than it used to be. .....(31).* *Sometimes you say oh I don't remember this, I forgot this, I don't remember that.....yes sometimes I forgot things.. Sometimes my children say 'Oh mummy but you said something' and I say 'no'. 'Yeah you said yesterday' and that is is worrying (44)* *ummm just I am having issues with ….walking into a room and thinking what did I come in here for (121).*	**General forgetfulness:** *I just think that little by little I lost my memory. I do things when I no have to do it and I put things where I cannot remember where I put it and I forgot appointments or I have to write down everything or I have to ask somebody to remind me because I think I been lost a lot of my memory… I can't remember sometimes things…. (44).* *…. getting confused just lately about meetings and things in yeah things in the diary that I've gotten wrong or things that I've forgotten to do that I wouldn't necessarily have forgotten before… (121).* **Losing things***:* *I've had a couple of incidents where …..I think I might have sort of forgotten things and I mistake things for ….objects for other things, like pens and pencils… I get… It's happened a few times, …… Like I would forget where I'd put my phone quite a bit….(55)*	*I'd forget simple things you know, like I'd go downstairs in the morning and find I'd left my watch or whatever, and I'd go back upstairs to get my watch and then come back down again and forget about the blasted thing you know… those sorts of things (30A).* *I have a lot of trouble remembering things…..It's worse. In the past if I tried to remember a name it would come eventually. At the moment it's as though somebodys put a black sheet of paper over it and I just can't see it, it's not there…. (31)* *It's just a bit…. like every time I leave I usually have to come back because I've forgotten something….. But that's been happening for years (55)* *I still kind of walk into a room and think I know I've walked in here for a reason,*

Themes	Subtheme	Codes	Sample quotes		
			T1	**T2**	**T3**
				I tend to leave things in the same place… but if for some reason my keys, if they're not where I usually put them then I can't then remember where I put them (57) *..where I put things, yeah, because I put my hearing aid somewhere, I'm damned if I can find them….(30A)* **Forgetting to pass on information***: Sometimes somebody says something to me and I've forgotten to pass the message, or something like that… (58)* **Forgetting to pay a bill:** *Oh I'd certainly forgotten to make a payment on my credit card that I thought I'd paid (121).*	*can't remember … walk backwards and then it comes to me (121).*
		Language	*I'll be sort of searching for the name but then I'll completely forget what the sentence was it was involved in." (31)*	*For the first three months, I found it very hard to pick out the right word and …. Sorry not the first three months, the three cycles (31)*	*Sometimes in finding the right word to say. Sometimes I'd use the wrong word (laughs). So I'd say something and somebody would look at me and go 'Is that what you meant?' (laughs) so….I think it got gradually worse throughout the chemo…..Now ….I still have that difficulty. I mean…., an example, over*

Themes	Subtheme	Codes	Sample quotes		
			T1	**T2**	**T3**
			I'm sort of …..yeah, not as clear in my thinking and speech (57). *I am having issues with grasping for the right word ……. I think the grasping the word has been feeling as if it's been getting worse (121)*	*I do crossword puzzles and sometimes I look at it and I know the answer but I can't bring it into my head and….er (57)* *..kind of phenomenon of saying 'Where's the doo-hickey that goes along the what's it called' kind of thing' I just said several words in a row, not even in a row, like several sentences at different times I just couldn't think of the right word. That happens to me occasionally…(68).*	*Christmas, I spent Christmas with my family and I called people by the wrong name so I called my sister by my daughter's name (laughs). My son by my partner's name… just came out (57).* *I am having issues with grasping for the right word ……. I think the grasping the word has been feeling as if it's been getting worse… (121).*
		Concentration	*Umm, concentration seems to have gone down a a bit… I've just noticed once or twice I'm sort of … (57)*	*.. I mean I like reading books, but … ummm I found it errr I found a sort of reading a sort of novel or something was too much on one go so I tended to read a errrr newspapers or things… (67a).* *….I lack in concentration although I can find it, if you know what I mean. If I really need to think 'I must think about this', um I tend to be able to concentrate a bit.* *….Yeah I don't read very much….yeah …. I can't find the concentration for that……. (57).*	*Concentration is limited….. I can read so long as there's not too many characters in it. But now if I try and watch anything that's a little too complex I just give up, I can't follow who the characters are.* *..[but] I'm doing something now that I wasn't doing when I was on the chemo. I'm attempting to do more complicated things (31)*
		Attention/	*…I noticed it over the last few months actually (before the operation) …I have some some little failures you know could be*	*……..it was difficult to keep up with other people's conversations. ….. (31)*	*One day I left the front door open and jumped in the car and drove off……But I think that was more preoccupied*

Themes	Subtheme	Codes	Sample quotes		
			T1	**T2**	**T3**
		distraction	*distraction I don't know…occasional ones…..Well there…Yeah there was one …. (laughs) er I found myself going down the stairs, I live on the second floor. I was … I was about to go out the door when I noticed I was wearing odd shoes…… they weren't the same colour or anything… one was a trainer and one was a black shoe (laughs)…totally different shoes… (131).*		*(laughing)…..Because when we came back, went to open the door and it was wide open…(66)* *I might start doing something in one room and then I'll get distracted and go and forget what I was doing… and then probably go back …errm probably about half hour …say I go in the bedroom and then I realise oh I didn't finish doing that …(91)*
		Dull/heavy head		*When I was on the Oxaliplatin I did feel that my brain was sort of going asleep, it wasn't as alert as it used to be, and I wasn't as quick at doing things. Since that stopped its improved but I'm certainly not up to the standard I was before I started on the chemo. …(31)* *….I had to think a little bit harder….I I was struggling reading which I do a lot of and I didn't I didn't want to read it….. because it just…my mind it felt… I don't know how to explain… the heaviness in my head and it was just like ….a bit dazy so I thought I just didn't want to read (79)*	

Affected cognitive domains:

Even before chemotherapy treatment had started, some patients reported experiencing problems with memory and language. However, very few patients thought that their concentration was worse than it was prior to the cancer diagnosis.

Memory

As can be seen in Table 10.3 prior to starting chemotherapy treatment a number of (although not all) participants felt, that their memory was worse than it was prior to diagnosis. Sometimes this involved difficulties remembering certain conversations:

> *Sometimes my children say 'Oh mummy but you said something' and I say 'no'. 'Yeah you said yesterday' and that is is worrying (44 at T1);*

At other times, it consisted of difficulty in remembering steps in a familiar activity (Table 10.3).

It was also interesting to note that two participants reported not noticing any impairment in memory yet spontaneously provided examples of walking into a room and not remembering why.

Language

Four of the participants that had mentioned changes in memory also tended to have trouble with word retrieval. This included examples of forgetting the names of people and things or not being able to find the right words to explain something as highlighted in Table 10.3. For example:

> *I am having issues with grasping for the right word ……. I think the grasping the word has been feeling as if it's been getting worse (121 at T1).*

Concentration

Participants were specifically asked about concentration but very few said that they had noticed any difference at any point in time. Only two people appeared to be affected by changes in concentration at T1.

10.3.2.2.2 T2 (mid-chemotherapy treatment)

Theme 1: Perceptions of CRCI at T2

The T1 theme regarding perceptions of CRCI also emerged at T2 with some slight differences. For example in relation to perceived causes of cognitive impairments, as time progressed different participants started attributing changes to different causes, such as age:

> *It's the occasional you know …what you call, a senior moment (66 at T2).*

There was also some suggestion that there was a priming effect for those who were participants in the study and had already been interviewed about their knowledge and experience of CRCI. An example of this awareness of CRCI particularly on the pre-arranged interview day and the possible effect that it had can be seen in the following quote:

> *Well I don't know whether it was because I was aware of this meeting today but this morning I was I was trying to update my diary and I was making all sorts of mistakes (laughs) and I don't know if that was a psychological '… oh my god I am going to be tested later' or whether it really is… (88 at T2).*

One woman appeared to attribute perceived experiences of changes in memory to an almost subconscious denial of having cancer (almost a form of rebelling against her

illness) rather than it being related in any way to her chemotherapy treatment:

> *don't know if that's down to the chemo, it could have been just some weird other thing..... like my husband would say, 'have you taken your pills?' .....I'd even bring them and have them in front of me on the table here and I just.... later on I'd go 'oh my god I forgot to take my pills'. That might be forgetfulness…But then again it might be I can't describe what I mean, some sort of psychological bulking… I don't like being sick, part of me doesn't want to take the pills, I might just have been. I don't know if it's memory failure or if it's a psychological problem (68 at T2).*

Theme 2: Participants experience of CRCI at T2

Whilst impairments in memory, language and concentration continued to be reported at T2, further implicated domains such as attention/distraction and general fogginess were revealed that had not occurred at T1 (Table 10.3).

Affected cognitive domains: Memory, language, concentration and attention

By T2, eight participants expressed problems with memory; four of whom had also mentioned this problem at T1, so there was no change for these participants. However not everyone who mentioned problems were able to provide any examples, whilst others provided one or two which were very similar to those reported at T1. The most often cited example was forgetting appointments (four out of the eight reported this experience). Other examples of memory loss included losing things, forgetting to pass on information and forgetting to pay bills.

At T2, six participants described difficulties in concentrating. Four of them talked about not being able to read anymore and one described how it now took him longer to do a Sudoku. A consequence of difficulty concentrating, or sustaining attention, is that it

often takes longer to complete tasks. One participant, who mentioned experiencing impaired concentration at T1, felt that it had further deteriorated at T2 although she described how when she really needed to do something she would put more effort into concentration.

> *….I lack in concentration although I can find it, if you know what I mean. If I really need to think 'I must think about this', um I tend to be able to concentrate a bit (57 at T2).*

Problems with paying attention were also reported by some participants in this study, and although very similar to concentration, participants were able to distinguish between the two. There was an implicit understanding that concentration is the ability to focus or sustain attention on one task, whereas directing attention requires the ability to focus on certain tasks in the presence of competing stimuli (Jansen et al, 2005). Some participants acknowledged that their ability to pay attention had changed (Table 10.3).

One participant also mentioned that she now had difficulty in multi-tasking:

> *I find it hard….I can only do 1 thing at a time now, whereas before I could I could probably juggle about 3 or 4 things at one go but now I can only do one thing at a time (91 at T2).*

Which is actually indicative of changes in executive function (Von Ah et al., 2013).

Dull head/fogginess

Although most of the participants who reported experiencing cognitive impairments of one type or another gave specific examples of memory failure and/or reduced concentration and attention, several also mentioned a general feeling of dullness or fogginess at T2. This is probably best interpreted as a lack of mental alertness.

Theme 3: Impact of cognitive changes during chemotherapy treatment (T2)

At T2, participants were asked how any cognitive changes that had been experienced affected their lives, in particular social activities.

Social activities

Although social activities were restricted throughout chemotherapy treatment for all participants except four, who said that it was the same as it was prior to treatment, no one attributed the changes to CRCI. Nearly all participants reported having restricted or stopped activities due to feelings of tiredness:

> *I think socially is more affected by the um…by the tiredness (57 at T2).*
>
> *I'm totally wrecked, like … tonight I'm meant to go to a social event that I'm really looking forward to but it's beginning to dawn on me, do you know …you're not going to be able to go, ……..I have also on purpose cut back on my relationships (68 at T2).*

One man stopped all social activity purely because of his feelings towards his stoma and another woman described how her social life had previously been inextricably linked to her work which she had had to give up due to undergoing chemotherapy treatment:

> *Well I don't have much social life now than before when I used to go to work and I used to share with my colleagues and things like that. Obviously now I I spend most of the time at home (44 at T2).*

Work/Study

Most participants in this study were not working either because they were retired or had taken sick leave prior to surgery and had not yet returned to work at T2 (Table 10.1). Therefore this was not discussed with participants other than with one man who

continued studying throughout although his attendance was restricted due to his physical side effects rather than any perceived cognitive changes.

> *most weeks, for example this week, I've been in three days….. So if there's not a pressing reason for me to go in, I wouldn't go in. Whereas before I would just go in. I just sort of try and take it a bit easier* (55 at T2).

Emotional impact of perceived CRCI

The only emotion mentioned in connection with experienced cognitive changes at T2 was frustration and it was in relation to memory:

> *I get frustrated when I cannot remember things or I forget things or I have to pay bills and I forgot the day or …sometimes if they don't remind me I forgot appointments, or things like that so it bothered me a lot (44 at T2)*

> *It got very frustrating because normally I've got a good memory (30A at T2).*

10.3.2.2.3 T3 (Three months post chemotherapy treatment)

Theme 1: Perceptions of CRCI at T3.

By T3 knowledge/awareness of CRCI was no longer an issue for the participants and was not discussed so no one mentioned what he or she thought might have caused any cognitive impairments experienced up until then. The researcher concentrated on experience of CRCI and its impact at this time as illustrated in Table 10.2.

Theme 2: Participants experience of CRCI at T3

Seven of the participants who had experienced CRCI at T2, continued to do so at T3, together with one additional participant.

Continuing impairments in the previously affected cognitive domains:

Some participants continued to report experiencing impairments in memory 3 months after their last scheduled chemotherapy treatment. They provided examples similar to those described at T2 such as forgetting where things were or had been put and/or why they had walked into a room. Only one person mentioned that her memory had actually deteriorated since finishing treatment (rather than having experienced such impairment during her chemotherapy journey). For the remaining participants the impairments appeared to be the same as during chemotherapy (T2) although two described their memory as being worse (Table 10.3).

By T3, no one reported experiencing any impairment in concentration suggesting that any perception of noticeable changes in concentration may resolve once treatment is completed. In addition, impairment in attention/distraction appeared to have improved in those patients who had reported it previously. Only one participant who had mentioned decreased attention and/or becoming easily distracted at T2 did so again at T3 (Table 10.3).

One participant did mention feeling something akin to the fogginess that had been described by others at T2, but he related that to the whole chemotherapy experience and going from being very busy with treatment and hospital visits to doing nothing at all:

> *I do find sometimes I feel a bit say with my head in the clouds but probably like I said I've stopped working and I've stopped going to the hospital and I find I have ……the whole morning doing nothing…..(83 at T3).*

Theme 3: Impact of cognitive changes at T3

Social activities

By T3, all participants except one recounted resuming normal activities and/or positive experiences surrounding their social life. Only one participant said that she had to modify her social activity post treatment but this was not connected to cognitive challenges rather to fear of recurrence or catching something or feeling a bit depressed by the whole experience:

> *I still don't go in the…. crowded places…..A little bit… ummm for the time being…. Until I find that I am fine. I get scared because I got my granddaughter I want to see her grow up so I don't want to recur or anything else…you know? For my precautions I don't go (58 at T3)*
>
> *it's okay yeah…..Ummm …..yeah it's a bit…sometimes I find it difficult to sort of motivate myself to go, go out out and things like that…but the majority of …I think it's just me feeling sorry for myself, I think, sometimes. I think it's just me sort of dwelling on stuff which I shouldn't be now because at the moment things are fine… (91 at T3)*

Return to work

However, perceived cognitive impairments did have an impact on those participants who had taken sick leave for the duration of treatment. On a return to work some participants found that their perceived cognitive impairments were highlighted, making it difficult to resume usual activities (Table 10.3).

> *…. when I went back to work when the kids were coming and asking miss how do you spell this? and I have to, I have to really think and I think 'what's the matter*

with you' , you know that sort of thing. So it was …that's…it was only when I went back to school, to work....with the children that I realised that my.. that sort of thing is sort of really starting to sort of get thingy. .., it's so frustrating (laughs) it really is (91 at T3).

Emotional impact of perceived CRCI

By T3, there was also less of an emotional response to the experience of CRCI. Only one person mentioned frustration this time. Rather a number of participants described the perceived cognitive changes that had been experienced as unimportant:

My view about memory has always been that if you can look it up it doesn't matter (122 at T3).

I mean so what if you forget something, it's not the end of the world (30A at T3).

Another was more concerned and upset about the loss of physical fitness experienced (he did not appear to notice any cognitive changes):

my main disappointment ….is ….the degree of loss of fitness and the slowness recovering it …..ummm…Definitely not as strong.. (122 at T3)

In line with the breast cancer research one lady attributed her perceived experience of cognitive impairments to the menopause:

I'd come through my menopause so I ..I always related it to that and just to getting older…(121 at T3).

Only one participant expressed worries about dementia:

I sometimes go 'oh god I hope I'm not getting dementia' (68 at T3)

10.3.3 Changes over time

It is evident from the above results that a sub-set of patients with CRC who were interviewed for this study experience some impairment in various cognitive domains before, during and after adjuvant chemotherapy treatment. However it is important to note that patients may experience adverse effects of surgery and anesthesia (Newman, Stygall, Hirani, Shaefi, & Maze, 2007), following a cancer diagnosis, which could influence cognitive ability at the pre-chemotherapy stage.

Although most participants were unaware of the existence of CRCI when they were first interviewed, a few did report experiencing impairments in memory (5/24 (21%)), language (3/24 (12.5%)), concentration (2/24 (8%)) and attention (2/24 (8%)) prior to starting chemotherapy, which is a lot less than the proportion who were found to have OCI on the NP assessments at T1. Some participants (7 out of the 24 (29%)) did not perceive experiencing any cognitive impairment at any time. As in Mitchell and Turton 's study (2011) some participants were keen to attribute cognitive impairment to everyday causes such as aging or the trauma of the illness and treatment, which they could understand, explain and justify.

Impairments in concentration, attention and feelings of dullness were reported with more frequency during chemotherapy treatment (i.e at T2) (Table 10.4) than at either of the other times (T1 or T3). Although it is important to note here that by T3 not all participants were interviewed again.

Changes in memory were reported by more of the participants both during (10/22 (approx. 43%) and after chemotherapy treatment (10/16 (approx. 62.5%) than any other type of cognitive change (Table 10.4). (Please note that one of these participants

although interviewed at T3 reported memory issues relating to T2 (as he missed T2) so his memory issue has been counted here rather than at T3 since he only spoke about the week following his first chemotherapy treatment.) Interestingly 3 out of 17 (approx. 18%) chemotherapy participants reported memory problems at T3 but **not** at T2, suggesting that for some chemotherapy patients' issues with memory may have become more noticeable after the chemotherapy treatment had finished and normal daily activities resumed. It is worth noting here that participants were asked to talk freely about their experience of changes (if any) in cognition, so it could also be argued that many simply used language that suggested memory impairment rather than any other impairment. The word "memory" is a familiar one, which is used in everyday conversation, whereas something like 'executive function' is quite a technical term that is rarely (if ever) used.

Memory issues contrast with other perceived impairments that reportedly improved 3 months after chemotherapy treatment, such as concentration and attention/distraction. Three of the participants (interviewed at both T2 and T3) who had mentioned poor concentration during chemotherapy did not mention it again several months after finishing chemotherapy treatment. Also 2 of the 3 participants interviewed at T2 who had mentioned problems with attention/distraction did not do so again at T3.

Table 10.4: A table of each participant's experience of the cognitive domains that were affected over time

Participant	Memory			Language			Concentration			Attention/Distraction			Dull/heavy head		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
30a	X	Y	Y	X	X	X	X	X	X	X	X	X	X	X	X
31	Y	X	Y	Y	Y	Y	X	X	Y	X	Y	X	X	Y	X
38	X	X		X	X		X	X		X	X		X	X	
44	Y	Y		X	X		x	Y		x	X		X	X	
55	X	Y	Y	X	X	X	X	X	X	X	Y	X	X	X	X
57	X	Y	Y	Y	Y	Y	Y	Y	X	Y	X	X	X	X	X
58	X	Y	Y	X	X	X	X	X	X	X	X	X	X	X	X
59	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
62	Y	Y	Y	X	X	X	Y	X	X	X	X	X	X	X	X
66	NR	X	X	NR	X	X	NR	X	X	NR	X	Y	NR	X	X
67a	X	X	X	X	X	X	X	Y	X	X	X	X	X	X	X
68	NR	X	Y	NR	Y	X	NR	X	X	NR	X	X	NR	X	X
69	X			X			X			X			X		
72	X	X		X	X		X	X		X	X		X	X	
73	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
79	X	X		X	X		X	Y		X	X		X	Y	
83	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
88	X	NR	NR	X	NR	NR	X	NR	NR	X	NR	NR	X	NR	NR
91	X	Y	Y	X	X	X	X	Y	X	X	Y	Y	X	X	X
94	X	Y		X	X		X	Y		X	X		X	X	
102	X		Y[1]	X		X	X		Y[1]	X		X	X		X
121	Y	Y	Y	Y	X	Y	X	X	X	X	X	X	X	X	X
122	Y	X	Y	X	X	X	X	X	X	X	X	X	X	X	X
131	X			X			X			Y			X		

Key: T1: Post surgery, pre chemotherapy treatment; **T2:** Mid chemotherapy treatment; **T3:** 3 months post last scheduled chemotherapy treatment; **NR**: No response. 102 Y[1]this participant only talked about the week immediately after his first chemo session; **X:** not affected or not mentioned as having been affected; **Y:** affected

10. 4 Step Two: Content analysis and results

10.4.1 Analysis

The initial analysis was successful in building crosscutting themes and clearly illustrated the perceived cognitive experiences of some of the participants at each time point. It did not, however, enable an examination of the changes that emerged over time as the context of the treatment changed (Murray et al, 2009). Therefore, the researcher conducted further analysis in order to explore the individual trajectories and examine whether there were any identifiable patterns in change in perceptions and experiences of CRCI in individuals across time (Saladans, 2003). An inductive qualitative analysis (Graneheim & Lundman, 2004) was conducted for each interview.

Once the content of an entire interview had been grasped (i.e. a sense of the whole had been grasped), meaning units were identified, consisting of words, sentences or paragraphs containing aspects that were related to each other through their content and context (Graneheim & Lundman, 2004). The meaning units for each interview for each participant were then condensed (i.e. shortened while still preserving the core) and labelled with a code. An example of meaning units, condensed meaning units and codes are shown in Table 10.5.

Table 10.5. An example of the analytical steps from meaning units to theme (31)

Meaning unit	Condensed meaning unit	Code
It was difficult to keep up with other people's conversations and I totally lost interest in current affairs so I wasn't reading newspapers which also made the brain feel a bit dull. ....For the first three months I found it very hard to pick out the right word	Difficulties in following conversations, current affairs, reading newspapers, and word retrieval.	Experiencing problems with concentration and memory

The whole context was taken into consideration during the condensing and labelling of the meaning units with codes. The various codes were compared based on differences and similarities and sorted into sub-categories and categories. Lastly, the underlying meaning, of the categories, was formulated into a theme, which Graneheim and Lundman (2004) described as being a thread of an underlying meaning through, condensed meaning units, codes or categories, on an interpretative level.

A summary for each interview was then formulated based on the content of the subcategories, categories and themes for each interview. The three time points for each participant were considered as a whole and reflected upon in light of the focus of this study – '*how can the cognitive journey for this person be described*?' A consideration of the changes and similarities for each persons' experiences, thoughts and feelings about their cognition lead to the emergence of three main patterns as described in Section 10.4.1.

Following a further analysis of the themes (as described in section 10.3) over the nine-month period, a number of patterns appeared to emerge across the participants.

10.4.2 Results

Three main patterns were distinguished as a result of this further analysis. They were: 1) No concern at any time and life continued as usual; 2) Concern with cognitive challenges were constant throughout the chemotherapy journey influenced by notions of dementia or concerns about work; 3) Cognitive issues were secondary to other concerns**.** Two participants did not fall into any of the patterns because they only did one interview at T1 and were therefore excluded from this analysis, as there was no journey to follow.

1) No concern at any time and life continued as usual

Three of the six participants who fell into this category had mentioned that they knew of the existence of CRCI (specifically changes in memory) prior to starting chemotherapy treatment but were unconcerned. Five of the participants were married and all six were retired or not working. Three participants did not experience any physical side effects at all during the treatment and did not perceive any noticeable changes in cognition at any time (38, 66, and 72). They all mentioned that nothing in their lives had changed and no one around them had noticed anything different either. It was interesting to note that two of the participants didn't give much thought to the cancer diagnosis possibly due in part to the fact that they did not experience any side effects (which for others were quite debilitating), they were just thankful that it was now gone:

> *"We've had the operation, the tumour's taken out, so that's the end of that. ….. So I don't dwell on the fact that I had cancer or whatever. It doesn't really come into my mind as such" (66, T2).*

"By the grace of God I was lucky that it was caught in time and what was done .." (38, T2).

The other three participants who fell into this pattern, did experience some physical side effects (such as tiredness, sensitivity to the cold and diarrhoea) during the treatment, which disappeared as soon as it finished; and although some social activities were restricted due to the tiredness nothing else changed and they did not experience any issues with cognition (other than what one of them called "usual" forgetfulness (73)) at any time (67a, 73,122).

2) Concern with cognitive challenges throughout the chemotherapy journey and the possibility of future dementia

Three participants reported having experienced both physical and some cognitive impairments prior to, during and after chemotherapy treatment although the overriding concern appeared to be about the possible future consequences of the cancer itself. For example, in response to a question about the impact that any perceived changes in memory and concentration may have had, one participant said:

hopefully the cancer is over now and you want to go forward. I think well what can I go forward doing? How much of the energy will come back? How much of the mobility will come back? How much of the cognitive powers are going to come back? (31, T3)

For the participants in this second pattern there appeared to be some sort of link between perceived CRCI and the physical side effects experienced. The more severe the physical side effects experienced during the treatment the more cognitive impairments were reportedly perceived but it is unclear whether this was also partly due to the fact

that by virtue of participating in the study they had been primed to the idea of experiencing CRCI. It is also worth noting that these participants were not working during the treatment and/or study period and may have had more time to think about all of their side effects both physical and cognitive. In addition their cognition was less likely to have been tested as they were not in a work environment and also others were less likely to notice or report cognitive impairments if they were not working.

Two of the participants in this second pattern were female and went on sick leave following the cancer diagnosis. Both had children and expressed a wish to return to work after treatment was completed, although only one of them actually did. However, both continued to report experiencing poor concentration and memory loss three months after treatment, to the extent that one was signed off work and the other found herself experiencing more memory impairments on her return to work.

3) Cognitive issues were secondary to other concerns (such as tiredness, stomas or severe physical side effects)

Eight participants who described experiencing severe tiredness or fatigue were not aware of very much else during the chemotherapy journey. So even when specifically asked if they had noticed any changes in memory or concentration the conversation always turned to fatigue or tiredness. Three of the eight acknowledged occasional forgetfulness but said that they were "*no more than prior to the operation"* (58, T2); they were "*nothing major"* (55, T2); "*annoying but no big deal*" (57, T3).

For one participant who experienced significant physical side effects during treatment, cognitive changes were not immediately evident:

*The truth is … my everyday activities are so limited, I'm lucky in that I can assign myself to do nothing. … So I just spend my time laying around. If I were out in the community trying to do something, it might be that I would fall apart, mentally. But…just as I say, laying around watching Big Bang Theory you don't even know if your capacity to express yourself is good or bad, you're just in a place of rest (*68, T2*).*

Once healing and physical side effects subsided and life routines returned to a relatively normal state of activity, the cognitive changes became more evident. However, two other participants had such severe side effects following the first chemotherapy cycle that the treatment was stopped and normal life resumed for them in all respects. Neither reported any issues with cognition were experienced after the first few days of having had chemotherapy (79, 102).

One participant who had a permanent colostomy bag (stoma) although aware of having experienced some forgetfulness, it really paled into insignificance as he was overwhelmingly concerned about his stoma and the embarrassment that it caused him to the extent that he stopped all social life and didn't tell any of his friends or family that he had been diagnosed with cancer:

" I have no, my social life is dead…..Because of this (points at stoma)…." (62).

10.5 Discussion

As reported by Staat & Segatore (2005) this study found that the potential for impairment in cognition is rarely (if ever) discussed with patients who are diagnosed with CRC prior to adjuvant chemotherapy treatment. This was apparent from the overwhelming lack of awareness of CRCI reported prior to the start of chemotherapy,

and a recounting of all of the possible physical side effects. However, as it was a phenomenon perceived to have been experienced by a number of patients who had been successfully treated for CRC it is reasonable to suggest that there is a clinical need to address this issue with patients. None of the participants in this study mentioned having discussed their experiences of cognitive impairments with the medical teams yet it was evident from this study that such changes were a source of frustration that also presented social and employment challenges.

Research has shown that informing participants that "chemobrain" might occur increases the incidence of reporting cognitive impairment during treatment (Schagen et al. 2009), and there was some suggestion of this occurring in this study. One participant did wonder whether simply knowing that he was to be assessed for the study made him more aware of his forgetfulness that day. Mitchell & Turton (2011) draw comparisons between the experience and reporting of "chemobrain" to the emergence of fatigue as a significant symptom experienced by patients with cancer. They describe how initially fatigue was ignored by clinicians but over the past 20 years fatigue has been increasingly recognised as a side effect of both cancer and chemotherapy and the incidence of patients reporting it has escalated.

This study highlights the fact that subjective experiences of cognitive change is a complex phenomenon. It is a continuing and evolving experience, which also, appears to be inextricably linked for some patients to the severity of the physical side effects experienced (as seen in the patterns that emerged over time). Approximately one third of the participants in this study felt that their memory and/or attention had been affected at some point along the chemotherapy journey (i.e. between T1 and T3) (Tables 10.3 and 10.4). These findings are broadly consistent with the current literature on

focus group/interview studies with breast cancer patients (Shilling & Jenkins, 2006), although slightly fewer participants appear to have reported experiencing such changes. However not all participants took part in all three interviews so it is possible that this affected the overall prevalence in this group of patients.

This study therefore builds upon the existing evidence in relation to CRCI in another type of cancer that is not breast, as is most often researched. One of the strengths is that it offers some insight into a range of people's experience of the changes from before the start of chemotherapy treatment until 3 months after. It is difficult to truly understand the trajectory and effect of perceived cognitive impairments without hearing from the participants on more than one occasion. Data from questionnaires do not fully capture the nuances or patterns that emerge in the same way that these interviews do. In corroboration of Kanaskie and Loeb's (2014) interview study with seven breast cancer patients, it was evident from the participants in this study that the experience of cognitive impairment could not be isolated or studied separately from the context of the participants' reality of having cancer. Where participants had severe fatigue for example there was no escaping this new reality (which caused them to sleep during the day and withdraw from all social activities etc) it was a constant reminder for them.

Similarly, to Von Ah et al's (2013) findings, although participants reported that cognitive changes had a negative impact on social activities and work ability, they still expressed gratitude and even satisfaction with their life. Many indicated that they were grateful that they were cancer free. In answer to a question about whether overall life satisfaction had changed because of the treatment journey the response was:

"No. I would say improved by the whole thing really. With my outlook on stuff, yeah there's been no negative effects really at all" (55, T3)

It would be interesting to see if the patterns change, again one-year post chemotherapy treatment as three months is quite a short period where survival rates are in excess of 10 years.

10.6 Summary

The present study explored the perceived changes in cognitive impairments over time in a subset of patients with CRC who underwent chemotherapy treatment.

The overall narrative indicated that some patients with resectable CRC do experience impairments in several cognitive domains such as memory, attention and concentration, which persist for at least 3 months after chemotherapy treatment, has finished. For some this was a frustrating experience and one that also caused problems on a return to work. The findings of this study could help inform psychological support especially in relation to illness and treatment progression. This study also highlighted the need for, further research related to employment challenges among cancer survivors who experience CRCI (Kanaskie & Loeb, 2015).

The following chapter will now bring together the findings from the quantitative and qualitative studies in order to discuss the contribution of the thesis to existing knowledge and the implications for research, theory, and practice.

Chapter 11: General Discussion

11.1 Introduction

This final chapter provides a discussion of the key findings of the quantitative and qualitative studies reported in Chapters 8 to 10 and how they fit with previous research reported in Chapters 3, 4 and 5. The discussion begins with the main aims of the thesis followed by an integrated synthesis of the findings from the quantitative and qualitative studies. The overall aims are discussed in relation to how these studies contribute to the literature in the area. The strengths and limitations of the current research are then outlined, followed by a discussion of the implications of the findings and recommendations for future research.

11.2 Aims of the thesis

This thesis examined CRCI (objective and subjective) in patients diagnosed with CRC. In particular, cognitive, psychosocial and HRQoL outcomes were considered using a comparative longitudinal, mixed methods design. The cognitive function and experiences of patients diagnosed with CRC scheduled to undergo adjuvant chemotherapy treatment were compared with a "surgery only" control group (prior to, during and after chemotherapy treatment) over a period of 9 months. Data were collected using NP assessments, self-report questionnaires and interviews and the findings of each component part of this thesis (as outlined in Chapter 6) were discussed in their corresponding chapters.

11.3 Study set up

Setting up the study took a considerable amount of work, before the PhD began. It was necessary to obtain at least one patient's perspective on the proposed study prior to requesting NHS ethics committee approval. Given the limited resources available at that time, it was difficult to obtain patient and public involvement (PPI). Nevertheless, adverts were posted on Beating Bowel Cancer's patient forum and MacMillan's Cancer Support online community, inviting members of the public who had been diagnosed with CRC to give their thoughts and opinions on the quantitative study design. It would most likely have been a more effective use of time (and had the resources been available) if PPI had involved the use of focus groups enabling a broader discussion with a larger group of people.

Nevertheless, the feedback received in relation to the design was positive. It was felt that the study was needed particularly if CRCI was found to be a side effect and something could be done about it to help future patients. Cancer survivors report oncologists and other health professionals rarely mention the possibility of CRCI prior to commencing cancer treatment (Boykoff, et al, 2009; Mitchell, Woodward & Hirose, 2008), despite survivors advising the health care professionals, that knowing about this possible problem would help them to prepare for it. Ethics approval of the Protocol (Appendix H) was granted in August 2013. Due to the limited PPI obtained, it was decided that a "feasibility trial" would provide the researcher with more insight as to the suitability and acceptability to CRC patients of the study design and measures. In addition, it was important to understand the feasibility of implementing the Protocol in this particular patient group recruited solely from London based NHS hospitals. It also

made it possible to determine the resources required to perform the study and to assess whether the Protocol could be implemented as designed or whether significant alterations would be required. If no significant changes were to be made to the Protocol, the data obtained from the participants during the course of the feasibility trial could be (and was) incorporated into the full study (Appendix J: the "Feasibility Trial").

It is arguable whether more extensive PPI would have led to greater success in recruitment. Perhaps individuals of differing ages who had experienced CRC and its treatment would have been able to provide the researcher with more valuable insight into the best way of approaching eligible participants. However, the Feasibility Trial provided this insight and although it entailed 'learning on the job', recruitment rates were on a par with other studies of this type conducted in the same patient group (e.g. Vardy et al, 2014). In addition, without having conducted the Feasibility Trial, the researcher would not necessarily have discovered through PPI alone that the age limit of 65 was too restrictive. This information came to light after attendance at the MDT'S. It became clear that potentially eligible participants needed to be carefully tracked from screening to post surgery in order to ensure eligibility, as final staging was not confirmed until after surgery. It is also unlikely whether a larger feasibility trial would have led to greater retention rates given the nature of the disease and its course.

11.4 Feasibility Trial

As mentioned in Chapter 8, the upper age limit on recruitment was lifted and the MOCA was abandoned as a result of carrying out the Feasibility Trial. Both changes were considered necessary in order to improve the rate of recruitment. In relation to the

MOCA there were people who failed to score sufficiently high to be allowed to continue into the study but who nevertheless wished to continue. There were also those who scored only a point or two lower than the cut-off but were simply not permitted to continue, which required a skillful exit on behalf of the researcher, as it may well have been considered to be unethical to tell the patient that he/she had a score suggesting MCI. As mentioned in Chapter 7, the MoCA is a screening tool that has been specifically designed to assess MCI and dementia in first line specialty clinics (Nasreddine, et al., 2005). Whilst it has a high sensitivity to detect probable MCI in older patients (Naserdine et al, 2005), its sensitivity and specificity have been found to vary in different clinical populations (McLennan, Mathias, Brennan, Stewart, 2011). It is arguable that the MOCA can be used to screen for cognitive impairments that may have other conditions that are ultimately diagnosed including delirium, long-standing cognitive impairment (Libert, Dubruille, Borghgraef, Etienne, Merckaert, et al, 2016). The patients who scored just below the cut off in this study may not have had the same risk of progression to dementia and it would have been unfair if a diagnosis such as MCI or dementia was communicated. It was therefore considered inappropriate to use the MOCA as a pre-screening tool in this study.

As the population ages, increasing numbers of patients with pre-existing MCI or dementia will be diagnosed with cancer, so examining the role that cancer and its treatment may play in the exacerbation of cognitive impairment in older adults will be very challenging (Gupta & Lamont, 2004). It would have been interesting to examine those patients who were already assessed as having MCI (according to the MOCA) and the effects of chemotherapy treatment on them over time if the sample size had been significantly larger and they had been warned in advance that by taking this test they

may receive a score suggesting MCI. This is an area that could be examined further in a larger study of this type.

11.5 Integration of the findings from the quantitative and qualitative studies

The following sections seek to integrate the findings from the quantitative and qualitative studies and discuss the overarching conclusions within the existing literature and the main implications of the study as a whole. The integration of the findings from mixed methods at the interpretation stage is considered important for achieving the full potential of this approach (O'Cathain, Murphy, & Nicholl, 2010). The assimilated findings provide various insights with regards to CRCI (objective and subjective) and its effects on patients with CRC.

11.5.1 Pre-chemotherapy

Cognitive Impairment:

As indicated in Chapters 2, 3 and 4, cognitive impairment (objective and subjective) has been measured and defined in numerous ways in the "cancer and cognition" literature, which has no doubt contributed to the inconsistent findings to date. In the literature reviews in Chapters 3 and 4 it became evident that the concentration on female breast cancer patients and the numerous methodological issues encountered produced inconsistent findings across all studies (quantitative and qualitative) that examined CRCI. These issues have limited the ability to draw clear inferences about the prevalence, extent, course, or lived experience of CRCI. The present study sought to examine CRCI in a different cancer population (affecting both men and women) over

time using some of the evolving recommendations of the ICCTF (Wefel et al, 2011) alongside some semi-structured interviews.

Early studies often assumed that patients diagnosed with cancer would have normal cognitive functioning prior to treatment, which would be adversely affected by exposure to certain chemotherapeutic agents (Ahles & Root, 2018). However, in this study, a higher than would be expected percentage of individuals diagnosed with CRC were found to have OCI at the first assessment (i.e. post-surgery and pre-chemotherapy treatment) in both groups. It is possible that this was due to the effects of the surgery. Postoperative cognitive dysfunction (POCD) affects surgical patients in all age groups on a short-term basis, but resolves faster in a younger population (Steinmetz, Christensen, Lund, Lohse, Rasmussen, 2009). Therefore, it is possible that the participants in this study (who had an average age of 63) were suffering from POCD at the time of the first assessment. However, it should be bourne in mind that most research in POCD has been carried out on cardiac patients who often endure long duration of cardiopulmonary bypass, which has been reported to be a significant risk factor for POCD (Krenk, Rasmussen, & Kehlet, 2010). Nevertheless both cardiac and non-cardiac research has shown that in individuals over the age of 60, POCD can last for months and may result in a reduced ability to handle everyday tasks and hold a job (Dijkstra, Houx, & Jolles, 1999).

The baseline assessment took place just several weeks after surgery (mean = 47.76 days in the chemotherapy group and 52.74 days in the “surgery only” group) as have many other longitudinal studies in the literature. For example, in Jenkins and colleagues (2006) study with breast cancer patients the first assessments took place a mean of 41.29 days after surgery in the chemotherapy group and 53.21 days in the non-

chemotherapy group. Also, Vardy and colleagues (2015) assessed patients with localised CRC scheduled to have chemotherapy at approximately 6.8 weeks post-surgery and those who were not scheduled for further treatment were assessed a mean of 9.2 weeks after-surgery. The reason for the later assessments in the "surgery only" patient groups could be due to hospital follow up appointments being scheduled later than for the chemotherapy patients who have a relatively short window within which time adjuvant chemotherapy has to commence. Although there was a statistically significant difference between the groups in time from surgery to first assessment in this study, it was a small effect size and there was no significant difference between the groups in relation to the type of surgery performed (i.e keyhole 'v' open surgery) or in the proportion of impaired individuals.

Although a higher than expected percentage of participants were found to have OCI at the first assessment in this study than would be expected by chance, the findings corroborate other studies that have examined pre-chemotherapy OCI in patients with CRC. For example, Cruzado and colleagues (2014) and also Vardy and colleagues (2015) found 37% and 48-52% impairment respectively using ICCTF criteria on NP tests in patients with localised CRC. Vardy and colleagues (2014) found no significant difference in rates of cognitive impairment between patients' pre and post-surgery arguing that causes other than surgery and anaesthesia, fatigue or anxiety and depression are responsible for the high rates of OCI in patients with CRC at baseline. Similarly, OCI was not found to be related to anxiety, depression or fatigue in this study. It may be that there is something about CRC itself that causes changes in cognition (Vardy et al, 2014). Although, the stress and shock of receiving a diagnosis of cancer was mentioned by several participants in the qualitative study as a possible contributory factor prior to

starting chemotherapy treatment. Hermelink and colleagues (2007 and 2015) found that post-traumatic stress symptoms mediated the relationship between breast cancer diagnosis and cognitive performance on an NP test prior to chemotherapy treatment.

Preliminary analyses of baseline quantitative data revealed no significant differences in objectively measured cognitive function between the chemotherapy group and "surgery only" group, which is in line with previous findings (e.g. Bender et al., 2006, Jenkins et al., 2006; Schagen et al, 2006; Vearncombe et al, 2009). However, these findings are opposite to a number of other studies in breast cancer patients. For example, Stewart and colleagues (2008) found a threefold greater risk of cognitive decline in the chemotherapy patients compared to hormonal patients (31 and 12%, respectively) although very few participants fell in the impaired range at any time (1.3% chemotherapy patients, 0.8% hormonal patients). Once again, this raises the possibility that CRC itself shares a common aetiology with cognitive impairment. Consequently, this finding adds to the debate surrounding pre-chemotherapy cognitive function in patients diagnosed with solid tumours other than breast cancer.

There were also no statistically significant differences found between the two groups in relation to perceived cognitive abilities or impairments at baseline (as measured by the FACT Cog PCA and PCI subscales). However, as mentioned previously, in the absence of any normative data it is not possible to say whether there was a greater incidence of SCI found in either group at baseline in this study than would be expected in the general population. Dhillon and colleagues (2018), found that the prevalence of cognitive symptoms reported pre-chemothearpy treatment in patients with CRC was 18 -24% which was less than the OCI that they found at that time. It would be interesting to examine whether the prevalence of SCI is the same in this study, using Dhillon and

colleagues definition; particularly as there was a higher percentage of participants that scored below normative ranges on NP assessments in this study, than in Dhillon's study. If a lesser incidence of SCI than OCI were to be found at baseline in this study, it is possible that some participants would simply not have realised just how many lapses in memory or concentration they experienced prior to the first chemotherapy treatment. If they already have OCI it is arguable whether they would notice that they were experiencing any cognitive problems; they would not be able to remember what they could not remember. There is evidence of this in the interview study. For example, one participant described how her memory problems (of which she was not totally unaware) had been commented on by family members prior to the start of chemotherapy treatment:

> *Sometimes my children say 'Oh mummy but you said something' and I say 'no'. 'Yeah you said yesterday' and that is is worrying…… but no not much …….but it don't affect my activities yet and I hope don't happen because it's terrible (44 at T1).*

Most commonly affected cognitive domains:

As discussed in the literature review, memory, processing speed and executive function appear to be the most affected cognitive domains (Wefel et al, 2011). Similarly, the most commonly affected domains (in both groups) in the NP testing in this study were verbal memory, motor function and executive function. Impairments in verbal memory were also implicated in the interviews prior to the start of chemotherapy treatment, with some of the chemotherapy participants reporting experiencing problems with memory and language (such as word retrieval).

Schagen, Das and van Dam (2009) demonstrated that priming or pre-existing knowledge regarding the concept of CRCI significantly increases the reporting of cognitive complaints. However, for ethical reasons, it was necessary to inform participants of the purpose of the research and so the association between chemotherapy and possible cognitive impairment is evident in the Participant Information Sheets (Appendix I). Priming may not be an issue in this work because although a few chemotherapy participants reported that they believed chemotherapy to be the cause of their cognitive difficulties, others dismissed this idea and described how these difficulties existed prior to the start of the chemotherapy treatment and instead were age-related or related to the surgery (Chapter 10). Additionally, unlike breast cancer patients who may have knowledge about CRCI through the media or cancer support groups (Schagen, Das and van Dam, 2009), the possibility of cognitive impairment is not often associated with CRC and its treatment and the interview findings confirmed this.

Mood, fatigue and HRQoL

It is interesting to note that the percentage of participants in both treatment groups reporting clinical levels of anxiety and depression at baseline were comparable to the estimated percentages found in the general adult population (Crawford et al, 2001; Keating et al, 2005). There were no significant differences between the two groups in baseline measures of anxiety or depression. It is possible that having recently undergone curative surgery meant that the participants in this study were not very anxious or depressed at the time of the first assessment. All participants having just recovered from major surgery to remove the cancer had a good prognosis (with chemotherapy being prescribed as a precautionary measure rather than as a lifesaver).

The greatest rates of depression have been found in those with advanced forms of cancer (40-50%) (Honda & Goodwin, 2004; Hewitt & Rowland, 2002; Fallowfield et al, 2001; Derogatis et al, 1983). There was however, evidence of feelings of anxiety prior to the start of chemotherapy in some of the interviews with the chemotherapy participants (Chapter 10), which may have been linked to some of the cognitive lapses experienced. For example, one participant described how:

> *Only to know that you have cancer and you are going to pass through to a lot of things is confusing and I think you have too much information in your head and too much thinking and worries that you get confused and sometimes you say oh I don't remember this, I forgot this, I don't remember that …….(44 at T1).*

In corroboration of Dhillon's (2017) findings SCI (as measured by the FACT Cog PCI subscale) in this study was significantly associated with depression, anxiety, fatigue and poorer HRQoL, yet neither FACT Cog PCI nor PCA were associated with NP performance at the first assessment. Shilling and Jenkins (2007) suggested that reports of memory problems are more indicative of psychological distress rather than objectively measureable memory change.

There were also no significant differences between the two groups in baseline measures of fatigue and HRQoL (Chapter 8). Although 38% of the chemotherapy participants reported having experienced clinically significant symptoms of fatigue after surgery at T1 (i.e. a score of < 37 on the FACIT Fatigue questionnaire), this was actually a smaller percentage than the 52% in Vardy and colleagues' study (2014) who were found to have reported fatigue. This could be partly because Vardy defined fatigue differently to the method used in this thesis. She defined moderately severe fatigue as "*equal to a*

standardised FACT F subscale score of < 68/100 which is 1 SD below the mean for the general US population".

It may also be that a large percentage of patients with CRC are more anaemic than patients with other solid tumours and consequently are more tired leading to poorer cognitive function at baseline. For example, Tas and colleagues (2002) found that 71% of patients with CRC had anaemia before the start of chemotherapy treatment, as opposed to 44% of patients with breast cancer. It would be have been interesting therefore, to monitor haemoglobin levels in both participant groups in this study at each assessment time point.

11.5.2 CRCI trajectory

OCI:

The "cancer and cognition" literature provides evidence of subtle OCI in a subset of breast cancer patients undergoing chemotherapy. The quantitative findings from this study revealed non-significant differences in the prevalence of OCI in those who received chemotherapy and those who did not, during or after chemotherapy. There were proportionately more people in both groups (compared to normative data based on age, gender and education) who were found to be cognitively impaired pre, during and after chemotherapy than would be expected in the general population.

Of particular interest in this study is the finding that there was a greater proportion of patients (in both groups) who were found to have OCI at T2 than there were at T3, suggesting that cognition improves with time for a subset of patients. This trend has been reported in a number of the breast cancer studies (e.g. Collins et al, 2009; Wefel et al, 2010; Ahles et al, 2010) (Chapter 3). In relation to the chemotherapy participants

this is not a surprising finding given that chemotherapy drugs are often administered with a host of other medications including opioids and/or anti-sickness drugs both of which have been found to be associated with poorer cognitive functioning (Kurita, Lundorff, de Mattos Pimenta, and Sjøgren, 2009). The use of medications before and after chemotherapy is not at all well documented in the literature (Phillips & Bernherd, 2003) and this data was also missing from this study; although it is thought that use of antiemetics can affect the central nervous system it is unlikely that they have a prolonged effect (Phillips & Bernherd, 2003). As this pattern was also found in the "surgery only" patient group, even though these participants did not continue on any further systemic treatment after surgery it could be linked to the cancer itself or perhaps these patients were also taking pain killers for a prolonged period of time. The results of the longitudinal analysis showed that after controlling for the baseline assessments there was very little change in objectively measured cognitive function over time. There was no statistically significant improvement. This could partly be due to the relatively large number of tests that were administered to a small sample of participants.

SCI:

Similar results were found in relation to the subjective reports of cognitive function as measured by the FACT Cog questionnaire. There were subtle but non-significant differences in the scores between the two groups, and over time. After controlling for baseline, the means scores on the FACT Cog in both groups were very similar at all follow up assessments.

Interviews from the qualitative study provided more detailed insight than the questionnaire data. They suggested that perceived difficulties in memory that had been experienced during chemotherapy treatment continued (and in some cases worsened) 3 months after chemotherapy for some participants. Whereas by 3 months post-chemotherapy treatment any problems with concentration that had been experienced during treatment had resolved. In addition, impairments in attention/distraction appeared to have improved in those patients who had reported it previously. During the interview's participants were gently probed about issues with memory and/or concentration and were allowed to talk freely about any cognitive issues that they had experienced. So, whilst the FACT Cog assesses memory and concentration it is done in a more focused fashion by a combination of negatively and positively worded questions. There is a suggestion that the negatively worded items of the FACT Cog PCI subscale might be tapping into more of the negative affect such as depressive symptoms, distress, etc (Von Ah & Tallman, 2015). Whereas in interview the participant is not necessarily thinking about mood when concentrating on discussing/describing experiences of memory lapses or difficulties with word retrieval. In addition, the questionnaires ask participants about experiences relating to the past seven days whereas in interview people talk about what they can remember has happened since the last interview (i.e. over a period of several months).

It is important to recognise that even subtle cognitive changes can have a detrimental impact on daily functioning and quality of life (Meyers & Perry, 2008; Vardy & Tannock, 2007), as evidenced by the qualitative findings. Findings from the interview study revealed that a subset of participants experienced cognitive difficulties, in particular memory difficulties, concentration difficulties and language difficulties. Excerpts

revealed that participants (i.e. the chemotherapy patients) experienced these cognitive difficulties more frequently than was perhaps suggested by the Fact Cog, and most notably between pre and mid chemotherapy treatment. Similar findings have been reported in previous qualitative work (e.g. Cheung et al, 2012; Downie et al, 2006; Munir et al, 2010; Myers, 2010). Furthermore, the impact of these cognitive difficulties on daily functioning included difficulty returning to the work:

> "*when I went back to work….I have to really think and I think 'whats the matter with you? You know that sort of thing'" (91 at T3)*

which corroborates findings reported by Myers (2010) and Thielen (2008). Chemotherapy patients in the current study also described difficulty reading a book and word-finding ability, as did the participants in Boykoff and colleagues (2009) and Cheung and colleagues (2012) studies.

In support of the quantitative findings, the qualitative findings also illustrated that for some individuals cognitive function improved by the final follow-up assessment, as documented by one chemotherapy patient:

> *"Now…its 100%. It's good" (102 at T3)*

when talking about memory. Although for others, issues with memory were only noticed after chemotherapy treatment had finished. Several chemotherapy patients noticed a decline in cognitive function while receiving chemotherapy, which is reflected by the decline in the FACT Cog PCI and PCA mean scores at T2. The mean scores were

very similar at T3 and did not return to pre- chemotherapy levels indicating that SCI may continue for a long time for some patients with CRC. This similar pattern was also found to occur in the "surgery only" patients which tends to point once again to a common aetiology between CRC and SCI. Perhaps the "surgery only" group were still taking painkillers and/or opiods at the second assessment? There were no significant differences found between the groups on any of the FACT Cog subscales irrespective of time and treatment.

11.5.3 Changes in mood, fatigue and HRQoL over time

Feelings of anxiety did not change over time and there were no significant differences between the groups. There were very few participants who scored in the clinically anxious range on the HADS scale. It may have been that anxiety levels were no more than would be expected to be found in the general population following surgery because patients were told that the cancer had been removed and any chemotherapy to be scheduled was merely a precautionary step to stop possible re-occurrence.

Depression however did change over time. There was a significant effect of treatment in relation to feelings of depression irrespective of time (i.e. there was an increase in depression during chemotherapy treatment) with a large effect size. This finding suggests that chemotherapy treatment may have an acute impact on depression. During chemotherapy treatment only 5.76% of the chemotherapy patients reported feelings of clinical depression (as measured by the HADS) which corroborates the findings in studies that have found no difference in the incidence of depression in patients with cancer and the general population (approximately 6%) (Keating, et al, 2005). However, by 3 months post chemotherapy treatment only 2.5% reported such feelings, which, is

in fact much less than would be expected, possibly because those patients who have completed chemotherapy treatment feel that they have been through the worst of the medication, and things really should start to improve.

Feelings of anxiety and depression were not really discussed in the qualitative interviews (possibly, because on average the chemotherapy group were not anxious or depressed, as indicated by the cut offs indicative of low mood or anxiety on the HADS) although some patients did allude to such feelings.

In addition, it was clear from the interview study that the combination of the diagnosis, subsequent operation and the fitting of a permanent stoma often caused feelings of depression (rather than any cognitive lapses that may have been experienced) and resulted in a complete withdrawal from social activities:

> *….it's the cancer that upset me ….. I always say 'why me? I worked so hard for 40 years looking forward to enjoying my retirement and look what happened now…. I am alone'. At Christmas ….yeah I am alone it's my choice….My social life is zero….Cos I am hiding… (55 at T3).*

It is not unusual for patients with CRC to experience associated changes in bowel habit, or have sexual or micturition problems after surgery whereas breast cancer patients do not have the same symptoms. So, it could be that for patients with CRC these symptoms may be related to psychological problems, which could persist throughout the years (Schag, et al, 1994) and remain a problem even among long-term survivors who achieve remission of CRC (Ramsey et al, 2000). However, physical function in patients with CRC would be expected to have stabilized 1 year after surgery (Ramsey et al, 2000) but this study only followed participants up to 10 to 11 months after surgery. Therefore, it

would be interesting to examine whether psychosocial factors might more strongly predict depression and psychological distress than any perceived issues with cognition or physical factors at least 1 year after surgery.

Feelings of fatigue also changed over time in relation to the whole participant sample. There was a significant improvement in reported feelings of fatigue at the third assessment (irrespective of treatment group). The qualitative findings provide further support for this trend by showing a more in-depth account of the subtle temporal fluctuations of participants' experiences. For example, a number of the participants reported a cyclical experience of feeling fatigued that coincided with each administration of chemotherapy, as illustrated by the following extracts:

> *"the side effects that was more…like more hard in the first week of the chemo" (44);*
>
> *"those three or four days, all the symptoms…. the concentration the tired…..are slightly worse" (57)*
>
> *"in the week immediately after the dose, then for several days I am pretty much laid up at home…. and then I gradually come out of it" (88).*

Taken together, the findings from the questionnaires and the interviews suggest that chemotherapy treatment can have a profound impact on the daily lives of patients with CRC, particularly the fatigue. This side effect inhibits patients from carrying out simple daily tasks and leaves patients needing to sleep a lot more than would be usual. Cancer related fatigue cannot always be alleviated by rest (Cella, et al 2002). This finding was emphasised in the interviews by eight (33.3%) participants who described experiencing

severe tiredness/fatigue during treatment and consequently they were not aware of very much else during the chemotherapy journey.

Feelings of physical well being improved significantly over time but there was no significant change over time in relation to functional, social or emotional well being or colorectal symptoms and there were no statistically significant differences between the two groups. The mean scores recorded for all domains of QoL suggest that undergoing adjuvant chemotherapy treatment for CRC affects feelings about all aspects of HRQoL, as they were lower on all domains mid-chemotherapy than they were before or after chemotherapy treatment. As indicated in the interviews very few people were able to continue with work or their usual daily activities during this period. Those that did continue to work/study reduced their hours. The mean scores of the chemotherapy patients on all subscales were also lower at 3 months post chemotherapy than they were for the "surgery only" patients (although they were not statistically significantly different).

Consistent with the literature in this area feelings of fatigue, anxiety and depression and HRQoL were all significantly related to subjective cognitive function at each time point (e.g. Castellon et al, 2004; Shilling & Jenkins, 2007; van Dam et al, 1998; Vardy et al, 2015). However, as this study only looked at relationships it was not possible to conclude whether those participants who felt that their cognition was impaired over the course of the study were more likely to experience feelings of depression or if the feelings of depression caused feelings of compromised cognition at any time. Castellon and colleagues (2004) studied breast cancer survivors two to five years after surgical treatment and found that those with self-reported cognitive impairments (e.g., lapses in attention and concentration) were more likely to report depressive symptoms

(depression and anxiety). Similarly, Jenkins and colleagues (2004) found that self-reported problems in cognitive functioning were related to depression in a sample of 94 breast cancer survivors enrolled in a randomized trial of antihormonal therapy (anastrozole, tamoxifen, alone or in combination).

11.5.4 Relationship between OCI and SCI

As expected, and commonly reported in the literature, there were no significant relationships found between subjective cognitive function (as measured by the FACT Cog) and OCI in this study pre-and mid chemotherapy treatment. However, 3 months following the last scheduled chemotherapy treatment there was a statistically significant negative relationship between those participants found to be impaired (according to the ICCTF's 2 SD criteria) and PCA as measured by the FACT Cog for the sample as a whole; indicating that as the occurrence of OCI increases perceived cognitive abilities get worse. This corroborates Dhillon and colleagues (2018) findings who suggested that PCA might better reflect cognitive ability than PCI, which may have stronger associations with other symptoms such as anxiety and depression. However, they qualified their findings by stating that the associations found between PCA and objective testing of NP performance were at best moderate and limited to specific cognitive domains (Dhillon et al, 2018). Unfortunately, it was not possible to explore the relationships between specific cognitive domains and each of the subjective domains in each of the participant groups, as the samples were too small, in this study.

A quantitative analysis of the interview data however, did go some way towards mirroring the findings from the quantitative study in terms of the most affected cognitive domains. For example, during chemotherapy treatment the most commonly

affected cognitive domains as measured by the NP assessments in both the chemotherapy and "surgery only" patient groups (when using the 1.5 SD criteria) were verbal memory (chemotherapy group: 21%; "surgery only" group: 25%), visual memory, motor function, and executive function. Similarly, when talking about perceived cognitive changes experienced during the period prior to the start of chemotherapy treatment up until the middle of chemotherapy treatment in the qualitative interview, 43% of the participants mentioned experiencing issues with memory (Table 10.4 and Section 10.3.3). It is interesting that memory was found to be the most affected cognitive domain in both the NP assessments and the interviews. There has been a recent suggestion that patient reported memory complaints are driven by initial learning difficulties that are misinterpreted as actual forgetting by patients in daily activities (Ahles & Root, 2018). Ahles and Root (2018) propose that when patients describe memory deficits but score within the normal range on NP tests of memory it is not because their perceptions of their memory problems are inaccurate but rather that they are related to deficits in earlier stages of information processing connected to attention rather than to memory per se.

It is perhaps also not surprising that a higher percentage of participants in the interview study than in the NP assessments were found to have memory issues given the fundamental differences in the measurement, the timelines and also the way in which the two data sets are gathered. NP assessments are carried out in a quiet room under controlled conditions at a particular point in time where the patient is required to concentrate on the task at hand. So, whilst there was measureable OCI, perhaps the NP assessments did not accuarately capture the extent of the impairments experienced or the more subtle impairments that an individual (particularly a highly functioning

individual) may experience over time whilst still falling within a normal population range of scores?

In addition, during the interview study, one man described how he had inadvertently put on completely different types of shoes one day:

> *I was about to go out the door when I noticed I was wearing odd shoes…I was wearing… they weren't the same colour or anything… one was a trainer and one was a black shoe (laughs)…totally different shoes… (131 at T1)*

He put this down to general distraction, yet this type of lapse would not have been identified by an NP assessment, which requires one to join dots in ascending order or match symbols to prescribed numbers.

11.5.5 Cognitive function and HRQoL

Despite the ever-increasing literature regarding the functional impact of cognitive impairment among patients with solid tumours, there is very little research that examines the effects of cognitive impairment on QoL/HRQoL. As more and more people are diagnosed with cancer and given the changing demographic of the workforce many individuals over the age of 65 will continue to work and lead active lives. Consequently, more cancer survivors now expect to recover and return to previous responsibilities (Ahles & Root, 2018) and cognitive function making the nature and extent of cognitive impairment and its affect on QoL an increasingly important outcome measure.

Subjective cognitive function and HRQoL:

Subjective reports of cognitive function as measured by FACT Cog PCI were significantly related to various HRQoL subscale scores in each patient group at every assessment time point in this study. However, it is interesting to note that FACT Cog PCI and PCA were only significantly related to fatigue in the "surgery only" group as opposed to each of anxiety, depression and fatigue in the chemotherapy group. This could be due to the fact that chemotherapy treatment most likely provokes a more emotional response than surgery alone in a lot of patients. In addition, cognitive issues alone may not have been of such great concern to the chemotherapy participants as they were going through the treatment cycles. Shilling and Jenkins (2007) found that when breast cancer patients were interviewed regarding their cognitive difficulties and asked to provide multiple examples of difficulties encountered, many were unable to do so. The same was true in this qualitative study, with a number of participants unable to recount specific examples of memory loss during interviews particularly mid chemotherapy treatment. They also often forgot what incident they wanted to talk about, Shilling and Jenkins (2007) concluded that this was because these accounts were not meaningful to the participants. However, an alternative interpretation is that subtle memory difficulties are frequent and can have an emotional impact, affect confidence and QoL.

OCI and HRQoL

The results of this study are congruent with the results of the systematic review (Chapter 5) which found limited evidence in the literature of a relationship between OCI and HRQoL. There were very weak negative relationships found between verbal memory and emotional well-being at T2 and verbal memory and social well-being at T3.

As problems with verbal memory increased perceived emotional well being and perceived social well being decreased mid-chemotherapy and 3 months post chemotherapy treatment respectively. Similarly, objective measures of verbal memory were found to be associated with poorer HRQoL five years after chemotherapy treatment for breast cancer in Mehnert and colleagues (2007) study. Further studies with larger sample sizes are warranted in this area as it was not possible to fully explore the relationships between each cognitive domain as measured by the NP tests and each domain of HRQoL (as measured by the FACT C) in each of the participant groups due to the small sample sizes at the second and third assessment time points.

11.6 Contribution to current knowledge

The findings from this research provide further evidence of the occurrence of cognitive impairment in patients diagnosed with a different solid cancer tumour, even prior to chemotherapy treatment. This thesis adds to the suggestion that cognitive impairment is not caused solely by undergoing chemotherapy treatment nor is it exclusive to chemotherapy treatment. It is more correctly labelled as "cancer related cognitive impairment". Its strength lies in the longitudinal comparative design and it demonstrates that men as well as women may experience impairment (objective and/or subjective) whether or not they undergo adjuvant chemotherapy treatment.

This thesis could help (a) health professionals to provide clear information to patients with CRC about the possibility of cognitive impairments associated with the cancer and its treatment; (b) identify appropriate interventions to support patients with CRC to effectively manage their daily tasks; and (c) inform employers of this potential deficit associated with CRC that survivors may experience and identify what adjustments may

be necessary to improve the successful transition back into the workplace. This research also exemplifies the value of employing a mixed-methods approach, which is currently under-utilised within psycho-oncological research, to provide a holistic understanding of side effects among CRC patients.

11.7 Methodological Considerations

As outlined in Chapter 7, the ICCTF has recommended that future research in this area adopts longitudinal designs (including pre-treatment baseline) with both treatment and healthy control groups to address the limitations associated with previous work (Wefel et al., 2011). This study addressed as many of the recommendations as was possible in light of the limited resources available for a PhD study. Although there were no significant between-groups differences at baseline in terms of gender, age or education, they were controlled for in the quantitative longitudinal analysis in order to ensure that any subtle differences did not affect the results.

The "Feasibility Trial" was beneficial in confirming that the Protocol was acceptable to both the patients and the medical staff at the participating hospitals. It also allowed for minor changes to be implemented fairly early on in the study which ensured that recruitment was not impeded by a restrictive age limit or pre-screening test. Whilst the MOCA could have been used to examine the effect of chemotherapy treatment on inidividuals with MCI, this study was limited in resources and participant numbers. However, future larger studies should consider using the MOCA in addition to the NP assessments in order to examine if chemothapy treatment exacerbates cognitive impairment over time.

Furthermore, the mixed-methods approach proved valuable, although it was not without its challenges. For example, several participants noted a cyclical nature to their side effects, such as feeling particularly tired and/or sick for several days following chemotherapy administration. However, the questionnaire survey did not capture these subtle temporal fluctuations due to the 3 and 6 months that elapsed between assessments. This is important to recognise when interpreting findings from longitudinal research.

The qualitative interviews took place immediately prior to the NP assessments, which may or may not have caused those participants to concentrate more whilst doing the assessments, as their impairments would have been at the forefront of their minds at that time. Although by the second assessment all participants (whether or not they were going to take part in the interview study) knew what would be expected of them in terms of the types of tests that they would be undertaking, so perhaps would have been more prepared to concentrate in any event. Even if it would have been more valuable to split the interview date from the NP assessments, it may not have been logisitically possible to do so and it would have been more burdensome for the participants who were already undergoing a time consuming and physically tiring treatment regimen.

There are issues regarding the generalisability of the findings to the wider CRC population in the UK for several reasons. Firstly, metastatic patients were excluded from the current study and secondly, patients were recruited only from London NHS Trusts. Due to the limited timeframe and resources inherent in a PhD project, it was not possible to recruit a larger cohort of patients to provide generalisable findings to this subpopulation. It is acknowledged that future studies with sufficient resources should also recruit healthy matched individuals as well as metastatic individuals to fully

investigate this subpopulation. As outlined in the Feasibility Study (Dwek et al, 2015; Appendix J) this is a very hard to reach group of patients with approximately 1 out of 2 patients approached refusing to take part in the study. Potential reasons for this low uptake may be poor health and competing priorities in terms of work and family; and in relation to the "surgery only" eligible patients, it may just be a wish to forget about having had cancer. Whilst recruitment from eight NHS hospitals around London was advantageous, further multi-centre research, spanning larger geographic areas is necessary in order to obtain larger samples and broaden the generalisability of the findings to the UK CRC population.

Nevertheless the overall sample size in this study is comparable to recent longitudinal studies examining cognitive difficulties in patients with CRC (Cruzado et al, 2014; Vardy et al, 2015). Although the "surgery only" group was relatively small, such small sample sizes are a common limitation in psycho-oncological research (e.g. Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008). Findings from the power calculations (Chapter 7) suggest that larger samples sizes than obtained would have been able to detect a larger effect size for all analyses conducted. Therefore, the findings from this thesis should be interpreted with caution. With regards to the interview study, the sample size was comparable to other qualitative work (for example, Downie et al, 2006; Mitchell et al, 2007;Munir et al, 2011; Myers, 2012; Von Ah, et al, 2013) and the rate of attrition was relatively low.

The attrition rate in longitudinal cognitive function studies in other illnesses range from 22 to 34% at the first follow-up assessment (Levin et al., 2000; Newman et al., 2001; Van Beijsterveldt et al., 2002). The attrition rate in this study is better than that for the chemotherapy group (17.46%) and at the lower end in the "surgery only" group

(22.86%) and at first follow-up assessment. It is believed that the benefits of the longitudinal design, in terms of the information that is yielded, outweigh the problem of attrition. Future, larger studies will need to over-sample to balance the effects of attrition and ensure adequate power to detect changes in cognitive function (Levin et al., 2000; Bender et al, 2005).

A shortcoming in this study however is the use of convenience samples. Although a highly popular recruitment strategy (e.g. Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008), convenience samples may not always result in a representative sample and findings must therefore be interpreted with caution. Although the sample characteristics of the chemotherapy group were similar in terms of gender, age and education as the "surgery only group" and also previous studies (e.g. Jansen et al., 2008), the "surgery only" participants had a lesser stage cancer or refused chemotherapy treatment. Those patients who refuse chemotherapy may possess characteristics that make them different from those who accept, however it was not possible to explore this given the small number of participants to whom this applied.

In addition, the literature reviewed in Chapter 3 suggested a dose response relationship with OCI. Patients with CRC may be assigned to a number of different treatment protocols (Chapter 2) some of which involve oral chemotherapy drugs others intravenous. However, the small sample precluded an evaluation of the differential effects of the treatment modes and dosages on cognitive function. In addition, a lack of resources and some logistical problems that were encountered meant that it was not possible to obtain sufficient information about each chemotherapy participant's treatment protocol and any changes made to it along the way. Future studies are needed to examine these differential effects (Bender et al 2005) as the etiologic

mechanisms underlying OCI may differ from one chemotherapeutic agent to another (Wefel et al 2004).

It is also important to remember that CRC is treated with multiple modalities that complicate the study of cognitive impairment and the identification of components of treatment responsible for the same. Insufficient data was collected on this study in relation to steroid use, analgesics and painkillers. One reason for this was the difficulties encountered in accessing the medical records at one of the participating Trusts for some of the participants. Although all of the participants in this study had undergone surgery, some may have been more affected by it than others, as surgery with general anesthetic can cause delirium and lasting cognitive changes particularly in older patients (Le Strat, 2012). There was also insufficient data to determine whether there was a relationship between co-morbidities and cognitive impairment or if co-morbidities were a predictor of cognitive changes over time. The more co-morbidities an individual has the worse the burden on cognition in illnesses such as Alzheimers for example (Haaksma, et al, 2017). In this study people with brain tumours and other medical conditions (such as stroke) known to have an impact on cognition were excluded. Perhaps future studies should also examine whether chemotherapy treatment makes more or less of a difference to the cognitive functions of those individuals who already have cognitive decline?

11.8 Implications of findings and ethical considerations

CRC is the fourth most commonly diagnosed cancer in the UK (Chapter 1). The survival rate is increasing and so individuals look to maintain a normal life during and beyond treatment. It is important that patients are aware of all possible complications

associated with the diagnosis, disease and its treatment, which includes cognitive impairment (whether it is objective or subjective).

11.8.1 Implications of findings for health professionals

This thesis has expanded the current knowledge of CRCI issues for patients diagnosed with CRC. Recent research has documented that health professional's lack information on CRCI (Cheung, Shwe, Tan, Fan, Ng, & Chan, 2012; Munir, Kalawsky, Lawrence, Yarker, Haslam, & Ahmed, 2011; Myers & Teel, 2008). However since the aetiology of CRCI is currently unclear, it is important that **all** patients are informed that psychosocial factors, systemic treatment and the cancer itself may contribute to cognitive changes. By providing this information, at an early stage, it could help to improve patients' management of these side effects. For example, they could implement coping strategies (Bender et al., 2008).

Most oncologists do not screen for CRCI during or after CRC treatment, for fear of priming or not believing that it is real or a common experience, and lack of knowledge about CRCI and how to treat it (Smidt, et al 2016). This study has gone some way to examining the effect of priming on patients, and it was clear from the interview study that the medical teams did not discuss the possibility of CRCI with the patients. However further studies are required to examine these issues in more detail.
It is also important that further qualitative work be conducted on the lived experiences of patients with CRC and other solid tumours so that healthcare professionals can provide patients with useful information on possible effects of cancer, surgery and chemotherapy on cognition. Skalla and colleagues (2004) found that cancer patients

want information about specific side effects of treatment as well as the impact of treatment on their lives. Future work could also explore whether there is a relationship between particular chemotherapeutic agents and dosages used in the treatment of CRC and objective or subjective CRCI.

11.8.2 Implications of findings for patients

It has been suggested that by health professionals acknowledging cognitive impairment as a problem associated with cancer and its treatment and providing emotional support it could help to reduce the stress that these patients live with (Vardy and Dhillon, 2017). Therefore, although no relationship was found between OCI and HRQoL in this study due to the very small sample sizes further exploration is required. However, even in the absence of a definite relationship between OCI and HRQoL, patients' perceptions of impairment are no less important than OCI, affecting all areas of life such as social activities and work and therefore there is still an argument for informing **all** patients of the possibility of CRCI following a colorectal cancer diagnosis, particularly as a large percentage of participants scored below normal ranges in this study on the NP assessments. It is possible that these individuals may be making mistakes without awareness which could have associated risks. People should know about the possibility of cognitive impairment even if it does not necessarily get worse over time.

The finding that cognitive function did not significantly differ between the two groups or over time is a somewhat reassuring finding for prospective chemotherapy patients, although qualitative findings suggested more subtle temporal changes could have a detrimental impact upon daily functioning.

This study has also raised the question as to whether there is something about the particular cancer itself that means that a higher proportion of CRC patients experience both objective and subjective cognitive impairment prior to the start of any adjuvant chemotherapy treatment?

11.9 Future research directions

These findings highlight the need for future research to:

Explore the longer term effects of treatment on objective and subjective cognition particularly as subtle cognitive difficulties may become more pronounced once patients resume functional ability, such as social and work activities (Ferguson, McDonald, Saykin, & Ahles, 2007; Meyers & Perry, 2008; Vardy & Tannock, 2007). It would be helpful to introduce diaries as part of the qualitative study in the future. They can be a very useful tool that would capture the temporal fluctuations in side effects. Such in-depth data could then be used to develop further measures; based on a comprehensive understanding of the treatment on a daily basis in order to help to inform interventions in a patient focussed manner. The qualitative findings in this study provided insightful contextual information relating to the cyclical nature of the side effects, which were experienced as being the worst during the first few days after the chemotherapy treatment was administered and gradually improved over the following week. It might also be useful to interview all participants who take part in the quantitative study (including the "surgery only" patients) in future studies rather than just a sub-set of the chemotherapy participants. This would provide a more complete picture of both participant groups and allow more comparisons to be drawn across the quantitative and qualitative studies and between the participant groups. Shilling and Jenkins (2007) interviewed all of the

breast cancer patients who had completed NP assessments at T2 and T3 and consequently obtained some very rich data.

Undertake collaborative studies as suggested by the ICCTF (Wefel, et al, 2011). As described in Chapters 3, 4 and 5, researchers examining CRCI have employed a diverse range of methodological designs (Vardy et al., 2008). Consequently, it is very difficult to compare findings across studies. Despite the growing literature on CRCI in all cancer populations, there is a need for greater collaborative efforts involving multicentre (possibly even multinational) recruitment sites to undertake large-scale standardised research (Hurria, Somlo, & Ahles, 2007; Wefel et al, 2011), using the same definitions and methods of assessing impairment.

Examine in more detail levels of anaemia in both participant groups by taking blood samples at the beginning of every assessment. Does chemotherapy treatment affect levels of anaemia? Does anaemia in patients diagnosed with CRC improve in either group over time? If so, when? Does it improve faster in the "surgery only" participants?

Further research needs to be conducted in other cancer populations, as these are currently under-researched and the findings of this thesis suggest that it occurs in individuals with cancers other than breast cancer.

11.10 Conclusion

To summarise, the findings from this study extend the literature in this area to a different solid tumour. The higher than expected prevalence of OCI suggests that it is not limited to female breast cancer patients. However, larger and more representative samples are required to validate the current findings. Perhaps if possible including a pre-surgery baseline assessment, with more information on type and duration of all

medications administered and haemoglobin levels prior to surgery and immediately afterwards, in order to more accurately assess whether cognitive impairment is present prior to any treatment at all.

The interviews offered valuable supplementary data to the quantitative analyses. Patients with CRC undergoing chemotherapy report some temporal changes to their physical and cognitive function, which reflect the course of their treatment. However, the aetiology of these experiences is unclear and further research is required to establish the exact causes.

In particular, as the survival rate for patients with CRC is increasing and prognosis improves, many patients look to resume pre-diagnosis levels of cognition and daily functioning following treatment and/or try to continue undertaking typical activities throughout treatment.

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APPENDICES

APPENDIX A

Appendix A: Other types of colorectal cancer

Gastrointestinal carcinoid tumors:

Carcinoid tumors develop in nerve cells called neuroendocrine cells, which help regulate hormone production. These tumors are among a group of cancers called neuroendocrine tumors (NETs).

Carcinoid tumors cells are slow-growing and may develop in the lungs and/or gastrointestinal tract. They account for 1 percent of all colorectal cancers and half of all cancers found in the small intestine.

Other types of rare colorectal cancers combined account for less than 5 percent of all cases and include:

- **Primary colorectal lymphomas:** A type of non-Hodgkin lymphoma (NHL), this cancer type develops in the lymphatic system, specifically in cells called lymphocytes. Lymphocytes are a type of white blood cell that helps the body fight infections. NHL may develop in many parts of the body, including the lymph nodes, bone marrow, spleen, thymus and the digestive tract. Primary colorectal lymphomas account for just 0.5 percent of all colorectal cancers and about 5 percent of all lymphomas. This colorectal cancer type usually occurs later in life, and is more common in men than women.

- **Gastrointestinal stromal tumors:** Also known as GISTs, this is a rare type of colorectal cancer that forms in a special cell found in the lining of the gastrointestinal (GI) tract called interstitial cells of Cajal (ICCs). More than 50 percent of GISTs develop in the stomach. While most other GISTs form in the small intestine, the rectum is the third most common location. GISTs are classified as sarcomas, or cancers that begin in the connective tissues, which include fat, muscle, blood vessels, deep skin tissues, nerves, bones and cartilage.

- **Leiomyosarcomas:** Another form of sarcoma, leiomyosarcoma essentially means "cancer of smooth muscle." The colon and rectum have three layers of the type of muscle affected by leiomyosarcoma, and all three work together to guide waste through the digestive tract. This rare type of colorectal cancer accounts for about 0.1 percent of all colorectal cases.

- **Melanomas:** Though most commonly associated with the skin cancer, melanomas may occur anywhere, including the colon or rectum.

Of the rarer types of colorectal cancer, gastrointestinal carcinoid tumors grow slowly, form in the neuroendocrine cell and make up 1 percent of all colorectal cancers, whereas primary colorectal lymphomas develop in the lymphatic system and account for 0.5 percent of colorectal cancers.

Source: https://www.cancercenter.com/colorectal-cancer/types/tab/overview/

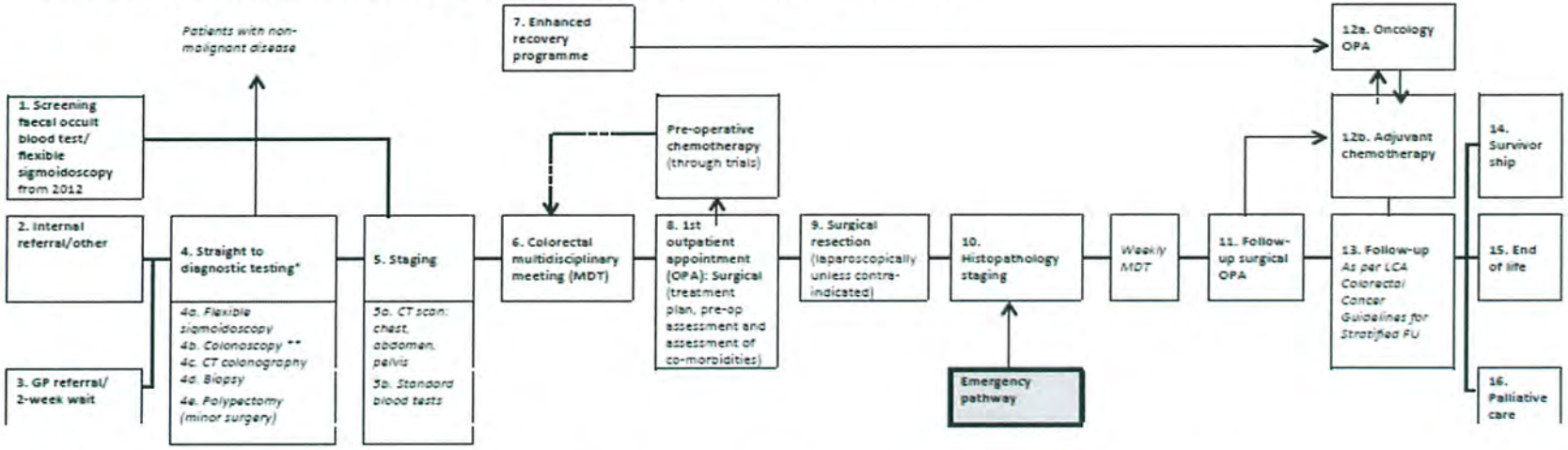
Last accessed on 4 October 2018

APPENDIX B

Appendix B: A Summary of the treatment pathways of CRC

Appendix 11: A Summary of the Treatment Pathways of Colorectal Cancer

Figure A11.1: Commissioning best-practice pathway for operable colon cancer (non-metastatic)



Notes:

*Best practice is for patients to go straight for diagnostic testing from GP referral except for complex cases with significant co-morbidity where they may not be fit for standard tests. If the test suggests cancer, a clinician should inform the patient at diagnostics appointment and arrange staging tests.

Source: LCA Colorectal Cancer Clinical Guidelines September 2014

APPENDIX C

Appendix C: Adjuvant Chemotherapy Protocols

Chemotherapy Treatment Protocols

Cancer therapy selection, dosing, administration, and the management of related adverse events is a complex process Adjuvant chemotherapy treatment protocols for resectable colon cancer are provided below. Adjuvant and neoadjuvant therapy for advanced or metastatic colon cancer are outside the remit of this thesis and are not included here.

Adjuvant Chemotherapy for Resectable Colon Cancer

Stage 0 and I:

Patients do not require adjuvant chemotherapy

Stage IIA, B and C (node-negative):

The value of adjuvant therapy in stage II disease is at best controversial; however, the following regimens may be used:

- Capecitabine 1250 mg/m ^{2} PO BID on days 1-14; repeat cycle every 21 days for eight cycles **or**
- Leucovorin 500 mg/m ^{2} given as a 2-hour infusion and repeated weekly for 6 weeks **plus** 5-fluorouracil (5-FU) 500 mg/m ^{2} given as a bolus 1 hour after the start of leucovorin and repeated six times weekly; every 8 wk for four cycles **or**
- Leucovorin 400 mg/m ^{2} IV over 2 h on day 1 **plus** 5-FU bolus 400 mg/m ^{2}, **then** 1200 mg/m ^{2}/day for 2 d (total 2400 mg/m ^{2} over 46-48 h) continuous infusion; repeat every 2 weeks

Stage II in high-risk or intermediate-risk patients:

Adjuvant therapy for high-risk patients with stage II is an option. Common regimens include 5-FU and leucovorin with or without oxaliplatin or capecitabine, as follows:

- mFOLFOX6: Oxaliplatin 85 mg/m ^{2} IV over 2 hours on day 1 **plus** leucovorin 400 mg/m ^{2} IV over 2 hours on day 1 **plus** 5-FU 400 mg/m ^{2} IV bolus on day 1, **then** 1200 mg/m ^{2}/day for 2 days continuous infusion; repeat every 2 weeks **or**
- FLOX: 5-FU 500 mg/m ^{2} IV weekly **plus** leucovorin 500 mg/m ^{2} IV weekly for 6 weeks (days 1, 8, 15, 22, 29, and 36) of each 8-week cycle **plus** oxaliplatin 85 mg/m ^{2} IV administered on days 1, 15, and 29 of each 8-week cycle for three cycles **or**
- Capecitabine 1250 mg/m ^{2} PO BID on days 1-14; repeat cycle every 21 days for eight cycles

Stage III (node-positive):

The following regimens are acceptable adjuvant therapies for stage III disease for resectable colon cancer:

- mFOLFOX6: Oxaliplatin 85 mg/m ^{2} IV over 2 h on day 1 **plus** leucovorin 400 mg/m ^{2} IV over 2 hours on day 1 **plus** 5-FU 400 mg/m ^{2} IV bolus on day 1, **then** 1200 mg/m ^{2}/day for 2-day continuous infusion; repeat every 2 weeks **or**
- FLOX: 5-FU 500 mg/m ^{2} IV weekly **plus** leucovorin 500 mg/m ^{2} IV weekly for 6 weeks (days 1, 8, 15, 22, 29, and 36) of each 8-weeks cycle **plus** oxaliplatin 85 mg/m ^{2} IV administered on days 1, 15, and 29 of each 8-week cycle for three cycles **or**
- Capecitabine 1250 mg/m ^{2} PO BID on days 1-14; repeat cycle every 21 days for eight cycles **or**
- CapeOx: Oxaliplatin 130 mg/m ^{2} over 2 hours on day 1 **plus** capecitabine 1000 mg/m ^{2} PO BID on days 1-14 every 3 weeks for eight cycles **or**

- Leucovorin 500 mg/m ^{2} given as a 2-hour infusion and repeated weekly for 6weeks **plus** 5-FU 500 mg/m ^{2} given as a bolus 1 hour after the start of leucovorin and repeated six times weekly; every 8 weeks for four cycles **or**
- Leucovorin 400 mg/m ^{2} IV over 2 hours on day 1 **plus** 5-FU bolus 400 mg/m ^{2}, **then** 1200 mg/m ^{2}/day for 2 days (total 2400 mg/m ^{2} over 46-48 h) continuous infusion; repeat every 2 weeks

APPENDIX D

Appendix D: Pro Forma Data Extraction form for the Systematic Review

Authors, year & country				
Title				
Study Design				
Research question/aim				
Cancer & stage				
Treatment regime	Chemotherapy Radiotherapy		Names of drugs:	
Participants	Number	Age range	Recruitment	No. refused to participate?
Study Criteria	Inclusion criteria:		Exclusion criteria:	
Measures	Cognitive Tests			
	Subjective Cognitive Tests			
	QoL Instruments			
	Other measures			
	Time administered			
Results	Analysis			
	Number of participants withdrawn			
	Results of analysis			

Limitations		
Other relevant or useful information		
Quality of Paper		

APPENDIX E

Appendix E: Quality Assessment Tool

Study identification *Include author, title, reference, year of publication*		
Assessed by:		
Section 1: INTERNAL VALIDITY		
In a well conducted study:	In this study the criterion is: (Circle one option for each question)	
1.1 **The study addresses an appropriate and clearly focused question/objective**	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
Selection of subjects		
1.2 **The study population is clearly specified and defined.** i.e. the type of cancer, type of treatment, population demographics etc are adequately described.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3 **The study indicates how many of the people asked to take part did so**	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4 **The likelihood that some eligible subjects might have the outcome (i.e. cognitive impairment) at the time of enrolment is assessed and taken into account in the analysis**	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5 **What percentage of individuals recruited into the study dropped out before the study was completed?**		
1.6 **Comparison is made between full participants and those lost to follow up**	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

ASSESSMENT		
1.7 **The outcomes are clearly defined**	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8 **The outcome measures and procedures are** reliable. Were cognition outcome measures objective? Was there any indication that measures had been validated?	Well covered Adequately addressed Poorly addressed	
1.9 **Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.**	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.10 The outcome measurements were complete. Were all aspects of cognition assessed?	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.11 **There was a similar follow up time in both groups**	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.12 **Follow up time was meaningful.** **i.e.** it was long enough to assess long term harms. Was it too long such that participants were lost to follow up? Was loss to follow-up after baseline 20% or less?	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
CONFOUNDING		
1.13 **The main potential confounders are identified and taken into account in the design and analysis**	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

ANALYSIS		
1.14 **Multiple explanatory variables were considered in the cognitive analyses** Were there sufficient explanatory variables considered in the analysis – for cog deficit analysis?	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.15 **The analytical methods were appropriate** for the QoL/Cog deficit relationship	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.16 **Was a sample size justification, power description, confidence intervals and/or p-values for effect estimates given or possible to calculate?** If precision is lacking, is this because the study is under-powered?	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
Section 2: OVERALL ASSESSMENT OF THE STUDY		
2.1 Are the study results internally valid (i.e. unbiased)? How well did the study minimise sources of bias (i.e. adjusting for potential confounders)? Were there significant flaws in the study design?	☐++ Comments: ☐+ ☐-	
2.2 Are the findings generalisable to the source population (i.e. externally valid)? Are there sufficient details given about the study to determine if the findings are generalisable to the source population? Consider: participants, interventions and comparisons, outcomes, resource and policy implications?	☐++ Comments: ☐+ ☐-	
Quality rating score		

Key for Section 2 (which relates to the overall assessment of the paper):

++ All **or most** of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought *very unlikely* to alter.

+ **Some** of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought *unlikely* to alter the conclusions.

– **Few or no** criteria fulfilled. The conclusions of the study are thought *likely or very likely* to alter.

Quality rating scores:

++ and ++	= 4	+ and -	= 1 (in any order)
++ and +	= 3 (in any order)	- and -	= 0
+ and +	= 2		

APPENDIX F

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WILEY

REVIEW

Is there a relationship between objectively measured cognitive changes in patients with solid tumours undergoing chemotherapy treatment and their health-related quality of life outcomes? A systematic review

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Abstract

Background This systematic review examines whether there is a relationship between objective measures of chemotherapy-related cognitive impairment in patients with solid cancer tumours and health-related quality of life (HRQoL).

Methods Multiple online databases were searched (including Ovid MEDLINE, EMBASE, PsycINFO, PsycARTICLES, CINAHL, PubMed, and Web of Science) to identify articles published between 1980 and 2016 examining the extent of chemotherapy-related cognitive deficit and its relationship with HRQoL in cancer patients. Of 2769 potentially relevant articles, 17 studies met the inclusion criteria for the current review.

Results Evidence for the presence of cognitive impairment in patients treated with chemotherapy was found in 15 of the 17 studies. Of the 15 studies finding some sort of cognitive impairment, 12 were in female breast cancer patients, 2 in bowel cancer, and 1 each in ovarian and lung cancer. Three of the 15 studies found a significant relationship between various objectively measured cognitively impaired domains and specific HRQoL outcomes. There was, however, only limited testing of the relationships between quantifiable cognitive dysfunction and HRQoL domains.

Conclusions This review suggests that in patients with solid tumours, where there is a relationship between chemotherapy treatment and cognitive impairment, the type and level of cognitive decline does not consistently appear to affect such patients' HRQoL. This could be partly explained by variations in study design, measures used, definitions of cognitive impairment, varying measurement time frames, small sample sizes, and differences in disease severity and type of treatment regimes.

KEYWORDS

cancer, chemotherapy, cognition, cognitive impairment, health-related quality of life, oncology

1 | BACKGROUND

The effectiveness of chemotherapy drugs in treating a range of cancers has improved significantly in recent decades. Whether used alone or used in combination with other treatments, the result has been a marked reduction in disease recurrence and an increase in survival rates[1] doubling in the United Kingdom in the last 40 years.[2] This has been most notable in the treatment of female breast cancer and colorectal cancer (CRC), with an increase in absolute survival between 1971/1972 and 2010/2011 of 38% and 35%, respectively.[2] The UK survival at 5 years for colon cancer patients diagnosed between 2005 and 2009 and followed up to 2010 rose to 54% for men and 55% for women from 26% and 25%, respectively, for those diagnosed between 1971 and 1975 and followed up to 1995. Similar increases were found in rectal cancer where 5-year survival was 55% for men and 57% for women compared to 27% and 29%, respectively, over

the same periods.[3] There has also been an increase in the 10-year relative survival for both sexes in CRC from just more than 30% among those followed up during 1981 to 1986 to more than 45% among those followed up during 1997 to 2001.[4]

These achievements have been attributed to screening, early detection, and treatments. Nonetheless, the pharmaceutical treatments used in these conditions do have side effects. The most common side effects of chemotherapy drugs are nausea, vomiting, and fatigue.[5] Additionally, a decline in cognitive function, colloquially known as "chemofog" or "chemobrain," has been reported by some patients following chemotherapy with estimates of patient numbers affected by this self-report of cognitive decline varying widely.[6,7] Individuals report experiencing problems with concentration, memory, learning, and language in their everyday life.[8] However, the number of patients reporting cognitive problems exceeds those with objectively measurable impairment, and even when present, the two do not necessarily co-occur.[8,9]

Studies have demonstrated that some degree of objectively measured postchemotherapy cognitive difficulty is experienced by 16% to 75% of adult patients with solid tumours.[5,10] Most of the studies are of breast cancer patients, with a smaller number for lung, prostate, colorectal, and ovarian cancer patients.[10–19] It is possible that the large degree of variation is due to a range of confounders such as patient population diversity, cancer stage, and treatment regimes as well as methodological differences between studies, including inconsistent definitions of cognitive impairment and the use of different measures to assess such impairment.[20–22] Early studies also suffer from methodological limitations such as small sample sizes, many using cross-sectional designs, and some failing to conduct pretreatment cognitive function evaluations.[22] Later studies used longitudinal designs, although sample sizes remained small and few studies used a comparison group. All of this has limited the conclusions that may be drawn from the data.

Nevertheless, some studies have examined a range of cognitive abilities and reported memory, processing speed, and executive function as being the most likely to be adversely affected by adjuvant chemotherapy treatment.[15,17,20,22,23] The degree of impairment observed is usually mild to moderate.[24–27] Even so, these cognitive deficits may have implications for patients' health-related quality of life (HRQoL)[28] as well as their daily functioning, work performance, and health care.[29,30]

HRQoL is an independent predictor of survival and response to therapy in cancer patients.[31–33] With the increase in survival times, HRQoL has become a meaningful outcome measure for cancer patients.[34] An understanding of any link between chemotherapy-related cognitive impairment and HRQoL domains (eg, emotional, physical, functional, social, financial, and spiritual status) will provide medical teams and patients with a broader picture of the related consequences of chemotherapy treatment. Such knowledge may be a helpful catalyst in the development of interventions, which aim to improve coping and adjustment.[35]

This review's primary aim is to identify and synthesise research concerned with the relationship between objectively measured chemotherapy-related cognitive impairment and HRQoL in adult patients who received chemotherapy for treatment of solid tumours. It also aims to establish whether particular chemotherapy-related cognitive deficits are associated with specific aspects of HRQoL. As far as the authors are aware, this is the first review of its type.

2 | METHODS

2.1 | Inclusion and exclusion criteria

The search was limited to papers published in English post-1980, as this period coincides with a prevalence of reporting and systematic investigation of postchemotherapy cognitive impairment.[20]

Articles were restricted to those that had recruited patients aged 18+ years with a solid tumour such as breast, ovarian, CRC, prostate, and lung treated with chemotherapy. Studies of patients with brain tumours and central nervous system tumours were excluded because of the inherent effects of the tumour on cognition, as well as the fact that treatments often involve brain irradiation and surgical interventions that are known to cause additional direct effects on brain tissue secondary to the lesions,[36,37] and consequent changes in neuropsychological functioning.[38]

Included studies were required to be full papers that assessed both cognition and HRQoL using standardised measures. In addition, to be included, studies needed to examine (by quantitative measurement) and/or report on the relationship between such objectively measured cognitive deficits (global cognitive deficits and/or domain specific ones) and (global or domain specific) measures of HRQoL. Reviews, commentaries, case reports, dissertations, and conference abstracts were all excluded.

2.2 | Search strategy

An electronic search was performed using Ovid MEDLINE, EMBASE, PsycINFO, PsycARTICLES, CINAHL, PubMed, and Web of Science on June 6, 2016, using a combination of search terms that included all known terms for cancer, such as neoplasms and oncology, treatment terms including chemotherapy and "systemic treatment," HRQoL terms, and terms referring to cognition and cognitive impairment (please see detailed search strategy in Data S1). The first author (M.R.D.) agreed the search terms with a specialist librarian and the third author (C.H.). A combination of both text words and indexed terms (such as MeSH) was applied in each database. Search terms were modified as necessary for each electronic database. The reference lists of all included articles were also searched for additional studies.

2.3 | Study selection

Once the duplicates had been removed, retrieved articles were screened by title, and if eligibility was unclear from the title alone, the abstracts were screened (by M.R.D. and 10% by C.H.). All articles potentially satisfying the inclusion criteria were retrieved in full and screened for eligibility (again by M.R.D. and 10% by the second author [L.R.]).

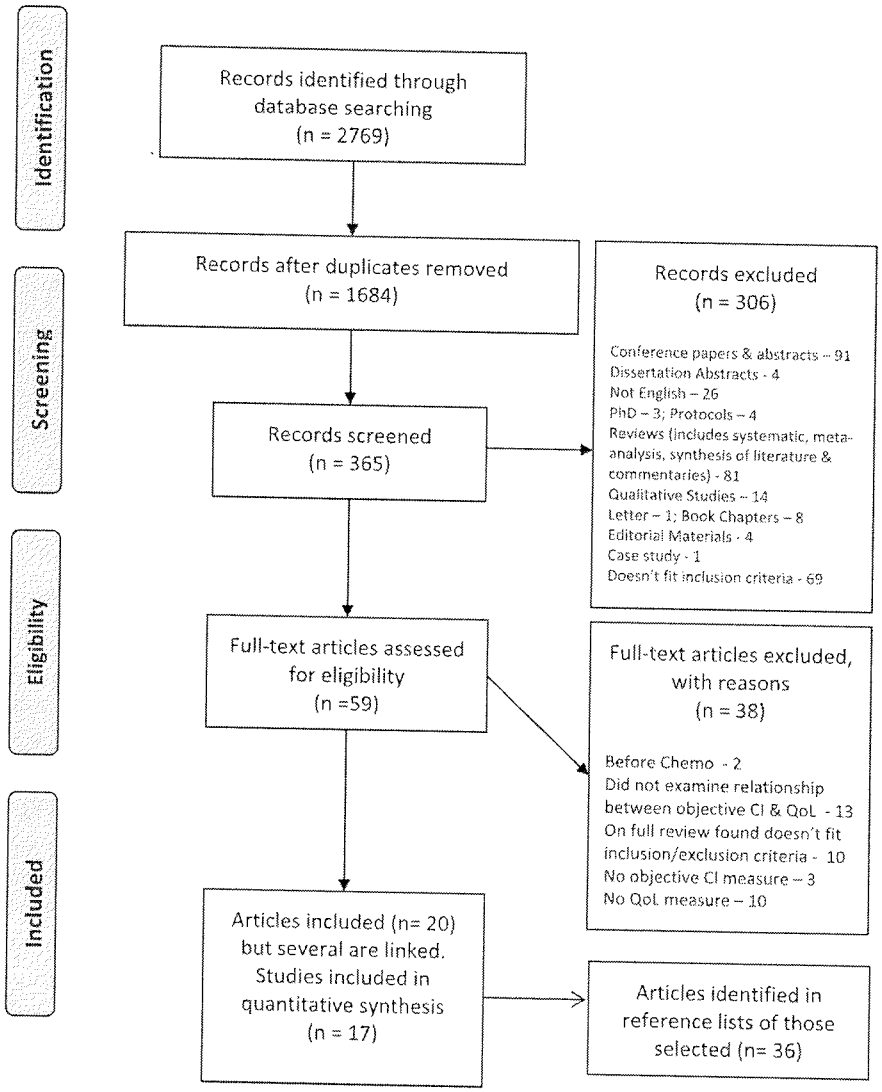

FIGURE 1 Preferred reporting items for systematic reviews and Meta-analyses flow diagram

2.4 | Quality assessment

As there is currently no agreed "gold standard" appraisal tool for observational studies, a quality-scoring tool was developed on the basis of methodological quality assessment checklists from the NICE *Methods for the development of NICE public health guidance* (Appendix 1).[39,40] Valid criteria (items) were selected from the NICE checklists and adapted for the purposes of this review in order to ensure that the 5 recommended aspects of internal validity (ie, a clearly focused question, selection of subjects, assessments, confounders, and statistical analysis), together with an overall assessment of the study, were addressed in the evaluation of quality. A total of 16 items were included that covered all aspects considered necessary to evaluate the quality of the evidence in relation to the research question. (See Data S3.) Authors were emailed to obtain any missing data or details to ensure the study quality could be evaluated.

The overall assessment for each paper was calculated by considering all 16 items and then attributing scores between 0 and 4 to the overall assessment of the study, considering the extent to which each study was internally and externally valid. The higher the score, the less bias in the study and the more external validity. Two studies had the highest overall rating score of 4,[39,41] five studies scored 3;[10/14.20.42,50/51,53] nine scored 2,[11.19,29,43–48] and one was rated 0.[49] Each included study was assessed by M.R.D. then L.R. independently coded the quality of the studies to check the reliability of the quality assessment. Agreement between the coders was substantial ($\kappa = 0.675$) and M.R.D.'s final score was used. Although the methodological quality of each study was evaluated and discussed, studies were not eliminated from this review because of poor quality.

3 | RESULTS

3.1 | Literature search results

Database searches identified 2769 citations, and 36 additional citations were retrieved from reference lists. Screening of titles and abstracts identified 365 potentially eligible articles (Figure 1).

The full texts of 59 papers were reviewed, 20 satisfied the inclusion criteria. An examination of the reference lists did not identify any additional papers that met the inclusion criteria. Several papers were linked and consequently treated as a single study (works of

Tchen et al and Fan et al;[10,14] Shilling et al and Jenkins et al;[50,51] and Vardy et al[41,52]). This resulted in the final inclusion of 17 studies, whose main characteristics are presented in Data S2.

3.2 | Defining cognitive impairment

The calculation and operational definition of what constitutes cognitive impairment varied widely across studies (see Table 1). More than half of the studies (n = 10) converted raw scores into standardised z-scores (mean = 0, SD = 1) using published normative data adjusted for age, education, and gender. However, the number of tests and the extent to which these z-scores had to deviate to constitute cognitive impairment varied across the studies. Definitions of cognitive impairment included z-scores of ≤ −1.4, −1.5, and −2 SDs below the mean in between 1 and 4 tests. (See Data S2 for the full list of operational definitions used.) The extent of impairment has been shown to be dependent on the method of analysis.[54] As a consequence of the differences across the studies, it is not possible to provide a simple estimate of the prevalence of cognitive impairment in patients treated with adjuvant chemotherapy. Ignoring these methodological differences, all but 2 studies[46,49] reported statistically significant cognitive dysfunction in some patients undergoing adjuvant chemotherapy treatment.

3.3 | Affected cognitive domains and assessment of objective cognitive impairment

The cognitive domains most affected varied widely across studies. Four studies[11,41,50,55] reported verbal memory as being most affected whereas 6 studies[29,41-44,53] found that the most common domains showing decline were processing speed and executive function. Two studies[46,49] reported that objective cognitive performance remained constant throughout treatment.

As shown in Table 1, multiple tools were used, and many different cognitive domains (as reported by the authors of the articles) were measured. Not only did the studies assess different areas of cognition but they also used different tests to assess the same domains. Overall, there were more than 54 different measures used across 17 studies to tap a variety of cognitive domains. Most of the studies (n = 15) used a battery of neuropsychological tests assessing a range of domains. The different psychometric qualities of each of the measures may have influenced the conclusions drawn regarding the cognitive domains most affected by chemotherapy treatment. For example, no impairment was reported by Iconomou et al[49] who used the Mini-Mental State Examination, which has been criticised for not being sensitive enough to detect subtle cognitive changes.[56,57]

This problem of diversity of assessments used has been recognised as an issue that needs consideration in future research by the International Cognition and Cancer Task Force (ICCTF).[58] In an attempt to bring some homogeneity to all studies, the ICCTF recommended that in future trials 3 core neuropsychological assessments (the Hopkins Verbal Learning Test-Revised, Trail Making Test, and the Controlled Oral Word Association of the Multilingual Aphasia Examination)[59-63] be used to measure learning and memory, processing speed, and executive function, supplemented with additional tests of working memory capacity, on the basis of the researchers own preferences.[58] This was justified by the assertion that research has shown that the domains assessed by these tests are most affected by chemotherapy treatment.[58] However, no study undertaken post-ICCTF's recommendations used the entire core battery to assess neuropsychological impairment although 3 earlier studies did.[44-46]

3.4 | Assessing HRQoL

HRQoL was assessed at the same time as cognition in all included studies. As with the neuropsychological assessments, some studies reported having analysed only global HRQoL scores[14,19,44,49] whereas others extended the analysis to the subscales of the HRQoL measure.[11,20,42,43,48,53,55]

Five studies assessed HRQoL using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ C30); the remaining studies used one or more of the questionnaires from the Functional Assessment of Cancer Treatment (FACT) battery. Both the EORTC-QLQ C30 and FACT-general (FACT-G) are generic core HRQoL questionnaires supplemented by disease-specific modules (eg, the FACT-B for breast cancer). Both have subscales measuring key aspects of HRQoL (physical, emotional, social, and functional); however, the EORTC-QLQ C30 also provides brief scales for cognitive functioning, financial impact, and a range of symptoms that are either not assessed by the FACT-G or are embedded within its well-being scale.[64,65] The EORTC-QLQ C30 also provides 5 "functioning" scales and 10 symptom scores compared to FACT-G, which gives 5 summary scales (4 "well-being" and 1 overall scale).[65] There are also differences between the 2 batteries' social domains. The EORTC-QLQ C30's social functioning scale assesses the impact on social activities and family life whereas the FACT-G social well-being subscale focuses on social support and relationships.[66] As both scales are widely used but measure markedly different aspects of HRQoL, a direct comparison of results between studies using different scales is not possible.[67]

3.5 | The relationship between objective cognitive dysfunction and HRQoL

Table 1 shows that 3 of the 17 studies[42,47,55] found a significant relationship between objectively assessed cognitive impairment and HRQoL. Two studies[42,47] demonstrated that the greater the cognitive impairment related to chemotherapy, the worse the patient's self-reported HRQoL as measured by the EORTC-QLQ C30 or the FACT battery. The third study[55] suggested that patients with lower functional well-being at baseline are at greater risk of cognitive impairment after chemotherapy. All 3 studies examined the interrelationships between various domains of HRQoL and specific impaired cognitive domains, with 2 of them[42,47] specifically examining the presence of posttreatment cognitive deficits whereas the third study[55] examined deficits over the course of treatment.

The significant relationships were different in all 3 studies. For example, one study[47] found that objective measures of verbal memory were associated with poorer HRQoL (as measured by EORTC-QLQ C30) 5 years after treatment. Another study[42] reported that poorer

TABLE 1 Summary of measures, cognitive domains as defined by the authors, CI, and the relationship between CI and HRQoL

				Cognitive Domain Measured									
					Memory			Attention					
Article and Year	CI?	HRQoL Measure	CI Significantly Correlated with HRQoL?	Processing Speed	Verbal	Visual	Working	Attention	Visual Motor/ Psychomotor Function	Learning Verbal	Executive Function	Self-regulation and Planning	Spatial Function	Language/ Verbal Function
[11] 2014	✓	EORTC-QLQ C30	X		Subtest of Barcelona Test—Imm Mem, Imm Mem-Q, Delayed Mem, Delayed Mem-Q			TMT A[a]	WAIS-R Digit Symbol		Stroop C-W, colour and word; TMT B[a]			
[46] 2002	X	FACT-B	X	TMT A[a] and B[a] PASAT Stroop word, colour, C-W COWAT	TMT B Category Test HVLT-R WMS-III[a]-faces I and II RBANS			TMT A[a] and B[a] Category Test HVLT-R[a] Faces I and II PASAT RBANS Stroop word, Colour, C-W COWAT	TMT A[a] and B[a] Grooved Pegboard RBANS Sensory Perceptual Exam		TMT B[a] Category Test PASAT Stroop C-W			HVLT-R[a] RBANS COWAT
[19] 2015	✓	FACT-O	X	CRT				CRT	CRT					
[45] 2006	✓	FACT-B	X		HVLT-R[a]	RCFT		TMT A[a]	WAIS-III Digit Symbol, TMT A and B		TMT B[a], Stroop colour and word, COWAT[a]		WAIS-III block design, RCFT	WRAT-3 reading subtest, Boston naming test, COWAT[a]
[49] 2004	X	EORTC-QLQ C30	X					MMSE						MMSE
[47] 2007	✓	EORTC-QLQ C30	✓		VLMT—form A	ROCFT	WMS-R	TMT A and B[a], TAP, Test D2			RWT, LPS-3, LPS-4			
[43] 2009	✓	FACT-B	X		WMS-III Logical Memory I and II, Visual Reproduction I and II, Rey AVLT delayed recall				WAIS-III Digit Span, TMT A[a]		TMT B[a], Stroop			COWAT[a], Category fluency
[42] 2010	✓	FACT-B and 1 single item question ("in general, how satisfied are you with your overall quality of life")	✓	TMT A and B[a]	WMS-III Logical Memory I and II, Rey AVLT delayed recall and trials 1-5						Stroop			COWAT[a], Category fluency
[53] 1999	✓	EORTC-QLQ C30	X	FVRT; FBCT; FVST	RAVLT	RCFT WMS-R Visual Reproduction—imm, delayed and recall		D2 WAIS-Digit Symbol WAIS-Digit Span	FFTT TMT A[a]		TMT B[a], Stroop			Word fluency subtest from S.A.N test

(Continues)

TABLE 1 (Continued)

Article and Year	CI?	HRQoL Measure	CI Significantly Correlated with HRQoL?	Cognitive Domain Measured										
				Processing Speed	Memory			Attention		Learning	Executive Function	Self-regulation and Planning	Spatial Function	Language/ Verbal Function
					Verbal	Visual	Working	Attention	Visual Motor/ Psychomotor Function	Verbal				
[50/51] 2006	✓	FACT-B and ES (patients only)	X	Letter cancellation task	WMS Logical Memory, Imm and delayed, RAVLT recall 1-7	RCFT	WMS-III spatial span, letter/ number sequencing and digit span				Stroop			
[10,14] 2005	✓	FACT-G version 4 FACT-ES	X	HSCS				HSCS, CPT	HSCS, TMT A and B[a]			HSCS	HSCS	HSCS
[20] 1998	✓	EORTC-QLQ C30	X	FVRT; FBCT; FVST	REY15 words	Complex figure		D2 test WAIS-Digit Symbol WAIS-Digit Span	TMT A[a] FFTT		Stroop TMT B[a]		RCFT (copy)	Word fluency subtest from the DAST
[52/41] 2015	✓	FACT-G	X	WAIS-III—Digit Symbol TMT A and B[a]	HVLT-R[a] CANTAB—VRM	BVMT-R	CANTAB—SWM	CANTAB—RVP	CANTAB—MOT and RVP and RTI	CANTAB—VRM				
[55] 2009	✓	FACT-G	✓	SDMT	AVLT	WMS-III Visual Reproduction –imm. delayed and recognition	WAIS-III Backward digit span	TEA Visual Elevator and Telephone search	Purdue Pegboard		WAIS-III matrix reasoning stroop, DKEFS card sorting, COWAT[a]			
[29] 2004	✓	FACT-B	X	WAIS-R—Digit Symbol, TMT A[a]	VSRT delayed recall, NVSRT delayed recall			WAIS-R Digit Span and arithmetic	Grooved Pegboard	VSRT long-term storage, NVSRT long-term storage	TMT B[a], Booklet category test, WAIS-R similarities		WAIS-R block design	
[44] 2010	✓	FACT-B	X	WAIS-R—Digit Symbol, TMT A[a]	HVLT[a]			WAIS-R Digit Span		HVLT[a]	TMT B[a], MAE COWA[a]			
[48] 2008	✓	FACT-L	X		HVLT-R[a], RCFT			Gordon CPT	WAIS-block design		COWA[a] WCST-64			

Abbreviations: BVMT-R, Brief Visuospatial Memory Test–Revised; CANTAB, Cambridge Neuropsychological Test Automated Battery; CI, cognitive impairment; COWAT/COWA, Controlled Oral Word Association Test; CPT, Continuous Performance Test; CRT, Headminder Clinical Research Tool; DAST, Dutch Aphasia Society Test; Delayed Mem, delayed memory; Delayed Mem-Q, delayed memory–questions; DKEFS, Delis-Kaplan Executive Function Scale; EORTC-QLQ C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; Faces I and II, Facial Recognition Tests; FACT, Functional Assessment of Cancer Therapy; FACT-B, for patients with breast cancer; FACT-ES, for patients with endocrine symptoms; FACT-G, Functional Assessment of Cancer Therapy–General; FACT-O, for patients with ovarian cancer; FACT-L, for patients with lung cancer; FBCT, Fey Binary Choice Test; FFTT, Fepsy finger-tapping task; FVRT, Fepsy Visual Reaction Test; FVST, Fepsy Visual Searching Test; HRQoL, health-related quality of life; HSCS, High Sensitivity Cognitive Screen; HVLT-R, Hopkins Verbal Learning Test–Revised; Imm Mem, immediate memory; Imm Mem-Q, immediate memory–questions; LPS, achievement measure test; MAE COWA, Multilingual Aphasia Examination Controlled Oral Word Association; MMSE, Mini-Mental State Examination; MOT, motor screening; NVSRT, Nonverbal Selective Reminding Test; PASAT, Paced Auditory Serial-addition Task; RAVLT/Rey AVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCFT, Rey Complex Figure Test; ROCFT, Rey-Osterrieth Complex Figure Test; RTI, reaction time; RVP, Rapid Visual Information Processing; SDMT, Symbol Digit Modalities Test; Stroop C-W, Stroop interference trial; S.A.N Test (please see full reference in); TAP, test battery for attentional performance; Test D2, D2 cancellation test; RWT, Regensburg Word Fluency Test; SWM, Spatial Working Memory; TEA, Test of Everyday Attention; TMT A and B, Trial Making Test Parts A and B; WAIS-III, Wechsler Adult Intelligence Scale–III; WAIS-R Digit Span, Wechsler Adult Intelligence Scale Revised Digit Span; WAIS-R Digit Symbol, Wechsler Adult Intelligence Scale Revised Digit Symbol; WCST-64, Wisonsin Card Sorting Test Conceptual Level Responses; WMS-III Logical Memory, Wechsler Memory Scale–Third Edition Logical Memory; WMS-III Visual Reproduction, Wechsler Memory Scale–Third Edition Visual Reproduction; WRAT-3, The Wide Range Achievement Test, Third Edition; VLMT, Auditory-Verbal Learning Test–German modified version; VRM, Verbal Recognition Memory; VSRT, Verbal Selective Reminding Test.

[a]This is one of the ICCTF's recommended core neurological assessments.

See Data S4 for all measurement references.

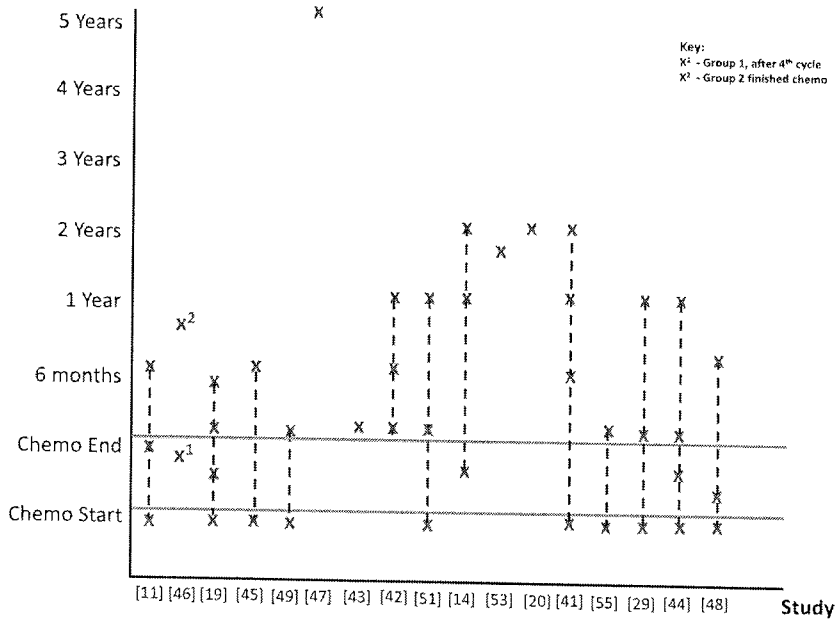

FIGURE 2 Measurement time points

functional well-being (as measured by FACT-B) was significantly associated with verbal fluency at 12 months postchemotherapy (although only a small proportion of participants' demonstrated objective cognitive decline). The third study[55] found that lower functional well-being at baseline (prechemotherapy treatment) significantly contributed to changes over the course of treatment in the cognitive domains of attention and executive function rather than declines in well-being affecting cognitive functioning shortly after finishing chemotherapy treatment.

The remaining studies included in this review found no correlation between overall objective cognitive impairment and overall HRQoL or between any of the specific domains. One study[45] did observe that those with the most dysfunction who improved also showed an improvement in overall global HRQoL. Unfortunately, no statistics or specific details were provided to back up this assertion.

3.6 | Methodological quality

Eleven studies (65%)[10/14,29,42-47,50/51,53,55] were exclusively on breast cancer, one was with a mixed solid tumour patient group,[49] 2 examined CRC patients,[11,41] another examined patients with ovarian cancer,[19] and one examined lung cancer patients.[48] In addition to variations in study samples, there were many differences in the designs and measurement points across the studies (Figure 2) that make it difficult to draw overall conclusions from this body of work. Twelve studies[11,14,19,29,41,42,44,45,48,49,51,55] were longitudinal, with 10 (59%) having prechemotherapy baseline assessments. Four of the longitudinal studies with pretreatment assessments[11,19,41,44] also examined cognition during chemotherapy treatment. Follow-up periods varied across the studies, ranging from end-of-treatment[49] to 2 years posttreatment.[14] One longitudinal study assessed cognition at 3 time points postchemotherapy.[42]

Eight studies[14,20,41,46,47,51,53,55] included more than one group. Three studies compared groups with different types of treatment or stages of disease (eg, standard dose chemotherapy compared to high dose[20,47,55]). Two studies[41,47] compared the different chemotherapy groups to an early stage cancer group who did not need chemotherapy; 3 studies compared chemotherapy patients to healthy controls.[10/14,41,51] The healthy control groups studies were peer-nominated (ie, friends and family of the patient participants). The healthy controls were a useful comparator as they were matched for age and socio-economic status. However, it should be noted that the cognitive evaluation in the patient group may be confounded by the stress associated with a cancer diagnosis and consequent surgery.[12] This raises the question as to whether a healthy control group is the ideal comparison group in this context. Two studies used 2 comparison groups[41,54] a nonchemotherapy group (postsurgery and had commenced endocrine therapy) and healthy controls (friends and family of the patient participants).[41,58]

Eight studies recruited participants from a single hospital site,[11,20,29,44-46,49,53] and the remaining 9 studies recruited from 2 or more sites making these results potentially more generalisable. Of the 8 single-site studies, 4 had sample sizes of fewer than 50 participants despite long recruitment periods. For example, one study recruited 28 breast cancer participants over 2 years[45] and another study[46] was a pilot study with only 17 participants. In contrast, 2 single-site studies[11,49] recruited more than 80 participants each, but both had high attrition rates (33% and 21%) and neither was sufficiently powered. Overall, 59% of studies[11,20,42-44,46-49,55] were underpowered and/or did not provide sample size justifications.

Of the studies with the most robust methodological[14,19,20,41,44,51,55] designs, 6 were longitudinal 5 of which had the largest sample sizes[14,19,41,51,55] a total of 206, 231, 434, 177, and

159 participants, respectively, with one or more comparison group as outlined above.

Six studies were graded as having high internal validity (ie, unbiased)[14,41,42,51,53,55], 10 as moderate,[11,19,20,29,43–46,48,51] and one as poor.[49] Only 3 studies[20,41,55] were graded as having high external validity, 13 as moderate, and one as having poor external validity.[49]

Methodological shortcomings mainly concerned 3 studies[44,45,50,51] that were exploratory in nature with no focussed objective, 7 studies[11,19,41–43,45,46] that failed to report the acceptance rate of invited participants, and eight (60%) of the longitudinal studies[11,14,19,41,42,44,48,49] that had attrition rates exceeding 20%.

Of the 3 studies that reported a relationship between objectively measured cognitive deficits and HRQoL, one was cross-sectional[47] and 2 longitudinal in design.[42,55] The focus of each was slightly different. For example, one study[47] examined neuropsychological impairment and HRQoL in high-risk breast cancer survivors 5 years after treatment. A second study[42] examined the relationship 1 month after treatment and followed up the participants for another 12 months, and the third study[55] investigated whether HRQoL significantly contributed to cognitive dysfunction reported after chemotherapy, examining cognition pretreatment and 4 weeks posttreatment.

In interpreting the quality of the studies that found a significant relationship between cognitive decline and HRQoL, the cross-sectional study[47] had a low quality rating (1), and therefore, the results should be treated with caution. Both longitudinal studies[42,55] received a higher overall quality score (3 and 4, respectively) suggesting that the results are more robust. All 3 studies examined cognitive impairment posttreatment, although one[55] also assessed pretreatment cognition. The results of these studies are difficult to compare because of their different aims, designs, participants, and measures.

4 | CONCLUSION

This review set out to examine studies that explored the possibility of a direct relationship between the adverse cognitive effects of chemotherapy treatment in patients with solid tumours and HRQoL. A critical examination of identified studies indicates that objective cognitive impairment is subtle and only occurs in a subset of patients. Processing speed, executive function, and verbal fluency were the most commonly reported affected domains in the papers reviewed here. Although the review established that there is limited evidence to indicate that such cognitive impairment puts patients treated with adjuvant chemotherapy at greater risk of poorer HRQoL, there is a suggestion that some HRQoL domains are affected.

There are a number of possible explanations for the limited number of studies reporting a significant relationship between impaired cognition and HRQoL. One explanation for some findings that failed to find any such relationship may be that the studies that used a global cognitive impairment score and/or a global HRQoL score masked the more subtle relationships or associations that possibly existed between specific cognitive domains and different aspects of HRQoL. For example, 2 studies[14,20] that combined test scores to produce an overall measure of cognitive impairment failed to find any correlation with HRQoL. In contrast, one study[42] did find evidence of women who experienced greater executive function deficits reporting more difficulties in functioning in social roles. This however cannot account for all the failures to find a relationship between impaired cognition and HRQoL as one study[48] that did examine possible relationships between each neuropsychological test result and all HRQoL variables also did not find any statistically significant correlations at the 3 assessed time points.

A further caution is required when considering the number of studies that failed to find any such relationship. Most of the studies did not set out to explore this relationship; rather it typically featured as an exploratory post hoc analysis.

Future research is needed to examine the relationship more thoroughly as more people who are diagnosed with cancer are surviving longer. If chemotherapy-related cognitive impairment is associated with feelings of low competence, survivors may encounter problems returning to work[6] and/or withdrawal from social life[30] both important consequences that need to be addressed.

An additional complication when attempting to gain clarity in this research revolves around different assessments used and the variability in the definition of cognitive impairment. Going forward, consistent use of the recommended tests and definitions should provide a clearer picture of the type and extent of deficits suffered by different cancer patients undergoing chemotherapy treatment.[58]

A similar issue relates to the definition and questionnaires used to assess HRQoL. There are many instruments available for assessing HRQoL, from generic (measuring multiple concepts relevant to a wide range of patients) to specific (a disease, population, or health dimension).[68] All studies in this review used one of the 2 instruments, the EORTC-QLQ C30 or the FACT battery. The findings indicated the difficulty in drawing meaningful comparisons between the results obtained by these 2 measures. There were insufficient data to examine which affected cognitive domains were related to which particular aspects of HRQoL. Even among the 3 studies that did find specific relationships, it was not feasible to draw any meaningful comparisons between them as they used different HRQoL measures. A further complication is that in the studies on women with breast cancer, some patients often received endocrine therapy as well as chemotherapy, making it difficult to distinguish the particular role of chemotherapy in relation to HRQoL.

Although almost all the studies found some type of cognitive impairment in a small subset of participants, such impairment often improved for some patients after treatment.[14,29,45,48] It is common with repeated assessments of neuropsychological performance that individuals show some improvement even when alternate forms of the same test are used. This emphasises the need for a control group to be able to examine and compare the practice effects when repeatedly using these tests over time.[58]

If the heterogeneity between future studies can be reduced, valuable information may be gained that could effectively inform suitable interventions for decreasing the effects of chemotherapy-related cognitive deficits and potentially improving HRQoL.[69] This would help those susceptible to impairment to cope or more fully understand the implications of side effects, particularly if their diagnosis means that chemotherapy is an option rather than a requirement.

4.1 | Strengths and limitations of the review

This review is not without its limitations. For example, all studies regardless of quality were included in the review because it is an under researched area. Most were of moderate quality at best and not necessarily methodologically robust enough to answer the review question.

4.2 | Implication

The review highlights the need for more appropriately powered studies with suitable comparison group(s) along with greater overlap of instruments used and consistency in concepts especially the definition of cognitive deficit to advance our understanding of chemotherapy, cognition, and HRQoL.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Dwek M-R, Rixon L, Hurt C, Simon A, Newman S. Is there a relationship between objectively measured cognitive changes in patients with solid tumours undergoing chemotherapy treatment and their health-related quality of life outcomes? A systematic review. *Psycho-Oncology*. 2017;26:1422–1432. https://doi.org/10.1002/pon.4331

APPENDIX G

CITY UNIVERSITY LONDON

Is there a relationship between objectively measured cognitive changes in cancer patients undergoing chemotherapy treatment and their health related quality of life? A SYSTEMATIC REVIEW

Marie-Rose Dwek, Alice Simon, Lorna Rixon, Catherine Hurt, Stanton Newman
Centre for Health Service Research, School of Health Sciences, City University London

Background

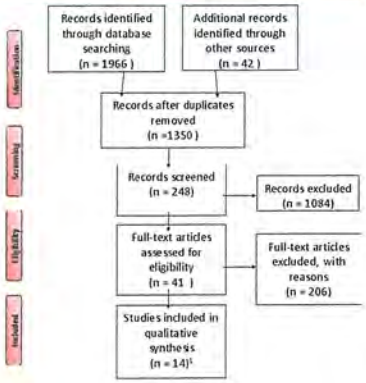
- Research indicates that chemotherapy may induce cognitive decline in cancer patients undergoing adjuvant treatment.
- With the increase in survival times in cancer patients, health related quality of life (**HRQoL**) has become a meaningful outcome measure.
- There has been no prior systematic review looking at the relationship between such decline and HRQoL.

Aims

Q1: To identify research concerned with the relationship between chemotherapy-induced objective measures of cognitive impairment (**CI**) and **HRQoL** in adult patients who have received chemotherapy for treatment of solid tumours.

Q2: To establish whether specific cognitive deficits induced by chemotherapy are related to a particular aspect of HRQoL.

Search



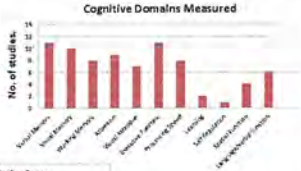
Results

Studies by Solid Tumour Type

Cognitive Domains Measured	No. of different tests across studies
Attention and visual-motor ability	12
Verbal Learning/Language/Verbal Fluency	8
Verbal memory	9
Visual memory	5
Working memory	3
Visuospatial skill/Spatial Function	7
Executive function	13
Processing Speed	6
Psychomotor skill	3
Self-regulation & planning	1
HRQoL Measures	2

- Overall 44 different tests were used across 14 studies to measure different areas of cognition.
- This huge diversity in the areas assessed and the measures used is an issue that needs to be addressed in future studies
- The International Cognition and Cancer Task Force (ICCTF) was founded in 2006 to "create research recommendations and guidelines to increase the homogeneity of study methods" (Wefel et al, 2011)

Cognitive Domains Measured



Overall Quality Rating Score

The higher the score the less bias there is in the study and the more external validity.

First Author	Study design		Comparison Group		Cognitive decline (CI) found		Relationship between CI and health related quality of life (HRQoL)	
	Cross Sectional	Longitudinal	Yes (number of comparison groups)	No	Yes	No	Yes	No
Cruzado (2014) *Spain*								
Hurria (2006) *USA*								
Iconomou (2004) *Greece*								
Mehnert (2007) *Germany*								
Reid-Arndt (2009) *USA*								
Reid-Arndt (2010) *USA*								
Shilling (2005) *UK*								
Jenkins (2006) - Linked to Shilling (2005) *UK*								
Tchen (2003) & Mar Fan (2005) linked to Tchen[1] *Canada*								
Van Dam (1998) *The Netherlands*								
Vearncombe (2009) *Australia*								
Wefel (2004) *USA*								
Wefel (2010) *USA*								
Whitney (2008) *USA*								

[1]These two papers have been treated as one longitudinal study for the purposes of this review and consequently 14 studies are included

For further information please contact Marie-Rose Dwek at Marie-Rose.Dwek.2@city.ac.uk

Discussion

- Q1: A critical examination of all identified studies exploring the relationship between CI and HRQoL has shown that objective cognitive impairment is subtle and only occurs in a subset of cancer patients.
- There is limited evidence to suggest that such cognitive impairment puts patients treated with adjuvant chemotherapy at greater risk of poorer HRQoL.
- The tests used to assess cognition and the definition of impaired cognition were not performed or used in a consistent manner, creating significant difficulties in making comparisons across studies.
- Also different instruments were used to assess HRQoL across the studies - The European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EROTC – QLQ C30)(4 studies) and the Functional Assessment of Cancer Treatment (FACT) battery (10 studies). It is hard to draw meaningful comparisons between the results obtained by these two measures as the EORTC system offers multiple specific scales and symptom scores, whereas the FACT system produces summary scales.
- Q2: There was insufficient data to answer the question 'which affected cognitive domains were related to which particular aspects of HRQoL?' as only three studies reported relationships between specific domains (Mehnert et al, 2007; Reid Arndt et al, 2010; Vearncombe et al, 2009).

Recommendations

- Longitudinal studies with larger sample sizes are required in all cancer groups to identify the extent and duration of chemotherapy induced cognitive decline.
- Researchers should try to use a set battery of cognitive measures and the same/similar definitions of cognitive decline to enable a pooling of results.
- These steps will enable investigation into the relationship between specific domains of cognitive impairment and HRQoL outcomes, as well as identifying the subsets of cancer patients that are at greater risk of CI and poorer HRQoL.

APPENDIX H

NHS
Health Research Authority

NRES Committee South West - Cornwall & Plymouth
Bristol Research Ethics Committee Centre
Level 3
Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1330

12 August 2013

Miss Marie-Rose Dwek
School of Health Sciences
London
EC1V 0HB

Dear Miss Dwek

Study title:	**A longitudinal study examining the extent of cognitive deficits attributable to chemotherapy treatment in patients who have colorectal cancer.**
REC reference:	**13/SW/0201**
IRAS project ID:	**118498**

Thank you for your letter of 06 August 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Charlotte Allen, nrescommittee.southwest-cornwall-plymouth@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management

permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Advertisement	1	28 June 2013
GP/Consultant Information Sheets	1	30 June 2013
Interview Schedules/Topic Guides	1	28 June 2013
Investigator CV		30 June 2013
Letter from Sponsor	Letter of indemnity	28 June 2013
Other: CV - Marie-Rose Dwek		30 June 2013
Other: Peer Reviewers Proforma - [redacted]		27 June 2013
Other: Peer Reviewers Proforma - [redacted]		27 June 2013
Other: CV - Stanton Newman	1	26 July 2013
Other: CV - Catherine Hurt	1	30 June 2013
Other: CV - Lorna Rixon		30 June 2013

Other: CV - Jennifer Deane	1	30 June 2013
Other: Consent to collaborate with City University's Research - UCLH	1	30 January 2013
Other: Consent to collaborate with City University's Research - Barts	1	02 February 2013
Other: Consent to collaborate with City University's Research - Charing Cross	1	02 April 2013
Other: Consent to collaborate with City University - Lewisham Healthcare NHS Trust		18 March 2013
Other: Neuropsychological Assessments		
Participant Consent Form: Feasibility Study	2.1	06 August 2013
Participant Consent Form: Main Study	2.2	26 July 2013
Participant Consent Form: Qualitative Study	2.3	06 August 2013
Participant Information Sheet: Main Study	2.2	26 July 2013
Participant Information Sheet: Feasibility Study	2.1	06 August 2013
Participant Information Sheet: Qualitative Study	2.3	06 August 2013
Protocol	3	06 August 2013
Questionnaire: Hospital Anxiety and Depression Scale		
Questionnaire: Multi-Dimensional Fatigue Inventory		
Questionnaire: EORTC QLQ-C30		
Questionnaire: FACT - Cognitive Function		
REC application	3.5	01 July 2013
Response to Request for Further Information		06 August 2013

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/SW/0201	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

[redacted]

[redacted]

Chair

Email:nrescommittee.southwest-cornwall-plymouth@nhs.net

Enclosures: "After ethical review – guidance for researchers" *(via email)*

Copy to: [redacted]

[redacted] *City University London*

[redacted] *UCLH Joint Research Office*

NHS
Health Research Authority

NRES Committee South West - Cornwall & Plymouth
Level 3
Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Tel: 01173421390
Fax: 01173420445

13 July 2015

Miss Marie-Rose Dwek
PhD student
City University London
School of Health Sciences
London
EC1V 0HB

Dear Miss Dwek

Study title:	**A longitudinal study examining the extent of cognitive deficits attributable to chemotherapy treatment in patients who have colorectal cancer.**
REC reference:	**13/SW/0201**
Amendment number:	**5**
Amendment date:	**26 June 2015**
IRAS project ID:	**118498**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The Sub-Committee reviewed the following amendment;

1. Extension of the qualitative study to follow up participants during and after chemotherapy.
2. Introduction of semi-structured interviews, pre-chemo, mid-chemo and post chemo.
3. Amended PIS and CF for qualitative study.
4. Changes to IRAS at A12, A13, A18 and A62.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Interview schedules or topic guides for participants [T2 - Chemo group]	1	26 June 2015
Interview schedules or topic guides for participants [T2 - Surgery only group]	1	26 June 2015
Interview schedules or topic guides for participants [T3 - chemo group]	1	26 June 2015
Interview schedules or topic guides for participants [T3 - Surgery only group]	1	26 June 2015
Notice of Substantial Amendment (non-CTIMP)	5	26 June 2015
Participant consent form [Patients in surgery group only]	2 - Tracked	26 June 2015
Participant consent form [Patients participating in qualitative study]	5 - Tracked	26 June 2015
Participant consent form [Patients in surgery only group]	2 - Clean	26 June 2015
Participant consent form [Patients participating in qualitative study]	5 - Clean	26 June 2015
Participant information sheet (PIS) [Qualitative study in surgery group only]	2 - Tracked	26 June 2015
Participant information sheet (PIS) [Qualitative study]	5 - Tracked	26 June 2015
Participant information sheet (PIS) [Qualitative study in surgery group only]	2 - Clean	26 June 2015
Participant information sheet (PIS) [Qualitative study]	5 - Clean	26 June 2015
Research protocol or project proposal	8 - Tracked	26 June 2015
Research protocol or project proposal	8 - Clean	26 June 2015

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

13/SW/0201: Please quote this number on all correspondence

Yours sincerely

[redacted]

Chair

E-mail: nrescommittee.southwest-cornwall-plymouth@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: [redacted] *UCLH Joint Research Office*
Miss Marie-Rose Dwek, City University London

NRES Committee South West - Cornwall & Plymouth

Attendance at Sub-Committee of the REC meeting on 17 July 2015

Committee Members:

Name	*Profession*	*Present*	*Notes*
[redacted]	Retired Hospital Chaplain	Yes	
[redacted]	Clinical Research Project Manager	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
[redacted]	REC Manager

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Chemotherapy induced cognitive changes in colorectal cancer patients

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product
( ) Clinical investigation or other study of a medical device
( ) Combined trial of an investigational medicinal product and an investigational medical device
( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
( ) Basic science study involving procedures with human participants
(●) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
( ) Study involving qualitative methods only
( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
( ) Study limited to working with data (specific project only)
( ) Research tissue bank
( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(●) No
b) Will you be taking new human tissue samples (or other human biological samples)?	( ) Yes	(●) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(●) No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

[x] England
[ ] Scotland
[ ] Wales
[ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (●) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which review bodies are you applying to?

- [x] NHS/HSC Research and Development offices
- [ ] Social Care Research Ethics Committee
- [x] Research Ethics Committee
- [ ] Confidentiality Advisory Group (CAG)
- [ ] National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

(●) Yes ( ) No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

( ) Yes (●) No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

( ) Yes (●) No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP) and you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before completing and submitting other applications.

6. Do you plan to include any participants who are children?

( ) Yes (●) No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

( ) Yes (●) No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

◉ Yes ○ No

Please describe briefly the involvement of the student(s):
This study is being undertaken for the purposes of obtaining a PhD. The student is Marie-Rose Dwek

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

NOTICE OF SUBSTANTIAL AMENDMENT

Please use this form to notify the main REC of substantial amendments to all research other than clinical trials of investigational medicinal products (CTIMPs).
The form should be completed by the Chief Investigator using language comprehensible to a lay person.

Details of Chief Investigator:

	Title	Forename/Initials	Surname
	Dr	Alice	Simon
Work Address	Health Services Research & Management Myddelton Street Building, City University London London		
PostCode	EC1V 0HB		
Email	[redacted]		
Telephone			
Fax			

Full title of study:	A longitudinal study examining the extent of cognitive deficits attributable to chemotherapy treatment in patients who have colorectal cancer.
Lead sponsor:	City University London
Name of REC:	South-West Cornwall and Plymouth
REC reference number:	13/LO/1073
Name of lead R&D office:	UCLH Joint Research Office
Date study commenced:	17 April 2014
Protocol reference (if applicable), current version and date:	Version 8: 26 June 2015
Amendment number and date:	Amendment 5: 26 June 2015

Type of amendment

(a) Amendment to information previously given in IRAS

(●) Yes ( ) No

If yes, please refer to relevant sections of IRAS in the "summary of changes" below.

Please see summary of changes below

(b) Amendment to the protocol

(●) Yes ( ) No

If yes, please submit <u>either</u> the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

Please see attached document listing the changes and giving both the previous and revised text

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

◉ Yes ○ No

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Information sheet for qualitative study in surgery only group. Version 26.06.15
Information sheet for qualitative study in chemo group. Version 26.06.15
Consent form for qualitative study in surgery only group Version 26.06.15
Consent form for qualitative study in chemo group Version 26.06.15

Is this a modified version of an amendment previously notified and not approved?

○ Yes ◉ No

Summary of changes

Briefly summarise the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study.
If this is a modified amendment, please explain how the modifications address the concerns raised previously by the ethics committee.
If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

We wish to extend the qualitative study for in order to follow up participants during and after chemotherapy (in line with the first three time points of the quantitative study).

Objectively measured cognitive impairment following chemotherapy is often only found in a small subset of cancer patients 15% to 50% (Vardy et al,2007) whereas self-reported perceived cognitive difficulties experienced by individuals in their everyday life, such as problems with concentration, memory, learning and language are more commonly reported (Pullens et al, 2010). Patients' perceptions of impairment are important due to its significant impact on quality of life (Hutchinson et al, 2012).

An analysis of the interviews conducted to date only confirm the fact that colorectal cancer patients have not heard of any possible cognitive side effects. Therefore by extending the study to interviews during and post chemotherapy treatment (and parallel time points for the surgery only group) the research team will be able to obtain fuller and richer data. The additional time points will enable the research team to more fully examine the subjective experiences, expectations and beliefs of patients undergoing chemotherapy treatment for bowel cancer. This exploration of personal accounts will supplement and complement the statistical examination of any group differences found between bowel cancer patients undergoing adjuvant chemotherapy treatment and the surgery-only control group.

The combination of quantitative and qualitative methods should provide a better and more complementary understanding of different aspects of the effect of chemotherapy induced cognitive changes. The qualitative methods can facilitate the understanding of human experience whereas the quantitative methods can facilitate the objective measurement of this experience (Sale, Lohfeld, & Brazil, 2002).

Although in recent years there has been an increase in the number of studies examining chemotherapy induced cognitive impairments there have been very few qualitative studies. Again these have been mainly in female breast cancer survivors. This study will build upon and extend the existing literature through in depth interviews with CRC patients who have had surgery and then undergo adjuvant chemotherapy treatment or no treatment at all at the same points in time as the quantitative study.

It is hoped that the semi-structured interviews will elicit the following information at the different time points:
T1: Pre chemo – participant expectations and beliefs
T2: Mid chemo – the participants' reality – what they are experiencing now in terms of side effects. (or in the case of surgery only patients what they are experiencing approximately 3 months after surgery)
T3: Post chemo - participants' views of how side effects have or have not improved (whether in chemo group or surgery only group)

All interviews will focus on cognition and quality of life as per the attached suggested guidelines for the interviews

Interviewing at 3 different time points along the course of the chemotherapy treatment will provide the research team with 'unfolding stories' as told by the participants rather than snapshots of expectations and/or experiences.

Follow up interviews will allow the research team to revisit participant experiences and encourage them to reflect more on various problems at different stages of their 'chemotherapy journey' or journey after surgery as the case may be.

Due to the inclusion of additional interviews we will now need to amend so the patient information sheets and consent forms for the qualitative study. Please find attached copies of these amended documents in clean and tracked versions.

For ease of reference the tracked versions highlight all of the changes made to the previous forms.

Changes will therefore need to be made to the following clauses in the REC Form:
A.12
Although in recent years there has been an increase in the number of studies examining chemotherapy induced cognitive impairments there have been very few qualitative studies. Again these have been mainly in female breast cancer survivors. This study will build upon and extend the existing literature through in depth interviews with CRC patients undergoing adjuvant chemotherapy treatment at the same points in time as the quantitative study. It will also help the researchers to fully explore the effect of any confounding variables such as age, fatigue and stage of cancer on any relationship between cognitive decline and quality of life.

A.13
Data will be collected for this study using interview schedules at three time points: 'T1' (post-surgery, prior to chemotherapy treatment), 'T2' (twelve weeks after first scheduled chemotherapy treatment) and 'T3' (three months after last scheduled chemotherapy treatment) and at parallel points in time for the surgery only participants.
The interviews will take place in the hospital at T1 or at such other place as the participant requests and an appointment for the subsequent scheduled assessments (T2 and T3) will be made.

A.18
Interviews will take place 3 times. The interviews will be conducted by trained researchers (Marie-Rose Dwek) in a private room in the outpatient departments of participating research sites or at the participants' home. Interviews will coincide with routine hospital appointments post-surgery, 3 months later and again 6 months after the second interview. Interviews will take between 10 minutes and 1 hour and will be tape recorded.

A.62
All interviews will be audio-recorded and transcripts will then be transcribed verbatim.
Data will be analysed using thematic analysis (Braun & Clarke 2006) to examine the key themes that emerge from the data.
In order to provide a rich thematic description of the entire data set, so as to discover/highlight the predominant or important themes and consequently the analysis will be data driven.

Any other relevant information

Applicants may indicate any specific issues relating to the amendment, on which the opinion of a reviewing body is sought.

List of enclosed documents

Document	*Version*	*Date*
Patient information sheet for qualitative study in surgery only group	2	26/06/2015
Patient information sheet for qualitative study	5	26/06/2015
Consent form for patients in surgery only group	2	26/06/2015
Consent form for patients participating in qualitative study	5	26/06/2015
Updated Proposal	8	26/06/2015
Interview Schedule for T2 - chemo group	1	26/06/2015
Interview Schedule for T2 - surgery only group	1	26/06/2015
Interview Schedule for T3 - chemo group	1	26/06/2015
Interview Schedule for T3 - surgery only group	1	26/06/2015

Declaration by Chief Investigator

1. *I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.*
2. *I consider that it would be reasonable for the proposed amendment to be implemented.*

This section was signed electronically by Dr Alice Simon on 03/07/2015 15:16.

Job Title/Post:	Honorary Lecturer
Organisation:	City University London
Email:	Alice.Simon.1@city.ac.uk

Declaration by the sponsor's representative

I confirm the sponsor's support for this substantial amendment.

This section was signed electronically by [redacted] on 26/06/2015 18:00.

Job Title/Post:	Associate Dean (Research), School of Health Sciences
Organisation:	City University London
Email:	[redacted]

Health Research Authority

Miss Marie-Rose Dwek
PhD student
City University London
School of Health Sciences
London
EC1V

Email: hra.approval@nhs.net

12 December 2016

Dear Miss Dwek

Letter of HRA Approval for a study processed through pre-HRA Approval systems

Study title:	**A longitudinal study examining the extent of cognitive deficits attributable to chemotherapy treatment in patients who have colorectal cancer.**
IRAS project ID:	**118498**
Sponsor	**City University London**

Thank you for your request for HRA Approval to be issued for the above referenced study.

I am pleased to confirm that the study has been given **HRA Approval.** This has been issued on the basis of an existing assessment of regulatory compliance, which has confirmed that the study is compliant with the UK wide standards for research in the NHS.

The extension of HRA Approval to this study on this basis allows the sponsor and participating NHS organisations in England to set-up the study in accordance with HRA Approval processes, with decisions on study set-up being taken on the basis of capacity and capability alone.

If you have submitted an amendment to the HRA between 23 March 2016 and the date of this letter, this letter incorporates the HRA Approval for that amendment, which may be implemented in accordance with the amendment categorisation email (e.g. not prior to REC Favourable Opinion, MHRA Clinical Trial Authorisation etc., as applicable). If the submitted amendment included the addition of a new NHS organisation in England, the addition of the new NHS organisation is also approved and should be set up in accordance with HRA Approval processes (e.g. the organisation should be invited to assess and arrange its capacity and capability to deliver the study and confirm once it is ready to do so).

Participation of NHS Organisations in England

Please note that full information to enable set up of participating NHS organisations in England is not provided in this letter, on the basis that activities to set up these NHS organisations is likely to be underway already.

The sponsor should provide a copy of this letter, together with the local document package and a list of the documents provided, to participating NHS organisations in England that are being set up in accordance with HRA Approval Processes. It is for the sponsor to ensure that any documents provided to participating organisations are the current, approved documents.

For non-commercial studies the local document package should include an appropriate Statement of Activities and HRA Schedule of Events. The sponsor should also provide the template agreement to be used in the study, where the sponsor is using an agreement in addition to the Statement of Activities. Participating NHS organisations in England should be aware that the Statement of Activities and HRA Schedule of Events for this study have not been assessed and validated by the HRA. Any changes that are appropriate to the content of the Statement of Activities and HRA Schedule of Events should be agreed in a pragmatic fashion as part of the process of assessing, arranging and confirming capacity and capability to deliver the study. If subsequent NHS organisations in England are added, an amendment should be submitted to the HRA..

For commercial studies the local document package should include a validated industry costing template and the template agreement to be used with participating NHS organisations in England.

It is critical that you involve both the research management function (e.g. R&D office and, if the study is on the NIHR portfolio, the LCRN) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

After HRA Approval

In addition to the document, *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC Favourable Opinion, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

The HRA website also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

IRAS project ID	118498

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/.

If you have any queries about the issue of this letter please, in the first instance, see the further information provided in the question and answer document on the HRA website.

Your IRAS project ID is **118498**. Please quote this on all correspondence.

Yours sincerely

[redacted]

HRA Approvals

Email: hra.approval@nhs.net

Copy to: [redacted] UCLH Joint Research Office
[redacted] *City University London*

APPENDIX I

CITY
UNIVERSITY OF LONDON
EST 1894

University College London Hospitals NHS
NHS Foundation Trust

Information Sheet for Participants
(Version 4, 01/04/2015)
Main Study

Title: Chemotherapy-induced cognitive changes in colorectal cancer patients

Introduction:
You are being invited to take part in a research study because you have been diagnosed with colorectal cancer. Before you decide whether you wish to take part in the study, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information.

Background information to the study:
Chemotherapy drugs can cause side effects. Some cancer patients report a condition anecdotally known as "chemofog" or "chemobrain" which affects their ability to process information, memory and attention ("cognitions"). However, the natural course of any cognitive decline (if it exists) and whether or not it causes observable difficulties for patients over time is relatively unknown. There are a lot of questionnaires available that researchers can use to capture health information from patients. However, there are very specific neuropsychological assessments that are required to assess any cognitive changes in patients.

What are the aims of the study?
The aims of this study are to collect information about cognitions from colorectal cancer patients both those undergoing chemotherapy and those that are not. We will be using assessments that have been specifically designed for this purpose. This is a study to examine the effect (if any) of chemotherapy on cognitions.

What does taking part in the study involve?
If you choose to take part in this study, you will be asked to complete a series of questionnaires during two of your routine clinic visits at the hospital that you go to for your chemotherapy, once 12 weeks after your last scheduled chemotherapy treatment, then 3 months later and also 6 months later. You will be asked whether you prefer to complete the third, fourth and fifth series of questionnaires at the hospital or at home.

The first session will take approximately 2 hours and 15 minutes to complete. The following sessions will take approximately 1 hour and 30 minutes to complete.

Your GP will also be informed of your participation in any part of the study.
If you want to be further involved, there is also an option to take part in a study that asks you to describe your experiences in a face-to-face or telephone interview. Alternatively you can just take part in the interview study and not complete these assessments.

Will my taking part in the research be kept confidential?
All information you provide during the course of the research will be kept strictly confidential. With your consent, any information collected from you will have your personal details removed so that you cannot be identified by it. All data will be stored using anonymous codes. The information you provide will only be accessible by members of the research team under the supervision of Professor Stanton Newman.

Will my hospital notes be accessed?
Your hospital notes may be accessed to find out certain information in relation to your cancer and its treatment. Importantly, only members of the research team already looking after you will be able to read your hospital notes: these include Dr Lorna Rixon, Dr Lucy Piggin and Ms Marie-Rose Dwek.

Will my records remain confidential?
All information will be kept confidential. All data will be stored using anonymous codes. The use of personal information is protected in law by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. If you have any questions about data protection, contact [redacted] the Information Compliance Officer at City University London on +44(0)20 7040 4000. Data collected for this project will be transferred to the City University London under the supervision of Professor S Newman. In relation to data processing, data storage and publication, no personal details will be revealed except to medical personnel who are already involved in your care.

Are there any risks involved in taking part?
There are no risks involved in taking part. If completing the questionnaires and/or assessments cause you any worry or distress, time will be made available for you to talk about this with a member of the team who may also refer you back to the cancer nurse specialist. There will also be facilities for referral to a local psychological support service. You can also withdraw from the research study at any time.

If you withdraw from the study you can either allow the research team to retain any data collected from you up until that point, or ask them to remove all of your data from the study

Following the assessments we will not be providing feedback on your individual scores at each assessment unless we identify a problem, in which case we will phone you and ask your permission to forward these results to your GP or cancer nurse specialist.

What are the benefits of taking part in this study?
We believe that in the future anyone undergoing chemotherapy treatment will benefit from your help with this research as it will lead to a greater understanding of the impact of chemotherapy on patient's lives.

What will be done with the results of this study?
The results of this study will be published as a paper in a medical journal. You will not be named in any publications. If you want to be provided with a summary of the results please contact a member of the team.

Who is organising and funding the project?
The study is organised by Dr Shashi Hirani and a team of researchers at City University London. The study has been made possible by the sponsorship of a PhD studentship from City University London and Barts Charity.

Do we have to take part?
It is up to you to decide whether or not to take part in this study. If you do decide to take part you will be given this information sheet to keep and you will be asked to sign an appropriate consent form prior to completing the questionnaires. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your present or future treatment in any way.

What if we have any further questions or worries?
If you have any questions regarding the study please contact the researcher, Marie-Rose Dwek on telephone number [redacted] If you are concerned about how the study is being run, please contact [redacted] on [redacted]

If you would prefer to discuss any issues in relation to the study with an independent party please contact INVOLVE.

THANK YOU FOR TAKING TIME TO READ THIS INFORMATION SHEET

CITY
UNIVERSITY OF LONDON
EST 1894

University College London Hospitals NHS

Information Sheet for Participants in surgery only group (Version 2; 01.04.2015)

Main study
Title: Chemotherapy-induced cognitive changes in colorectal cancer patients

Introduction:
You are being invited to take part in a research study because you have been diagnosed with colorectal cancer. Before you decide whether you wish to take part in the study, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information.

Background information to the study:
Chemotherapy drugs can cause side effects. Some cancer patients report a condition anecdotally known as "chemofog" or "chemobrain" which affects their ability to process information, memory and attention ("cognitions"). However, the natural course of any cognitive decline (if it exists) and whether or not it causes observable difficulties for patients over time is relatively unknown. There are a lot of questionnaires available that researchers can use to capture health information from patients. However, there are very specific neuropsychological assessments that are required to assess any cognitive changes in patients.

What are the aims of the study?
The aims of this study are to collect information about cognitions from colorectal cancer patients both those undergoing chemotherapy and those that are not. We will be using assessments that have been specifically designed for this purpose. This is a study to examine the effect (if any) of chemotherapy on cognitions.

What does taking part in the study involve?
If you choose to take part in this study, you will be asked to complete a series of questionnaires during your routine clinic visit at the hospital post-surgery. You will also be asked to complete a second, third, fourth and fifth series of questionnaires 12 weeks after the first set and approximately 6 months, 9 months and 12 months after that.

The first session will take approximately 2 hours and 15 minutes to complete. The following sessions will take approximately 1 hour and 30 minutes to complete.

Your GP will also be informed of your participation in the study.

If you want to be further involved, there is also an option to take part in a study that asks you to describe your experiences in a face-to-face or telephone interview. Alternatively you can just take part in the interview study and not complete these assessments.

Will my taking part in the research be kept confidential?
All information you provide during the course of the research will be kept strictly confidential. With your consent, any information collected from you will have your personal details removed so that you cannot be identified by it. All data will be stored using anonymous codes. The information you provide will only be accessible by members of the research team under the supervision of Professor Stanton Newman.

Will my hospital notes be accessed?
Your hospital notes may be accessed to find out certain information in relation to your cancer and its treatment. Importantly, only members of the research team already looking after you will be able to read your hospital notes: these include Dr Lorna Rixon, Dr Lucy Piggin and Ms Marie-Rose Dwek.

Will my records remain confidential?
All information will be kept confidential. All data will be stored using anonymous codes. The use of personal information is protected in law by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. If you have any questions about data protection, contact [redacted] the Information Compliance Officer at City University London on +44(0)20 7040 4000. Data collected for this project will be transferred to the City University London under the supervision of Professor Newman. In relation to data processing, data storage and publication, no personal details will be revealed except to medical personnel who are already involved in your care.

Are there any risks involved in taking part?
There are no risks involved in taking part. If completing the questionnaire or cognitive assessments causes you any worry or distress, time will be made available for you to talk about this with a member of the team who may also refer you back to the cancer nurse specialist. There will also be facilities for referral to a local psychological support service. You can also withdraw from the research study at any time.

If you withdraw from the study you can either allow the research team to retain any data collected from you up until that point, or ask them to remove all of your data from the study.

Following the assessments we will not be providing feedback on your individual scores at each assessment unless we identify a problem, in which case we will phone you and ask your permission to forward these results to your GP or cancer nurse specialist.

What are the benefits of taking part in this study?
We believe that in the future anyone undergoing chemotherapy treatment will benefit from your help with this research as it will lead to a greater understanding of the impact of chemotherapy on patient's lives.

What will be done with the results of this study?
The results of the study will be published as a paper in a medical journal. You will not be named in any publications. If you want to be provided with a summary of the results please contact a member of the team.

Who is organising and funding the project?
The study is organised by Dr Shahsi Hirani and a team of researchers at City University London. The study has been made possible by the sponsorship of a PhD studentship from City University London and Barts Charity.

Do we have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and you will be asked to sign an appropriate consent form prior to completing the assessments and/or interview. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your present or future treatment in any way.

What if we have any further questions or worries?
If you have any questions regarding the study please contact the researcher, Marie-Rose Dwek on telephone number [redacted]. If you are concerned about how the study is being run, please contact [redacted] on [redacted]

If you would prefer to discuss any issues in relation to the study with an independent party please contact INVOLVE.

THANK YOU FOR TAKING TIME TO READ THIS INFORMATION SHEET

CITY UNIVERSITY LONDON

University College London Hospitals NHS
NHS Foundation Trust

Information Sheet for Participants (version 5, 26/06/2015)
Qualitative Study

Title: Chemotherapy-induced cognitive changes in colorectal cancer patients

Introduction:
You are being invited to take part in a research study because you have been diagnosed with colorectal cancer. Before you decide whether you wish to take part in the study, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information.

Background information to the study:
Chemotherapy drugs can cause side effects. Some cancer patients report a condition anecdotally known as "chemofog" or "chemobrain" which affects their ability to process information, memory and attention ("cognitions"). However, the natural course of any cognitive decline (if it exists) and whether or not it causes observable difficulties for patients over time is relatively unknown. There are a lot of questionnaires available that researchers can use to capture health information from patients. However, there are very specific neuropsychological assessments that are required to assess any cognitive changes in patients.

What are the aims of the study?
The aims of this study are to collect information about cognitions from colorectal cancer patients both those undergoing chemotherapy and those that are not. We will be using an in-depth interview format.

In-depth semi structured interviews with up to 40 patients will enable us to explore patients' beliefs and expectations about the possible side-effects associated with chemotherapy treatment. The aim is to understand what the expectations, beliefs and experiences are concerning cancer treatments and how such treatments might or do affect one's mental and physical health.

What does taking part in the study involve?
If you wish to take part in this study you will be invited to interview before your first

session of chemotherapy and then again during the treatment cycle and lastly three months after your last scheduled chemotherapy treatment. The interviews will take between 15 minutes and 1 hour each time and will give you an opportunity to discuss in depth your experience of chemotherapy. **With your permission we would like to audio tape the interviews.**

The interviews will take place at times and locations that are convenient to you.

Your GP will also be informed of your participation in any part of the study.

Will my taking part in the research be kept confidential?
All information you provide during the course of the research will be kept strictly confidential. With your consent, any information collected from you will have your personal details removed so that you cannot be identified by it. All data will be stored using anonymous codes. The information you provide will only be accessible by members of the research team under the supervision of Professor Newman.

Will my hospital notes be accessed?
Your hospital notes may be accessed to find out certain information in relation to your cancer and its treatment. Importantly, only members of the research team already looking after you will be able to read your hospital notes: these include Dr Lorna Rixon, and Ms Marie-Rose Dwek.

Will my records remain confidential?
All information will be kept confidential. All data will be stored using anonymous codes. The use of personal information is protected in law by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. If you have any questions about data protection, contact [redacted] the Information Compliance Officer at City University London on +44(0)20 7040 4000. Data collected for this project will be transferred to the City University London under the supervision of Professor Newman. In relation to data processing, data storage and publication, no personal details will be revealed except to medical personnel who are already involved in your care.

Are there any risks involved in taking part?
There are no risks involved in taking part. If the interview causes you any worry or distress, time will be made available for you to talk about this with a member of the team who may also refer you back to the cancer nurse specialist. There will also be facilities for referral to a local psychological support service. You can also withdraw from the research study at any time.

If you withdraw from the study you can either allow the research team to retain any data collected from you up until that point, or ask them to remove all of your data from the study

What are the benefits of taking part in this study?
We believe that in the future anyone undergoing chemotherapy treatment will benefit from your help with this research as it will lead to a greater understanding of the impact of chemotherapy on patient's lives.

What will be done with the results of this study?
The results of this study will be published as a paper in a medical journal. You will not be named in any publications. If you want to be provided with a summary of the results please contact a member of the team.

Who is organising and funding the project?
The study is a PhD project organised by Professor S Newman and a team of researchers at City University London. The study has been made possible by a studentship grant from City University London.

Do we have to take part?
It is up to you to decide whether or not to take part in this study. If you do decide to take part you will be given this information sheet to keep and you will be asked to sign an appropriate consent form prior to the interview. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your present or future treatment in any way.

What if we have any further questions or worries?
If you have any questions regarding the study please contact the researcher, Marie-Rose Dwek on telephone [redacted] If you are concerned about how the study is being run, please contact [redacted] on [redacted]

If you would prefer to discuss any issues in relation to the study with an independent party please contact INVOLVE.

THANK YOU FOR TAKING TIME TO READ THIS INFORMATION SHEET

CITY
UNIVERSITY OF LONDON
EST 1894

Consent Form

(Main Study: Version 4, 01/04/2015)

Study Title: Chemotherapy induced cognitive changes in colorectal cancer patients

NOTES FOR PARTICIPANTS

You have been asked to take part in a research study. The person organising that study is responsible for explaining the project to you before you give consent.

Please ask the researcher any questions you may have about this project, before you decide whether you wish to participate.

If you decide, now or at any other stage, that you do not wish to participate in the research project, that is entirely your right, and you will not in any way prejudice any present or future treatment.

You will be given an information sheet, which describes the research project. This information sheet is for you to keep and refer to. **Please read it carefully.**

If you have any complaints about the way in which this research project has been or is being conducted, please first discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please either contact Marie-Rose Dwek the Researcher [redacted] or [redacted] the Research Development Manager [redacted]

CONSENT - please initial each of the following statements:

1. **I confirm that I have read and understand the information sheet (Version 4, 01/04/2015) for the above study and have had the opportunity to ask questions.** ☐

2. **I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.** ☐

3. **It may be necessary for sections of my medical notes to be assessed by the research team or legal governmental bodies, who monitor how medical research is carried out. I agree to this.** ☐

4. **I agree to take part in the study.** ☐

.....	.....	.....
SIGNED (Patient)	**PRINTED**	**DATE**

.....	.....	.....
SIGNED (Researcher)	**PRINTED**	**DATE**

CITY
UNIVERSITY OF LONDON
EST 1894

Consent Form

(Surgery Only Main Study: Version 2, 01/04/2015)

Study Title: Chemotherapy induced cognitive changes in colorectal cancer patients

NOTES FOR PARTICIPANTS

You have been asked to take part in a research study. The person organising that study is responsible for explaining the project to you before you give consent.

Please ask the researcher any questions you may have about this project, before you decide whether you wish to participate.

If you decide, now or at any other stage, that you do not wish to participate in the research project, that is entirely your right, and you will not in any way prejudice any present or future treatment.

You will be given an information sheet, which describes the research project. This information sheet is for you to keep and refer to. **Please read it carefully.**

If you have any complaints about the way in which this research project has been or is being conducted, please first discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please either contact Marie-Rose Dwek the Researcher ([redacted] or [redacted] the Research Development Manager [redacted]

CONSENT - please initial each of the following statements:

1. **I confirm that I have read and understand the information sheet (Version 2; 01.04.15) for the above study and have had the opportunity to ask questions.** ☐

2. **I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.** ☐

3. **It may be necessary for sections of my medical notes to be assessed by the research team or legal governmental bodies, who monitor how medical research is carried out. I agree to this.** ☐

4. **I agree to take part in the study.** ☐

.....	.....	.....
SIGNED (Patient)	**PRINTED**	**DATE**

.....	.....	.....
SIGNED (Researcher)	**PRINTED**	**DATE**

CITY
UNIVERSITY OF LONDON
EST 1894

Consent Form for patients participating in the qualitative study (Version 5: 26/06/2015)

Title: Chemotherapy induced cognitive changes in colorectal cancer patients: Qualitative Study.

NOTES FOR PARTICIPANTS

You have been asked to take part in a research study. The person organising that study is responsible for explaining the project to you before you give consent.

Please ask the researcher any questions you may have about this project, before you decide whether you wish to participate.

If you decide, now or at any other stage, that you do not wish to participate in the research project, that is entirely your right, and you will not in any way prejudice any present or future treatment.

You will be given an information sheet, which describes the research project. This information sheet is for you to keep and refer to. ***Please read it carefully.***

If you have any complaints about the way in which this research project has been or is being conducted, please first discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please either contact Marie-Rose Dwek the researcher on [redacted] or [redacted] the Research Development Manager on [redacted]

CONSENT - please initial each of the following statements:

1. **I confirm that I have read and understand the information sheet (version 5, 15/06/2015) for the above study and have had the opportunity to ask questions.** ☐

2. **I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.** ☐

3. **It may be necessary for sections of my medical notes to be assessed by the research team or legal governmental bodies, who monitor how medical research is carried out. I agree to this.** ☐

4. I understand that the interview will be audio-recorded ☐

5. I agree to take part in the study. ☐

NAME:

.....	.....	.....
SIGNED	PRINTED	DATE

.....	.....	.....
SIGNED (Researcher)	PRINTED	DATE

APPENDIX J

EDELWEISS PUBLICATIONS
OPEN ACCESS

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Cancer Open Access

Research Article

Examining Chemotherapy-Related Cognitive Changes in Colorectal Cancer Patients: A Feasibility Trial

Marie-Rose Dwek[1], Lorna Rixon[1], Alice Simon[2], Catherine Hurt[1], Stanton Newman[1]*

Abstract

Introduction: Research suggests that chemotherapy may be related to decline in patients' cognitive functions.

Objectives: To assess the feasibility and acceptability of a multi-site study designed to examine the nature and extent of chemotherapy-related cognitive changes in colorectal cancer patients.

Method: Data was collected over 8 months using objective and self-reported measures of cognitive functioning and self-reported quality of life, fatigue and mood questionnaires. The assessment battery was administered pre- and mid-chemotherapy treatment to a consecutive sample of colorectal cancer patients across three London-based NHS Trusts. Participants included patients who had undergone colorectal surgery and were scheduled to have adjuvant chemotherapy treatment, or no further cancer treatment.

Main outcome measures: Recruitment procedures, rate of recruitment, suitability of exclusion/inclusion criteria, acceptability of data collection procedures and the battery, and attrition rates.

Results: From 1 April 2014 to 1 December 2014, 42 eligible participants were invited to take part in the trial. Of the 17 that completed pre-chemotherapy assessments, only 1 withdrew at follow-up due to reasons of ill health from disease recurrence. All participants completed the entire battery and indicated that they found the trial acceptable.

Conclusions: What went wrong: Strained researcher resources; loss of eligible participants to competing studies, restrictive upper age limit.

Possible solutions: Removal of upper age limit, an increased dedicated research team to increase rate of recruitment.

The large multi-site study is feasible with suggested amendments and is acceptable to patients and medical teams. Acceptability of trial to medical teams is further evidenced by requests of collaboration from two additional London based NHS Trusts.

Lessons learned: This feasibility trial provides evidence to other researchers designing similar studies in this area of an acceptable design and the need for appropriate funding for resources to recruit large enough consecutive samples of patients with solid tumour cancers

Introduction

Research suggests that chemotherapy may be related to a decline in cognitive functions such as memory and attention in some solid tumour cancer patients [1-4]. However, the presence, extent and course of any cognitive decline and whether or not it causes observable difficulties for patients remain unclear.

The majority of research studies to date have explored cognitive function in cancer patients after treatment has been completed [5]. Few studies have measured patients' cognitive function prior to the commencement of chemotherapy treatment and hence these studies do not have any baseline. Measuring cognitive function both before and after chemotherapy would make it possible to identify changes occurring during treatment and the duration of such treatment related changes.

An additional limitation of existing studies is that they have often lacked a comparison group (e.g. cancer patients who have not required chemotherapy) against which to compare cognitive function scores. Furthermore, the majority of cognitive

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Citation: Dwek MR, Rixon L, Simon A, Hurt C, Newman S (2016) Examining Chemotherapy-Related Cognitive Changes in Colorectal Cancer Patients: A Feasibility Trial. COA 1:5-8

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Published: August 16, 2016

research to date has focussed on female breast cancer patients. This has precluded an exploration of gender differences in relation to cognitive decline.

This study examines the feasibility of a protocol designed to examine the nature and extent of chemotherapy related cognitive changes in colorectal cancer ("CRC") patients (the "Protocol") [6]. Given the proposed scale of the study, it was considered appropriate to first conduct a feasibility trial (the "Trial"). It is good practice and important for research to carry out this type of feasibility trial prior to a full study [7]. The Trial would determine the resources required, whether the Protocol could be implemented as designed, or whether any alterations were necessary.

Objectives

Bowen et al [8] suggested eight general areas of focus that may be addressed by feasibility studies for proposed interventions. This was narrowed to four areas, as the Trial did not involve an intervention. (See Table 1, which defines how the areas of focus correspond to the Trial objectives).

The primary objectives of this Trial were to evaluate:

Recruitment procedures: In order to assess the maximum number of eligible participants, the most efficient procedures for recruitment were examined so as to establish and confirm the:

a) Extent to which the suggested recruitment procedures could be carried out as proposed

b) Similarities/differences in recruitment procedures between the three collaborating London based NHS Trusts (the 'Trusts')

c) Extent to which the clinical teams were supportive of the Trial

d) Ease of identifying eligible participants

e) Number of eligible participants per Trust.

Participant numbers: A critical issue was to examine the patient flow as determined by the consent rate of eligible participants entering this Trial in order to [9-11]:

Areas of Focus	Trial Objectives
Implementation (*the extent to which and the likelihood that the proposed multi-site study can be fully implemented in accordance with the Protocol*[1])	To what extent can the recruitment procedures be carried out as proposed? How willing are the clinical teams to facilitate and/or help recruit participants?
Practicality (*an exploration of the extent to which the Protocol may be delivered given available resources and time*[1])	Capacity of staff and logistics.
Acceptability (*how will the individual recipients (both patients and clinicians) react to the procedures and assessments*[1])	Acceptability of the data collection procedures and assessments to participants and clinicians?
Practicality	Attrition rates and time needed to collect and analyse data

[1]These are an adaptation of the definitions of each area of focus provided by Bowen et al, 2009

Table 1: Areas of Focus and Trial Objectives.

a) Determine the time necessary to recruit a sufficient sample

b) Make projections of the funding and resources needed to execute an appropriately powered multi-site study

c) Assess the suitability of inclusion/exclusion criteria.

Methodology/testing of data collection procedures and assessments: The piloting and assessing acceptability of the proposed technique of data collection [11] according to the Protocol, was important, as each participant was required to undergo a series of neuropsychological assessments and questionnaires (the "Battery").

Attrition rates: Similar research in breast cancer treatment suggests that attrition rates in longitudinal cohort studies range from 10% to 33% [12-15]. The extent to which these data would be generalisable to the proposed population who differed in age, gender, cancer type and course of treatment needed to be determined.

Ethical Approval

Ethical approval was obtained from the NHS Health Research Authority – NRES Committee South-West Cornwall & Plymouth in August 2013. As part of the approval process it was also necessary to obtain a patient's perspective and view of the proposed Trial. Therefore prior to commencing the Trial an advertisement was posted on the Macmillan's Cancer Support online community noticeboard (http://community.macmillan.org.uk/volunteering/noticeboard/default.aspx) and also on Beating Bowel Cancer's patient forum (http://www.beatingbowelcancer.org/forum), asking bowel cancer patients for their general opinions and thoughts on the Trial. The feedback received was positive. The study was considered to be "worthwhile".

Methods

In accordance with the Protocol, a longitudinal cohort study was implemented between 1 April 2014 and 1 December 2014 inclusive (the 'Trial Period'). Data was collected at:

- 'T1" post-surgery and prior to chemotherapy treatment
- 'T2" twelve to fourteen weeks after first scheduled chemotherapy treatment or 3 months post surgery (as appropriate)
- 'T3" three months after last scheduled chemotherapy treatment or approximately 6 months after T2 (as appropriate).

Participants

During the Trial Period, a consecutive sample of patients between the ages of 18 and 65, diagnosed with resectable CRC under the care of the CRC team were invited to participate.

Eligibility required patients to:

a) Have undergone colorectal surgery

b) Not have distant metastases; and

c) Require adjuvant chemotherapy treatment or no post-surgery treatment at all.

Patients with prior exposure to chemotherapy and those with significant psychiatric or medical comorbidities, which might affect ability to participate in the Trail, were excluded. Patients could not enter the Trial if they were unable to read and speak English.

Measures

The measures used are detailed in the Protocol [6].

Trial sample size

Extrapolating from the Protocol's power calculation and assuming a total sample size of 156 participants (78 per group) to be recruited over 18 months, an average of eight to ten patients per calendar month would need to be consented into the Trial.

Procedure

Potential participants were identified at the weekly CRC multi-disciplinary team (MDT) meetings held by each Trust.

Proposed recruitment procedures were as follows:

- At the participant's post-surgery follow-up appointment, typically three to six weeks after surgery ('OPA'), a member of the clinical team would introduce the researcher to the patient.
- The researcher would then provide the patient with written information about the Trial and answer questions raised.
- The patient would be asked if they would be willing to be contacted by telephone within a few days to discuss participation in the Trial. Patients who agreed to participate were then given an appointment to meet with the researcher either at the hospital or at home.

Those patients who did not wish to participate after reviewing the information sheets were not contacted again.

T1 assessments were planned to take place one to two weeks after the OPA and prior to the patient's first scheduled chemotherapy appointment or at a parallel point in time for the surgery-only group. Eligible participants were to be consented into the Trial immediately prior to T1. The assessments for T1 were expected to take each participant approximately 2 hours and 30 minutes to complete.

At the end of T1 participants were advised that they would be contacted again via telephone within approximately 10 to 12 weeks to arrange the meeting for T2. T2 would be scheduled for between 12 and 14 weeks after T1 or between cycle 6 and cycle 7 in the case of the chemotherapy treatment group and at a parallel point in time for the surgery only group.

The same process would be utilised for T3, with assessments carried out at participants' homes at approximately 3 months after the final scheduled chemotherapy treatment, and at a similar point in time for the surgery-only participants.

Based on the sample size calculation set out in the Protocol, the attrition rate could not exceed 22%.

Results

Recruitment procedures

The Trial indicated that procedures were quite similar at each Trust. At all Trusts the surgery-only follow-up appointments were more difficult to determine than the chemotherapy patients.

Participant numbers

Recruiting from three Trusts (six hospital sites), attending all MDT's, surgical and chemotherapy clinics whilst also carrying out all assessments exceeded the single researcher's capacity; indicating that recruitment would require additional staff.

The surgery only control group proved more complex to recruit, as there were multiple surgeons at each hospital site making it difficult to identify all follow up OPAs. In addition eligible surgery-only participants approached by the researcher often refused participation as they asserted that they had completed treatment.

Forty-two CRC patients across 3 Trusts were invited to participate during the Trial Period, twenty-three agreed and were consented; however five changed their minds prior to completing T1. At the end of the Trial Period eighteen had completed T1 and eight T2. Seventeen of the eighteen remained in the Trial after the Trial Period and completed T2. One patient withdrew after T1 due to the appearance of a new cancer lesion. The sample at T1 was made up from 38.8% males and 61.2% females with a mean age of 59.7% years.

Fourteen of the eighteen participants (77.8%) were in the chemotherapy group. However, one participant was advised to start chemotherapy treatment several weeks after completing T1 and another that started in the chemotherapy group stopped treatment after three cycles but continued in the Trial.

The rate of recruitment was approximately three per month once the recruitment procedures and working practices were established. This indicated that significantly more research capacity and sites were required as it would take approximately four years to recruit the 156 participants required with the current resource.

Inclusion/exclusion criteria

Eligible participants were lower in number than expected in part due to the inclusion/exclusion criteria, age and also competing trials. Following ethics approval the age criterion was altered to have no upper age limit to increase recruitment.

Methodology/Testing of data collection procedures and assessments

All participants completed the full Battery. Consequently the administration of the Battery was deemed appropriate.

A suitable testing environment was achieved by administering the Battery in a quiet space both at the hospitals and participants' homes.

At the completion of T1, participants were asked how they felt about the assessments. The comments made suggested that participants in both groups found the design, methods and procedures employed in the Trial appropriate.

ID 1: *"this was very enjoyable"*

ID 14: *"It took my mind off things, I enjoyed doing it"*

Attrition rates

During the Trial Period, attrition at T2 was very low with only 1 participant withdrawing due to ill health. All participants who completed T1 expressed a desire to continue in the Trial. Continued participation in the Trial would suggest that the proposed multi-site study is worthwhile.

Conclusions

The Trial provided evidence that the Protocol is feasible subject to increasing the number of researchers and collaborating sites both to improve recruitment rates and to prevent clashes with assessments.

One possible solution to improving the rate of recruitment was implemented during the Trial Period, by removing the upper age limit for eligible participants. This has since made a difference in number of consented participants.

The number of patients consenting to the Trial and a very low attrition rate suggests that many CRC patients are willing to participate and that the Battery is feasible and well tolerated by patients.

Another strength of the proposed Protocol evidenced during the Trial was the acceptability of the multi-site study to clinical teams demonstrated by requests of collaboration from two additional London based NHS Trusts. In addition, the Trial provides valuable information to other neuropsychologists interested in the cognitive effect of chemotherapy treatments in the form of a realistic plan. It also makes clear the requirement for sufficient funding and resources. This could in turn allow for a large multi-institutional study across several English speaking cities and/or countries. All institutions could administer the same neuropsychological battery to a very large number of solid tumour cancer patients and pool all data as suggested by the International Cognition and Cancer Task Force [4].

One potential limitation of the proposed study however, is that the majority of patients had never heard of chemotherapy related cognitive changes, which may cause concern and/or priming effects. However, in the event that priming does occur it will do so in both the chemotherapy group and the surgery only group, so useful comparisons between the groups of any observed objective changes may still be made. In addition, any possible priming effects will not prohibit the researchers from being able to examine the impact of chemotherapy related subjective cognitive changes on the individuals' quality of life.

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Post script: Funding from Barts Charity was subsequently awarded to City University London in order to run an extended study and appoint further researchers. Grant Number: 477/2313.

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APPENDIX K

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STUDY PROTOCOL

Examining the effects of adjuvant chemotherapy on cognition and the impact of any cognitive impairment on quality of life in colorectal cancer patients: study protocol

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Abstract

Background: Research suggests that chemotherapy can cause deficits in both patients' objectively measured and self-reported cognitive abilities which can in turn affect their quality of life (QoL). The majority of research studies have used post-treatment retrospective designs or have not included a control group in prospective cohorts. This has limited the conclusions that can be drawn from the results. There have also been a disproportionate number of studies focussed on women with breast cancer, which has limited the generalisability of the results to other cancer populations.

Aim: This study aims to identify the extent and impact of chemotherapy-induced cognitive decline in colorectal cancer patients. Possible associations with poorer QoL will also be explored.

Design: This will be a longitudinal controlled cohort study. Questionnaires measuring subjective cognitive functioning, QoL, fatigue and mood, and neuropsychological assessments of objective cognitive function will be collected pre-, mid- and post- chemotherapy treatment from a consecutive sample of 78 colorectal cancer patients from five London NHS Trusts. A further 78 colorectal cancer surgery only patients will be assessed at equivalent time points; this will allow the researchers to compare the results of patients undergoing surgery, but not chemotherapy against those receiving both treatments.

Pre- and post-chemotherapy difference scores will be calculated to detect subtle changes in cognitive function as measured by the objective neuropsychological assessments and the self-reported questionnaires. A standardised z-score will be computed for every patient on each neuropsychological test, and for each test at each time point. The post-chemotherapy score will then be subtracted from the pre-chemotherapy score to produce a relative difference score for each patient.

ANCOVA will be used to compare mean difference z-scores between the chemotherapy and surgery-only groups while controlling for the effects of gender, age, depression, anxiety, fatigue and education.

Discussion: The result from this study will indicate whether a decline in cognitive functioning can be attributed to chemotherapy or to disease, surgical or some other confounding factor. Identification of risk factors for cognitive deficits may be used to inform targeted interventions, in order to improve QoL and help patients' cope.

Keywords: Cognitive dysfunction, Chemotherapy, Colorectal cancer, Quality of life

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Background

Chemotherapy has been shown to increase survival for a range of different cancers. This impact has improved considerably over the years - most notably for breast cancer and colorectal cancer (CRC) [1]. However, these drugs can cause severe side effects; the most commonly perceived amongst the general public have changed in recent years from nausea, vomiting, loss of appetite and hair loss [2] to fatigue and psychosocial QoL concerns [3]. This is due the fact that there has been a significant reduction in chemotherapy-associated toxicities [3] and the use of very effective anti-nausea medications.

Many cancer patients also report a decline in cognitive function following chemotherapy, colloquially referred to as "chemofog" or "chemobrain". Research in this area suggests that memory, processing speed and executive function may decline as a result of chemotherapy treatments following surgery [4–9]. These cognitive deficits could have implications for patients' QoL, daily functioning and work activity for long term cancer survivors and are therefore an important concern [10]. The natural course and extent of any cognitive decline over time and whether this decline translates into observable functional difficulty for patients is relatively unknown.

"Chemobrain" was first identified by female breast cancer survivors [11]. The majority of existing research has taken place in this patient group [12, 13] where a number of differing treatment combinations (e.g. anaesthetics and hormonal therapies) could augment the effects on cognitive dysfunction. Chemotherapy induced cognitive impairment research has probably continued to focus on the female breast cancer population because it is the most frequently diagnosed cancer in women in the world, comprising 18 % of all female cancers [11]; with 78 % of those diagnosed surviving for ten or more years [1]. However, this focus has precluded the possibility of exploring gender differences in cognitive decline, despite reports from other, mixed-gender, cancer populations (such as lung and CRC patients) that both men and women are affected by the same constellation of symptoms [11, 14].

CRC patients are an obvious population in which to carry out this type of research in a mixed-gender setting. CRC is the fourth most prevalent cancer in many developed countries, affecting men and women almost equally [15]. Such patients have a comparatively high survival rate. After surgery, 48 % of those with Stage three bowel cancer will live for at least 5 years [16]. The majority of resected Stage three CRC patients are offered a 24-week course of adjuvant chemotherapy, administered as part of standard treatment. This makes them a good patient group for a longitudinal study examining chemotherapy-induced cognitive changes over time.

One of the major limitations of earlier research has been a failure to measure cognitive function prior to chemotherapy treatment in order to provide a baseline against which to detect changes over time and to determine whether there was impairment prior to the commencement of the treatment [12, 17]. Measuring cognitive function both before and after chemotherapy treatment would identify any changes occurring due to treatment.

The few recent longitudinal studies have produced mixed findings [18–22]. One study reported a subtle negative influence of chemotherapy on cognitive function in breast cancer patients compared to women receiving only adjuvant hormonal therapy [21]. One of the few longitudinal studies in CRC patients reported no effect on cognitive function [22]. This study, however, used only a small sample ($N = 57$)), whilst Cruzado and colleagues (2014) [14] found that at the end of adjuvant chemotherapy treatment for CRC there was an acute decline in verbal memory in 56 % of patients. Neither of these two studies used a control group which meant it was not possible to establish whether any differences in cognitive functioning were due to the general effects of cancer and its symptoms or to the chemotherapy treatment. Altogether this represents a limited research base with a limited methodology and as a result it is not possible to draw firm conclusions about the extent and nature of any cognitive decline arising from chemotherapy treatment.

Our proposed study will address the limited generalisability of the existing literature by examining a larger CRC population, assessing patients pre-, mid- and post-treatment. The design also follows one of the International Cognition and Cancer Task Force (ICCTF) recommendations to compare *"patients who receive the same ensemble of treatments with or without chemotherapy"* [18] by including a surgery only control group (www.icctf.com) [18].

All of the participants in this study will have undergone the same type of surgery but those in the control group will not go on to have chemotherapy treatment. However, it is expected that all participants will experience the same range of emotions such as anxiety and depression that can accompany a cancer diagnosis and consequent treatment. This research design will allow the research team to detect the effect that adjuvant chemotherapy may have on cognition in addition to surgery. It will also permit the researchers to control for the impact of a cancer diagnosis on levels of psychological distress and QoL, both of which might affect cognitive functioning. Although it is recognised that cancer severity may differ between the chemotherapy and surgery only groups, these effects will be controlled for statistically. It would not be feasible to attempt to match

participants for disease severity because those who are offered adjuvant chemotherapy following surgery would usually have a more advanced cancer stage than those who require no further treatment after surgery.

The ICCTF also developed recommendations for a core set of neuropsychological tests, common criteria for defining cognitive impairment and cognitive changes, and common approaches to study methods across such research [18]. These will be followed in this study.

Study objectives

The aim of this study is to establish the extent of chemotherapy-induced cognitive deficits and its effect on QoL and daily functioning in both men and women undergoing treatment for CRC. Specifically the study will:

1. Determine the extent of cognitive deficits attributable to adjuvant chemotherapy treatment by conducting neuropsychological assessments in CRC patients pre-, mid- and post-treatment.
2. Compare the extent and pattern of cognitive deficits in CRC patients against a similar control group (e.g. patients who have had colorectal surgery but do not require chemotherapy).
3. Determine the effect of treatment-related cognitive decline on QoL and psychological distress.
4. Examine the relationship between patients' self-reported cognitive functions and their objectively assessed cognitive functions.

Methods

Design

This study will use a longitudinal design. Data will be collected using neuropsychological assessments and QoL questionnaires at three time points: post-surgery but prior to chemotherapy treatment ('T1'), between 12 and 14 weeks after first scheduled chemotherapy ('T2'), and 3 months after last scheduled chemotherapy ('T3') (Please see Fig. 1). A total of 156 participants (50 % of whom will receive chemotherapy and 50 % will be non-chemotherapy surgical patients) will be recruited from 5 NHS Healthcare Trusts across London. For those patients who are not receiving chemotherapy data will be collected at T1 and then in parallel with the chemotherapy group at T2 and T3.

Participants

Adult CRC patients under the care of the Consultant Oncologists at five participating NHS Trusts with London-based hospital sites who have had colorectal surgery will be invited to take part in the study.

Patients who have had prior exposure to chemotherapy or significant psychiatric or medical comorbidities, which might affect ability to participate in the study, will be excluded. Patients who are not sufficiently literate in English will also be excluded as a failure to understand English would make completion of the questionnaires impossible. Only those patients over the age of 18 years who have had surgery following a diagnosis of CRC will be eligible to participate, provided that they are then offered adjuvant chemotherapy treatment and start it at least 3 weeks after surgery or no other cancer related treatments at all and are fluent in written and spoken English.

During the post-surgery follow-up appointment nurses/trial co-ordinators at each location will provide a consecutive series of patients (satisfying the inclusion criteria) with information about the study. A research assistant will also be available at that time to answer any questions that the patient may have about the study. Those patients who provide the researcher with

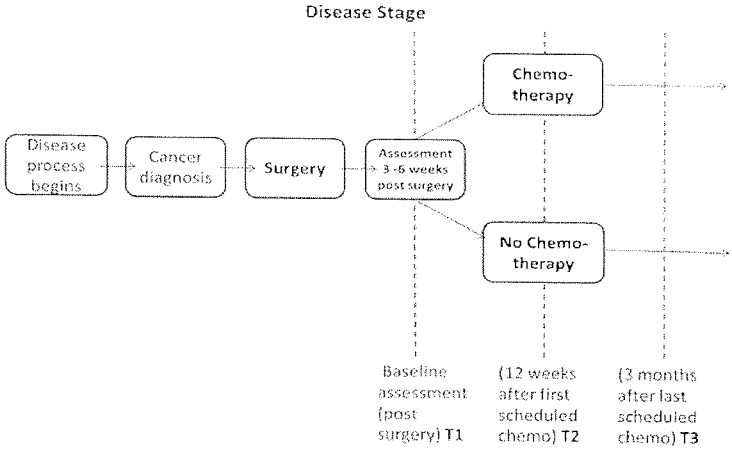

Fig. 1 Study measurement time points

telephone numbers will be contacted after 48 h and invited to participate in an interview, either at their chemotherapy clinic or at home. This interview will take place prior to the commencement of chemotherapy treatment for those in receipt of chemotherapy and at a parallel point in time for the surgery only control group (T1). At the beginning of the interview the patient will be guided through the information sheet again and the consent form by the researcher and written informed consent will be obtained. In the event that a patient declines to provide the researcher with a telephone number or refuses to take part he/she will not be contacted again about the study.

The questionnaires and assessments will be completed by the patient in the hospital at T1 and an appointment for the subsequent assessments (T2, T3) will be made. Patients' participation in the research will take approximately 2 h and 15 min at T1 and 1 h 50 min at T2 and T3 and will take place at the time of the appropriate outpatient appointment or at an equivalent point in time for the control group.

Measures

Pre-screening test

At T1, consented participants over the age of 65 will be asked to complete the Montreal Cognitive Assessment (MoCA) version 3 [23] as a pre-screening test in order to exclude those with mild cognitive impairment (MCI) from taking part in the study. In the event that such a participant obtains a raw score of less than 26 they will not progress into the study, as this is considered to be the cut off point for MCI.

The following measures will be collected at T1, T2 and T3 unless otherwise specified:

Neuropsychological assessments

The following battery of assessments has been designed to measure a wide range of cognitive domains and includes all of those recommended by the ICCTF [10]. All measures are standardised, validated and taken from published test batteries with healthy population norms, which will provide the researchers with another important comparison:

i) The Hopkins Verbal Learning Test-Revised (HVLT-R) [24] for verbal memory; this is a brief verbal learning and memory test that includes delayed recall and recognition trials. Alternate forms will be used at each of T1, T2 and T3.
ii) Trail Making Test (TMT) A and B [25] to measure psychomotor speed and aspects of executive function and spatial organisation, visual pursuits, recall, and recognition.
iii) The Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination [26] that measures speeded lexical fluency requiring aspects of executive function.

The above-recommended measures will be supplemented with the following:

iv) The Digit Span subtest of the Wechsler Adult Intelligence Scales – Third Edition, (WAIS - III Digit Span) [27] consisting of two mental activity tests involving auditory attention and short term memory retention capacity.
v) The Symbol Digit Modalities Test (SDMT) [28, 29] assesses complex visual scanning and tracking [29]. It is a simple substitution task.
vi) Letter Cancellation of the Behavioural Inattention Test (BIT) [30, 31].
vii) Grooved Pegboard Test [32, 33], a manual dexterity test measuring visuo-motor coordination.
viii) The Benton Visual Retention Test (BVRT) [34] for visual perception, visual memory and visuo-constructive ability. There are three near-equivalent forms (Forms C, D, and E) of the BVRT. Form C will be used at T1, Form D at T2 and Form E at T3, which will allow for retesting while minimizing practice effects. Administration A (of the 4 possible methods) will be used throughout.

Self-reported cognitive functioning

Functional Assessment of Cancer Therapy-Cognitive scale (FACT-Cog, Version 3) [35] is a validated self-report measure of cognitive function. It evaluates mental acuity, attention and concentration, memory, verbal fluency, functional interference, deficits observed by others but reported by the patient; change from previous functioning, and impact on quality of life.

Mood

Anxiety and depression will be measured using the Hospital Anxiety and Depression Scale (HADS) [36].

Fatigue

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F, version 4) [37] a 13-item self-report subscale of the FACT-G (see below). The FACIT-F is a well-validated quality of life instrument widely used for the assessment of cancer-related fatigue in clinical trials [37–40]. The items include physical and functional consequences of fatigue [37].

Quality of life

The Functional Assessment of Cancer Therapy - General (FACT-G, Version 4), will be used to measure 4 quality

of life domains [38]: physical, emotional, family/social and functional well being in the previous 7 days. Participants will also complete the 9-item FACT-C subscale that evaluates symptoms related specifically to CRC.

IQ

This will only be measured at T1 using the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI –II) Vocabulary and Matrix Reasoning [41] to assess background level of intellectual ability.

Socio-demographic information

This information will be collected at T1 via a structured questionnaire and will include age, sex, employment (i.e. full or part-time employment, retired and unemployed) and marital status (married, cohabiting, single, separated, divorced, widowed). Specific information relating to surgery date, planned treatments and comorbidities will also be obtained.

Medical records and treatment plan

Participants' disease and treatment-related factors will be recorded from medical records (including the type of chemotherapy administered, any dose adjustments made, the actual number of cycles completed, any neurotoxicity experienced and the anti-emetic regimen) once the participant has consented.

Sample size

A recent meta-analysis of chemotherapy and cognitive function [42] estimated mean effect sizes in a range of cognitive domains. The effect sizes ranged from d =−0.11 to−0.51. A sample size calculation was performed using GPower 3.1. Taking into consideration the resource constraints of the study, the sample size was calculated with the aim of detecting a medium effect size. To detect an effect size of−0.26 with 80 % power and a significance level of 0.05 at the final time point, a minimum sample size of 120 participants was indicated. Based on medium effect sizes in the meta-analysis, a sample size of 120 would allow effects to be detected in the following domains: executive function, information processing speed, language, motor function, verbal memory and visual memory. However, it is acknowledged small effects may not be detected in the following domains: attention and visuospatial skills. Assuming an overall attrition rate of 22 % (based on SCOT trial attrition rates[1]), a total sample size of 156 participants will be sought (78 per group).

Analysis

In order to detect subtle changes in cognitive function, pre- and post-chemotherapy difference scores will be calculated. This approach has been successfully applied in cardiac research exploring post-surgery cognitive decline [43]. A standardised score (z-score) will be computed for every patient on each neuropsychological test by dividing the test score by the standard deviation of the pre-chemotherapy test score of all study participants. A standardised score will be computed for each test at all-time points using the pre-chemotherapy standard deviation. The post-chemotherapy standardised score will then be subtracted from the pre-chemotherapy standardised score to give a relative difference score for each patient. A total z-score can then be computed for all neuropsychological tests.

ANCOVA will be used to compare mean difference z-scores between the chemotherapy and surgery-only groups while controlling for the effects of gender, age, depression, educational level and extent of disease. This method of analysis is preferable to conventional deficit/no deficit analysis as it allows for detection of subtle changes in cognition and accounts for pre-chemotherapy cognitive performance [44] and will increase the power of the analyses.

Multiple and logistic regression analyses will be used, as appropriate, to explore the relationship between cognitive impairment (total z-score) and quality of life (FACT G & C), adjusting for age, gender, SES and anxiety and depression (HADS). Finally, correlation and regression analyses will be also used to initially examine the relationship between subjective (FACT-Cog) and objective (total z-score) cognitive impairment.

Ethics and acceptability feasibility

Ethical approval for the study was obtained from the NHS Health Research Authority – NRES Committee South-West Cornwall & Plymouth in August 2013.

All of the assessments are standardised and have been widely used across many patient groups including cancer patients. At the beginning of each assessment participants will be reminded that they have the right to withdraw at any time and can avoid answering questions that are felt to be too personal or intrusive. Participants will be assured that any future treatment will not be affected in any way should they choose to withdraw. However, in the unlikely event that the assessments and content of the questionnaires cause distress or any discomfort to any of the participants, the researcher will remind the participant that he/she is entitled to refuse to answer any question that may cause upset or distress and that he/she may stop and withdraw from the study at any time. If they feel the need to have professional help they will be encouraged to raise this with their consultant or the consultant will be informed by the researcher if the patient would prefer.

Data management and data confidentiality

Confidentiality will be adhered to at all times. All questionnaires will be kept anonymous by assigning codes to participants. All data will only be identified by that code, not by the participant name or any other information that could identify them. All questionnaires will be kept in locked cabinets and/or password protected computers.

Data will be collected, transferred and stored in compliance with the NHS data protection requirements and be managed by a data manager. The data manager will also advise on current regulatory framework regarding data protection and data management procedures in compliance with the Data Protection Act 1998 and other regulations. The data manager will design and set up a bespoke database in MS Access, which will have integrated data validation checks and a full audit trail. Patient identifiable and pseudonymised data will be stored separately. The data manager will advise on and set up data transfer systems and encryption systems so that all patient identifiable data is encrypted. The data manager will also advise on storage, back up and archiving of data to ensure databases are regularly backed up to ensure data is safeguarded from accidental loss. The study master file and all study documentation will be archived for 10 years.

Discussion

At the time of writing, a feasibility study based on this protocol is being carried out to assess participant numbers, attrition rates, recruitment procedures and methodology.

The proposed study has a number of strengths. It is a multi-site study that should provide access to large numbers of potential participants, thus ensuring that the findings are more generalizable than results garnered from a single site study. In contrast to other studies in this area, this project is longitudinal and includes a comparison group in a gender-neutral cancer population. This follows advice supplied by the ICCTF. The study also uses all of the core neuropsychological tests recommended by the ICCTF.

The study includes a pre-screening tool in order to exclude anyone with pre-existing cognitive dysfunction from taking part. This has been done in few studies to date, leaving open the possibility that the results could be skewed by those who have pre-existing cognitive conditions. The MoCA was specifically designed as a rapid screening instrument for MCI. It assesses different cognitive domains relative to our study in 10 min, which should allow us to preclude those potential participants with existing cognitive deficits.

The study does also have some limitations. Treatment regimes differ across participants such that some are prescribed intravenous treatments every 2 weeks whilst others take oral tablets every 3 weeks. Additionally, treatment regimes can change over time for some patients, and this may mean that the treatment protocol will not be the same for all chemotherapy patients. Secondary analysis will be conducted if noticeable differences are identified between chemotherapy regimens although these results will need to be interpreted with caution in the event that this does occur as the comparisons will be underpowered.

It is also acknowledged that the time from diagnosis to start of treatment (particularly the period between the surgery and the start of chemotherapy) is an emotionally stressful time. Given that the anaesthetic from surgery and general emotional distress can have an adverse effect on cognitive functioning; it may be that testing during this period will not provide a true index of abilities [45]. To control for this the measures of emotional distress will be examined in relation to cognitive performance. However as per the ICCTF's recommendations, given the logistical difficulties of carrying out the assessments pre surgery, they are all being done after surgery but before adjuvant chemotherapy treatment begins.

Potential research implications

The result from this study will indicate whether a decline in cognitive functioning can be attributed to chemotherapy or to disease, surgical or some other confounding factor. Identification of risk factors for cognitive deficits may be used to inform targeted interventions, either compensatory or rehabilitating cognitive strategies to manage cognitive deficits or challenging unhelpful perceptions of cognitive functioning to lessen the negative effects on QoL.

Potential benefits to research participants

There are no immediate benefits for the research participants. There is anecdotal evidence to suggest that cancer patients like to talk about 'chemofog/chemobrain' so there is a small benefit in terms of validation that such participants may feel by being asked about this effect; however this may only be apparent in their subjective views of their cognition.

There will be long term benefits to future cancer patients in terms of the possibility of making a direct contribution to the improvement of cancer patients' lives that may ultimately lead to changes in care. For example, results may lead to making the case for integrating neuropsychological assessments into the treatment programme in order to identify those with specific deficits and unfulfilled needs.

Endnotes

[1]Personal communication with Dr Bridgewater of UCLH.

Abbreviations

CRC: Colorectal cancer; QoL: Quality of life; T1: Post-surgery, prior to chemotherapy treatment (i.e. approx. 3–6 weeks after surgery); T2: Twelve weeks after first scheduled chemotherapy or a parallel point in time; T3: Three months after last scheduled chemotherapy (i.e. approx. 9 months after T1); MoCA: Montreal cognitive assessment version 3; HVLT-R: The hopkins verbal learning test-revised; TMT: Trail making test; COWA: The controlled oral word association; SDMT: The symbol digit modalities test; BIT: Letter cancellation of the behavioural inattention test; BVRT: The benton visual retention test; FACT – Cog: Functional assessment of cancer therapy-cognitive scale; HADS: Hospital anxiety and depression scale; FACIT –F: The functional assessment of chronic illness therapy –fatigue version 4; FACT – G: The functional assessment of cancer therapy - general version 4; WASI-II: Wechsler abbreviated scale of intelligence – second edition vocabulary and matrix reasoning.

Competing interests

None of the authors have declared any competing interests

Authors' contributions

Marie-Rose Dwek (MRD) conceived the overall study for her PhD together with her supervisors Lorna Rixon (LR), Alice Simon (AS), Catherine Hurt (CH) and Stanton Newman (SN) who all contributed to the design of the study. MRD obtained ethical approval and is responsible for data collection. LR has also been involved in data collection and obtaining consent from collaborating Trusts. MRD drafted the study protocol and allauthors read and approved the final manuscript.

Authors' information

Marie-Rose Dwek has previous experience of collecting similar questionnaire data from patient populations and is carrying out this study as part of her PhD which is being sponsored by City University London.

Dr Lorna Rixon, BSc, MSC, PhD, C.Psychol. is a chartered health psychologist and post-doctoral research fellow in health services research. Her doctoral thesis examined the role of cognition and emotion in quality of life in cancer survivors. She also has extensive experience of working with cancer patients, including return to work, recovery from cancer, and developing theory based interventions.

Dr Alice Simon is a registered health psychologist who has extensive experience in the field of cancer research.

Dr Catherine Hurt is an experienced chartered psychologist with a particular focus on neurodegenerative diseases and cognitive impairment.

Professor Stanton Newman is Dean of the School of Health Sciences at City University London. He is Professor of Health Psychology and completed his B.Soc. Sci. (Hons) degree and doctorate at the University of Natal, South Africa. He is also a clinical psychologist at UCLH.

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The views and opinions expressed are those of the authors alone.

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APPENDIX L

Participant ID: MRN/NHS:	**Trust/Hospital:**

Sex: Male ☐ Female ☒	**DOB:**

Co-Morbidities:

Diagnosis Date:	
Diagnosis: Pre-Surgery Staging:	

Surgery Date:	Surgery Type: Open ☐ Laparoscopic ☐	Device: Stoma: Yes ☐ No ☐ Reversible: Yes ☐ No ☐
Description: Hospital Stay:		

Date of <u>first</u> Chemotherapy:	**Date of <u>last</u> chemotherapy:**
Protocol/Regimen: Anti-Sickness:	

Number of Cycles:	Delivery: Oral ☐ Intravenous ☐ Cannula ☐ Central/Hickman ☐ PICC ☐ Portacath ☐
Notes (e.g. treatment delays, changes in Protocol, notable side-effects and complications):	

	T1 Date	T2 Date	T3 Date	T4 Date	T5 Date
Estimated					
Actual:					

Additional Information:

APPENDIX M

APPENDIX M: Qualitative Interview Schedule

T1: Post surgery and pre chemotherapy treatment

Tell me what treatment you have/are expecting to receive for cancer

What is your understanding of the side effects that you might experience from the treatment that you receive for cancer?

What do you know about the side effects of chemotherapy?

Where have you received most of your information about the side effects of chemotherapy?

What side effects do you think that you personally might experience?

Of these side effects what are you most concerned about?

How long do you think you will experience these side effects for?

Before reading the information sheet for this study had you ever heard that some people complain of difficulties with their memory and thinking ability after treatment?

If yes:

Where have you heard/read about this?

Is this something that you are concerned about?

If yes:

How long do you expect these problems to last?

Have you noticed any changes in your memory and thinking ability since you were diagnosed with CRC (or around that time?)

If yes:

Can you give examples of any changes or difficulties?

Changes in ability to remember and think clearly e.g. do you forget things that people have told you or events that happened recently? Do you misplace things? Do you have difficulty concentrating when reading a book or watching TV? Do you have any problems dealing with money e.g. working out the correct change in shops? Do you find it harder to concentrate on more than one task at a time? (NOTE: only record recent changes not pre-existing problems)

Have these changes impacted on your daily activities? (How so)

Roughly when did you start to notice these problems?

What do you think is the cause of these problems?

How long do you expect these problems to last?

T2: Qualitative Interview Schedule

Aim: T2: Mid chemo – the participants' reality. The purpose of this follow up study is to obtain an in depth understanding of CRC survivors' actual experiences of the treatment and what they are feeling in terms of side effects and severity of perceived cognitive impairment; looking at the impact of the impairments (if any) on relationships, daily functioning, work and overall life satisfaction.

CHEMO GROUP:

1. Can you tell me how many cycles of chemotherapy treatment you have had to date?

2. Have all cycles run according to schedule?

3. Since you started chemotherapy treatment have you experienced any side effects?

If yes go to 2b if no go to 3

2. (b) Can you tell me a little about the kind of symptoms you have had so far? (*If they have had nausea ask if they were given anti-emetics*)

Possible prompts: Nausea? Vomiting? Tingling in fingers and/or toes? Changes in appetite? Weight? Pain or discomfort? Tiredness? Difficulty sleeping?

2. (c) Has the way you have been feeling physically changed at different times during the chemotherapy cycles?

2. (d) Can you tell me how they changed?

3 (a). Have you been aware of any changes in the way your mind/thoughts worked since you started chemotherapy treatment?

Possible Prompts: Have you noticed any difficulties in remembering things? E.g. Where you put your keys or wallet? Phone numbers?

If yes go to 3b if no go to 4

3.(b) Can you tell me a bit about this?

3.(c) Has this been constant throughout your treatment cycles?

3. (d) What types of things were you having problems with?

3.(e) Have the changes in the way you think bothered you or interfered with your everyday life in anyway so far? Can you tell me how?

Possible prompts: Is there anything that you do that helps make this better? E.g. lists?

4. Have any of your friends or relatives told you that you seem to have trouble remembering information? Or that you seem to have trouble speaking clearly?

5 a. What about concentration, have you noticed any changes in your concentration since your treatment started? Have you had any difficulty concentrating?

Possible prompt: Are social conversations affected at all? Do you find that your thinking is slower than usual? Can you keep track of what you are doing?

If yes go to 5b if no go to 6

5. (b) Can you tell me a bit about this?

5. (c) Has this constant throughout your treatment cycles?

5. (d) Can you give me some examples of when your concentration hasn't been very good?

Possible prompt: Can you watch an entire film? Read a book without losing track of where you are up to?

5. (e) Do the changes in your concentration bother you or interfere with your everyday life in anyway? Can you tell me how?

6. Have any of your friends or relatives noticed any changes in your concentration? Do they ever tell you that seem to have trouble thinking clearly? Or that you seem confused?

7. Of all the symptoms that you have experienced up to now are there any that are upsetting you? Do any of these problems interfere with your ability to do things that you would normally enjoy?

8. Does your medical team help in any way?

If so – how? What do they do or advise you to do?

9. Do you think that any of the side effects that you are experiencing have any impact on you personally and on your relationships with others?

If yes – in what way? Can you describe what impact they have?

10. How is your social life?

11. Are you working at the moment?

If yes – full time? Same as before?

If no – were you working prior to treatment?

12. What, if any, impact have these changes in your thinking and/or concentration had on your overall life satisfaction?

13.a Have there been times during your treatment cycles when you have felt particularly down or worried?

If yes go to 13 b if no go to 14

13. (b) Can you tell me about those times?

13. (c) Has this been fairly constant throughout the cycles or is there some variation? Do you know roughly when these feelings are strongest?

13. (d) Have you had any help for this, e.g. do you see a counsellor, specialist nurse or GP?

14. Do you have any problems with sleeping?

15. Do you take any pills to help with sleep, anxiety or depression or anything else? If so, since when?

16. What information would you have found helpful prior to starting chemotherapy treatment?

17. Is there anything else you would like to share about your experience?

T3: Qualitative Interview Schedule – to be audiotaped

Aim: T3 3 months after end of last scheduled chemo treatment. The purpose of this follow up study is to obtain an in depth understanding of CRC survivors' beliefs and actual experiences since treatment has finished; do they feel that they are back to normal? What has happened in terms of side effects and severity of perceived cognitive impairment – particularly in relation to relationships, daily functioning, work and overall life satisfaction?

CHEMO GROUP:

1. Can you tell me the date of your last chemotherapy treatment?

2. How many cycles did you have?

3. Since your last chemotherapy cycle have you continued to experience any side effects?

If yes go to 3b if no go to 4

3. (b) Can you tell me a little about the kind of symptoms you had? (*If they have had nausea ask if they were given anti-emetics*)

Possible prompts: Nausea? Vomiting? Tingling in fingers and/or toes? Changes in appetite? Weight? Pain or discomfort? Tiredness? Difficulty sleeping?

3. (c) Did the way you felt physically change at different times during the chemotherapy cycles?

3. (d) Can you tell me how they changed?

3. (e) And now? Are you still experiencing any of these side effects?

4 (a). Were you aware of any changes in the way your mind/thoughts worked during chemotherapy treatment?

Possible Prompts: Did you notice any difficulties in remembering things? E.g. Where you put your keys or wallet? Phone numbers?

If yes go to 4b if no go to 5

4.(b) Can you tell me a bit about this?

4.(c) Was this constant throughout your treatment?

4. (d) What types of things were you having problems with?

4.(e) Did the changes in the way you were thinking bother you or interfere with your everyday life in anyway? Can you tell me how?

Possible prompts: Was there anything that you did that helped make this better? E.g. lists?

4 (f) What about now? Do you still have any of these problems?

5. Have any your friends or relatives told you that you seem to be having trouble remembering information? Or that you seem to have trouble speaking clearly? Now or at any time during your treatment?

5 a. What about concentration, did you notice any changes in your concentration while you were having treatment? Did you have any difficulty concentrating? And now?

Possible prompt: were/are social conversations affected at all? Did/do you find that your thinking was/is slower than usual? Could/can you keep track of what you were doing?

If yes go to 5b if no go to 6

5. (b) Can you tell me a bit about this?

5. (c) Was this constant throughout your treatment? And now?

5. (d) Can you give me some examples of when your concentration hasn't been very good?

Possible prompt: Can you watch an entire film? Read a book without losing track of where you are up to?

5. (e) Did/do the changes in your concentration bother you or interfere with your everyday life in anyway? Can you tell me how?

6. Did/do any of your friends or relatives notice any changes in your concentration? Did/do they ever tell you that seemed/seem to have trouble thinking clearly? Or that you seemed/seem confused?

7. Of all the symptoms that you experienced are there any that were or are still upsetting? Did/do any of these problems interfere with your ability to do things that you would normally enjoy?

8. Has your medical team helped in any way?

If so – how? What did they do or advise you to do?

9. Do you think that they have any impact on you personally and on your relationships with others?

If yes – in what way? Can you describe what impact they have?

10. How is your social life? Has anything changed compared to before you started treatment?

11. Have you gone back to work? To the same job as before?

If no – why not?

12. What, if any, impact have these changes in your thinking and/or concentration had on your overall life satisfaction?

13.a Have there been times either during your treatment or now when you have felt particularly down or worried?

If yes go to 13 b if no go to 14

13. (b) Can you tell me about those times?

13. (c) Can you remember roughly when these feelings were strongest?

13. (d) Have you had any help for this, e.g. did you see a counsellor, specialist nurse or GP?

14. Do you have any problems with sleeping? Did you during the treatement?

15. Have you been on any pills to help with sleep, anxiety or depression or anything else? If so, since when?

16. What information would you have found helpful prior to starting chemotherapy treatment?

17. What information would you have found helpful once you began to notice changes in your thinking or memory?

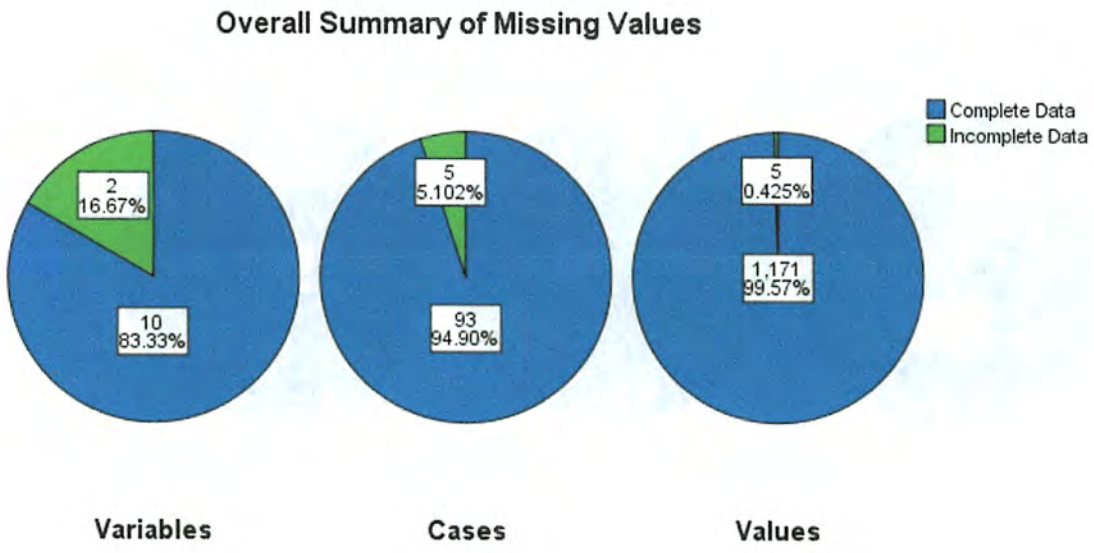
18. Did you receive any information on what to expect during the period after your treatment?

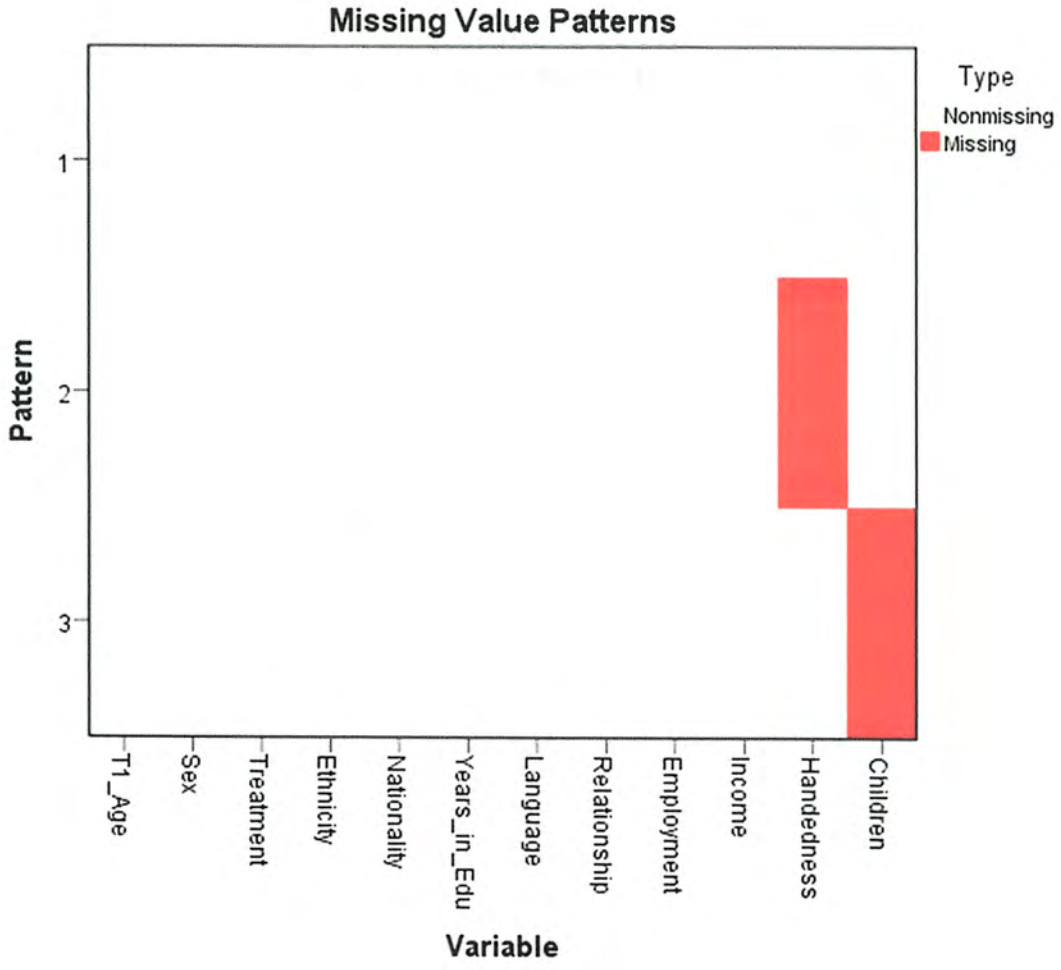
19. Is there anything else you would like to share about your experience?

APPENDIX N

APPENDIX N: MISSING VALUES

PARTICIPANT DEMOGRAPHICS





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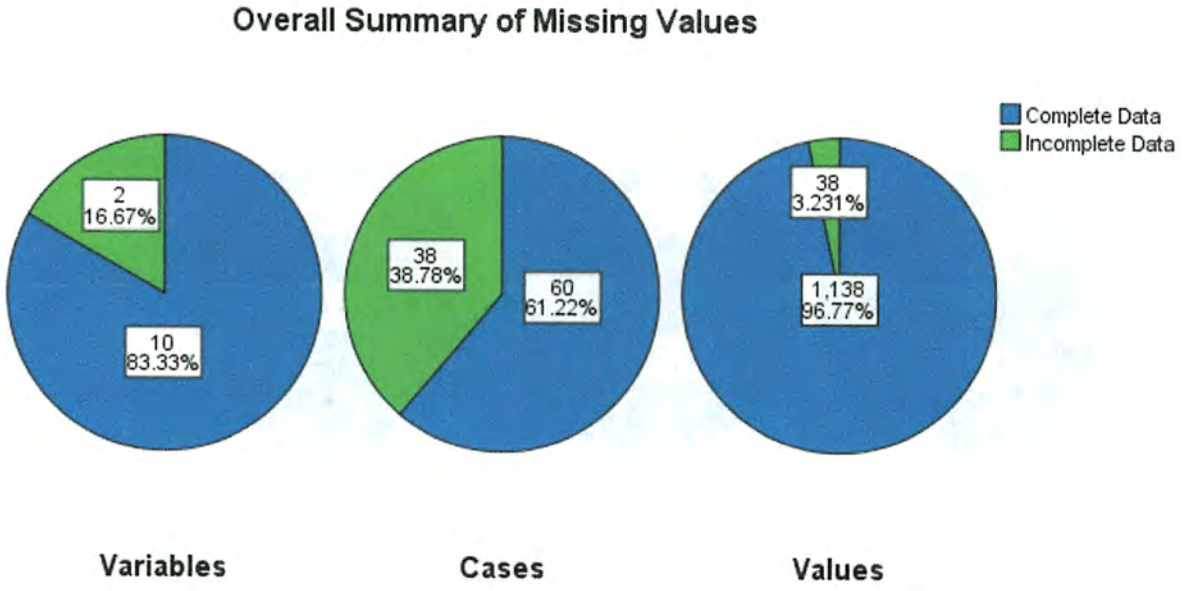

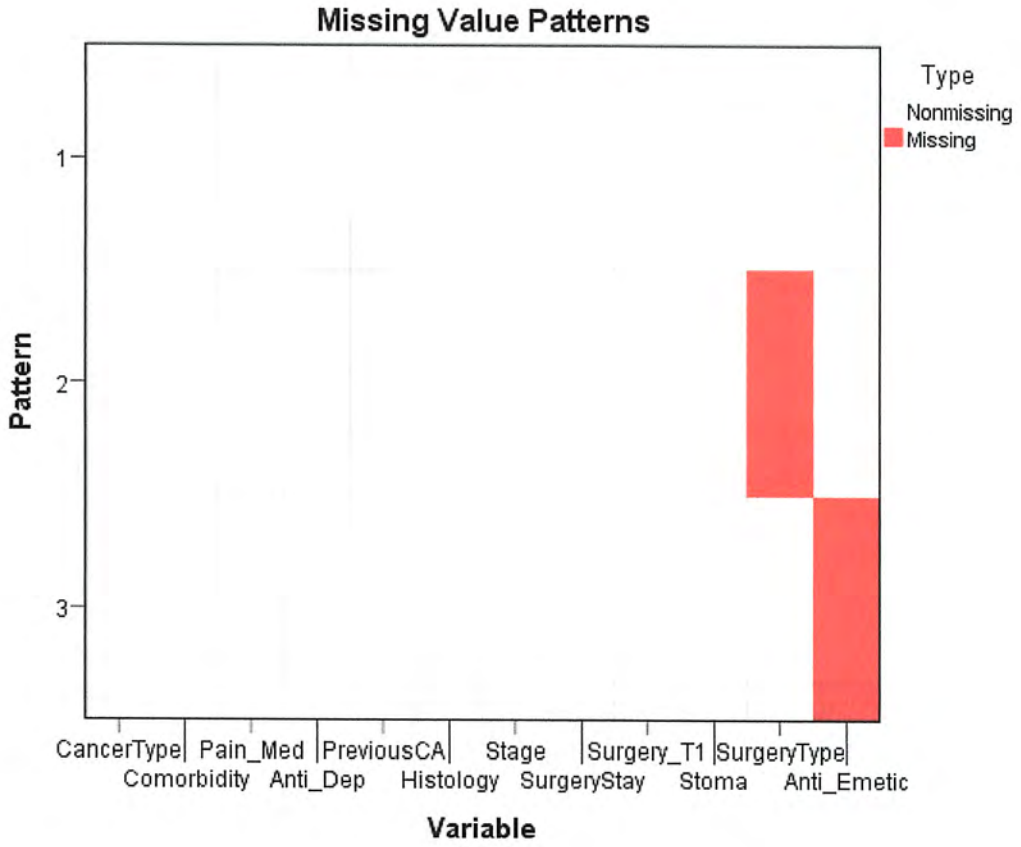

APPENDIX O

Tests of Normality at baseline (T1)

Kolmogorov-Smirnov for demographic variables

	Statistic	df	Sig.
Age	.121	98	.001
Years in education	.455	98	.000
Nationality	.489	98	.000
Is English first language?	.479	98	.000
Relationship	.372	98	.000
Employmen tstatus	.382	98	.000
Type of cancer	.375	98	.000
Cancer staging post-surgery - I-III	.274	98	.000

Interpretation key- A significant ($p<0.001$) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution.

Kolmogorov-Smirnov for neuropsychological test scores (raw scores)

	Statistic	df	Sig.
T1 Digit Span - Forward	.149	98	.000
T1 Digit Span - Backward	.102	98	.014
T1 Symbol Digit - Written	.111	96	.006
T1 Symbol Digit - Oral	.083	96	.100
T1 TMT A	.223	98	.000
T1 TMT B	.128	93	.001
T1 Hopkins Verbal Learning - Recall	.075	98	.200
T1 Hopkins Verbal Learning - Delayed Recall	.125	98	.001
T1 Hopkins Verbal Learning - Retention	.175	98	.000
T1 Hopkins Verbal Learning - Recognition	.213	98	.000
T1 Benton Visual Retention Test - Number Correct	.180	98	.000

T1 Benton Visual Retention Test - Number of Errors	.146	98	.000
T1 GP - Dominant Hand	.264	92	.000
T1 GP - Non-Dominant Hand	.165	88	.000
T1 COWA	.074	98	.200

Interpretation key- A significant (p<0.001) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution.

Kolmogorov-Smirnov for psycho-social variables (raw scores)

	Statistic	df	Sig.
T1 HADS Anxiety Subscale	.123	98	.001
T1 HADS Depression	.178	98	.000
T1 FACT-C Physical Wellbeing Subscale	.196	96	.000
T1 FACT-C Social/Family Well being Subscale	.198	96	.000
T1 FACT-C Emotional Wellbeing Subscale	.138	97	.000
T1 FACT-C Functional Wellbeing Subscale	.082	97	.104
T1 FACT-C Additional Functional Concerns (Colorectal-Specific)	.117	97	.002
T1 FACT-C Total Score	.061	95	.200
T1_FACIT_Fatigue	.123	97	.001
T1 FACT Cognitive - Perceived Impairment Scale	.136	95	.000
T1 FACT Cognitive - Comments from Others Scale	.390	97	.000
T1 FACT Cognitive - Perceived Abilities Scale	.135	97	.000
T1 FACT Cognitive - Impact on QoL Scale	.198	97	.000

Interpretation key- A significant (p<0.001) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution.

APPENDIX P

Norms used for Neuropsychological Assessments

1. Digit Span

LeZak (p.404) advised that it *'makes more sense to deal with the data in raw score form than to convert them'*. Taking into account that the normal range for digits forward is 6 +/- 1 (G.A. Millller, 1956; Spitz 1972). A span of 5 (i.e. score of 7 or 8) may be marginal to normal limits, a span of 4 (i.e. score of 5 or 6) is definitely borderline and 3 (i.e. score of 3 or 4) is impaired (LeZak). Age tends to affect forward span only minimally beyond ages 65 or 70 as reported in most studies (Craik, 1990; Jarvik, 1988)

When evaluating digits reversed on the basis of the raw score, scores of 4 or 5 can be considered within normal limits, 3 is borderline to impaired, depending on the patients educational background (Botwinick and Storandt, 1974; Weinberg, Diller et al 1972) and 2 is impaired for everyone. The reversed span typically decreases about 1 point during the seventh decade (LeZak).

2. Symbol Digit Modalities Test (SDMT) (A. Smith, 1982)

TABLE 9.5 Symbol Digit Modalities Test Norms for Ages 18 to 74

Age Group	*Mean Education*	*Mean Written Administration*	*Mean Oral Administration*
18–24 (n = 69)	12.7	55.2 (± 7.5)	62.7 (± 9.1)
25–34 (n = 72)	13.5	53.6 (± 6.6)	61.2 (± 7.8)
35–44 (n = 76)	12.1	51.1 (± 8.1)	59.7 (± 9.7)
45–54 (n = 75)	11.7	46.8 (± 8.4)	54.5 (± 9.1)
55–64 (n = 67)	11.3	41.5 (± 8.6)	48.4 (± 9.1)
65–74 (n = 61)	10.7	37.4 (± 11.4)	46.2 (± 12.8)

Based on studies by Carmen C. Centofanti.

Source: Lezak p.

3. TMT

Statistical properties for age, education, gender, Trails A and B (s) for each normative group

	Statistics				
Age groups	Mean (S.D.)	Median	Minimum-maximum	Skewness	Kurtosis
Age group 18-24 (*n* = 155)					
Age	20.17 (1.48)	20.00	18-24		
Education	.12.92 (1.01)	13.00	10-15		
Gender	1.59 (0.49)				
Trail A (s)	22:93 (6.87)	21.70	12-57	1.64	4.46
Trail B (s)	48.97 (12.69)	47.00	29-95	.91	.92
Age group 25-34 (*n* = 33)					
Age	29.42 (2.87)	30.00	25-34		
Education	14.18 (1.61)	14.00	11-18		
Gender	1.58 (0.50)				
Trail A (s)	24.40 (8.71)	23.00	10-45	.78	.21
Trail B (s)	50.68 (12.36)	50.00	29-78	.14	- .59
Age group 35-44 (*n* = 39)					
Age	39.74 (2.94)	41.00	35-44		
Education	13.59 (2.06)	14.00	10-20		
Gender	1.59 (0.50)				
Trail A (s)	28.54 (10.09)	26.00	12-50	.64	-.35
Trail B (s)	58.46 (16.41)	58.00	29-95	.59	.01
Age group 45-54 (*n* = 41)					
Age	48.54 (2.96)	48.00	45-54		
Education	13.68 (2.80)	14.00	8-21		
Gender	1.61 (0.49)				
Trail A (s)	31.78 (9.93)	31.00	18-56	.83	.44
Trail B (s)	63.76 (14.42)	64.00	32-92	-.32	-.32
Age group 55-59 (*n* = 95)					
Education 0-12 years (*n* = 58)					
Age	5(>.90 (1.31)	57.00	55-59		
Education	I1.05 (1.05)	11.00	8-12		
Gender	1.55 (0.50)				
Trail A(s)	35.10 (10.94)	32.00	19-72	1.42	2.18
Trail B (s)	78.84 (19.09)	73.50	42-127	.73	.09
Education 12+ years (*n* = 37)					
Age	57.05 (1.45)	57.00	55-59		
Education	15.32 (1.93)	16.00	13-18		
Gender	1.51 (0.51)				
Trail A (s)	31.72 (10.14)	30.00	18-55	1.25	.77
Trail B (s)	68.74 (21.02)	65.00	30-121	.91	1.29
Age group 60-64 (*n* = 86)					
Education 0-12 years (*n* = 55)					
Age	62.33 (1.28)	63.00	60-64		
Education	10.84 (1.27)	11.00	7-12		
Gender	1.56 (0.50)				
Trail A (s)	33.22 (9.10)	33.00	20-49	.04	-1.39
Trail B{s)	74.55 (19.55)	72.00	40-138	1.23	2.14

Age groups	Statistics				
	Mean (S.D.)	Median	Minimum- maximum	Skewness	Kurtosis
Education 12+ years (n = 31)					
Age	*61.94* (l.5Q)	62.00	60-64		
Education	15.45 (1.31)	16.00	13-18		
Gender	1.52 (0.51)				
Trail A (s)	31.32 (6.96)	31.00	20-47	.50	-.45
Trail B (s)	64.58 (18.59)	60.00	37-116	1.15	1.68
Age group 65-69 (n = 97)					
Education 0- 12 years (n = 65)					
Age	67.04 (1.63)	67.00	65-69		
Education	10.87 (1.71)	12.00	5-12		
Gender	1.62 (0.49)				
Trail A (s)	39.14 (11.84)	39.00	17-71	.48	.16
Trail B (s)	91.32 (28.89)	86.00	49-190	1.23	2.12
Education 12+ years (n = 32)					
Age	67 22 (1.43)	67.00	65-69		
Education	15.91 (1.87)	16.00	13-21		
Gender	1.58 (0.50)				
Trail A (s)	33.84 (6.69)	32.00	23-47	.55	- .67
Trial B (s)	67.12 (9.31)	68.00	48-84	-.41	- .64
Age group 70-74 (n = 106)					
Education 0-12 years (n = 76)					
Age	71.99 (1.40)	72.00	70-74		
Education	10.50 (I. 72)	11.00	6-12		
Gender	1.45 (0.50)				
Trail A (s)	42.47 (15.15)	38.00	20-89	1.47	2.51
Trail B (s)	109.95 (35.15)	IO1.00	45-190	.59	-.61
Education 12+ years (n = 30)					
Age	7,2.07 (1.60)	72.00	70-74		
Education	15.43 (2.21)	15.00	13-22		
Gender	1.47 (0.51)				
Trail A (s)	40.13 (14.48)	36.00	26-75	1.52	1.49
Trail B (s)	86.27 (24.07)	83.50	55-159	.97	1.26
Age group 75-79 (n = 108)					
Education 0-12 years (n = 74)					
Age	77.32 (1.35)	78.00	75-79		
Education	10.80 (1.50)	11.50	6-12		
Gender	1.58 (0.50)				
Trail A (s)	50.81 (17.44)	50.00	25-109	1.11	1.56
Trail B (s)	130.61 (45.74)	120.00	57-274	.75	.31
Education 12+ years (n = 34)					
Age	77.21 (1.49)	77.00	75-79		
Education	15.29 (1.80)	15.00	13-18		
Gender	1.53 (0.51)				
Trail A (s)	41.74 (15.32)	40.00	19-75	.57	-.27
Trail B (s)	100.68 (44.16)	87.00	53-207	.85	- .21

	Statistics				
Age groups	Mean (S.D.)	Median	Minimum-maximum	Skewness	Kurtosis
Age	81.94 (1.41)	82.00	80-84		
Education	10.48 (1.54)	11.00	7-12		
Gender	1.52 (0.50)				
Trail A (s)	58.19 (23.31)	52.50	25-116	.84	.11
Trail B (s)	152.74 (65.68)	139.50	55-315	.81	-.06
Education 12+ years ($n = 34$)					
Age	81.56 (1.52)	81.00	80-84		
Education	15.50 (2.54)	16.00	13-25		
Gender	1.41 (0.50)				
Trail A (s)	55.32 (21.28)	48.00	29-105	1.30	.91
Trail B (s)	132.15 (42.95)	128.00	67-249	1.42	1.85
Age group 85-89 ($n = 29$)					
Education 0-12 years ($n = 16$)					
Age	86.38 (1.50)	86.00	85-89		
Education	9.88 (1.96)	10.50	6--12		
Gender	1.69 co.48)				
Trail A (s)	57.56 (21.54)	54.50	36-120	1.75	3.87
Trail B (s)	167.69 (78.50)	142.50	83-366	1.26	1.80
Education 12+ years ($n = 13$)					
Age	86.31 (1.65)	86.00	85-89		
Education	16.23 (2.45)	16.00	13-22		
Gender	1.62 (0.51)				
Trail A (s)	63.46 (29.22)	53.00	35-127	1.60	1.82
Trail B (s)	140.54 (75.38)	121.00	63-308	1.24	.77

Source: T.N. Tombaugh I Archives of Clinical Neuropsychology 19 (2004) 203-214 207

4. HVLT - R

See next page

Table 2.1
Demographic Characteristics and Performance Results for the HVLT-R Normative Sample by Age Group

	16-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80+ years	*p*
Sex									
Men (*n*)	13	42	58	40	31	48	50	18	
Women (*n*)	16	42	72	85	93	74	468	29	<.001
Age (mean years)	18.21 (±0.68)	25.24 (±2.98)	34.47 (±2.95)	44.16 (±2.82)	54.82 (±2.94)	64.75 (±2.91)	73.96 (±2.74)	83.09 (±3.63)	<.001
Education (mean years completed)	11.76 (±0.95)	14.22 (±2.20)	13.90 (±1.79)	13.67 (±2.04)	13.81 (±2.62)	14.32 (±3.04)	12.95 (±3.27)	14.17 (±3.27)	<.001
MMSE score[a]	—	28.96 (±1.49)	28.52 (±1.72)	28.84 (±1.28)	28.52 (±1.54)	28.48 (±1.58)	28.24 (±1.69)	27.70 (±1.55)	.023
HVLT-R scores									
Learning Trial 1	7.69 (±1.23)	7.90 (±1.82)	7.48 (±1.79)	7.84 (±1.80)	7.40 (±1.73)	6.90 (±1.77)	5.81 (±1.83)	5.87 (±1.84)	<.001
Learning Trial 2	10.55 (±1.18)	10.05 (±1.50)	9.81 (±1.80)	9.84 (±1.64)	9.56 (±1.75)	9.43 (±1.77)	8.13 (±2.03)	7.83 (±2.15)	<.001
Learning Trial 3	10.90 (±0.94)	10.81 (±1.22)	10.75 (±1.34)	10.86 (±1.30)	10.55 (±1.35)	10.31 (±1.57)	9.21 (±2.02)	9.06 (±1.89)	<.001
Total Recall	29.14 (±2.77)	28.76 (±3.92)	28.04 (±4.43)	28.54 (±4.23)	27.50 (±4.06)	26.65 (±4.46)	23.16 (±5.24)	22.77 (±5.19)	<.001
Delayed Recall	10.14 (±1.41)	10.51 (±1.55)	9.92 (±2.04)	10.20 (±2.08)	10.04 (±1.84)	9.50 (±1.92)	8.25 (±2.70)	7.68 (±2.80)	<.001
Retention (%)	91.18 (±10.77)	96.12 (±11.14)	91.15 (±13.07)	92.62 (±15.37)	93.99 (±12.59)	90.55 (±13.59)	86.86 (±21.23)	81.42 (±20.99)	<.001
Results for Subgroup 1 (Forms 1, 2, & 4)									
Delayed Recognition true-positive responses	11.87 (±0.35)	11.76 (±0.54)	11.58 (±0.95)	11.74 (±0.56)	11.55 (±0.89)	11.47 (±1.00)	11.28 (±1.22)	11.22 (±1.07)	.002
Delayed Recognition semantically-related false-positive errors	0.33 (±0.62)	0.83 (±1.12)	0.57 (±0.68)	0.62 (±0.91)	0.70 (±0.91)	0.71 (±0.83)	0.90 (±1.05)	0.75 (±1.05)	.044
Delayed Recognition semantically-unrelated false-positive errors	0.00 (±0.00)	0.05 (±0.22)	0.04 (±0.20)	0.04 (±0.27)	0.05 (±0.22)	0.06 (±0.29)	0.09 (±0.30)	0.13 (±0.34)	.515
Recognition Discrimination Index	11.53 (±0.74)	10.88 (±1.36)	10.97 (±1.27)	11.07 (±1.24)	10.80 (±1.42)	10.70 (±1.42)	10.28 (±1.79)	10.34 (±1.47)	<.001

Table 2.1 (continued)

Demographic Characteristics and Performance Results for the HVLT-R Normative Sample by Age Group

	16-19 years	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	80+ years	*p*
sults for Subgroup 2									
Forms 3, 5, & 6)									
layed Recognition ue-positive responses	11.86 (±0.53)	11.74 (±0.59)	11.84 (±0.42)	11.66 (±0.64)	11.63 (±0.76)	11.74 (±0.44)	11.47 (±1.04)	10.47 (±1.41)	<.001
layed Recognition mantically-related lse-positive errors	0.07 (±0.27)	0.07 (±0.26)	0.14 (±0.40)	0.25 (±0.55)	0.23 (±0.56)	0.37 (±0.76)	0.48 (±0.89)	0.47 (±0.92)	.002
layed Recognition mantically-unrelated lse-positive errors	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	0.02 (±0.14)	0.05 (±0.21)	0.08 (±0.32)	0.13 (±0.35)	.052
cognition iscrimination Index	11.79 (±0.58)	11.67 (±0.69)	11.70 (±0.74)	11.41 (±0.85)	11.38 (±1.06)	11.33 (±1.04)	10.87 (±1.83)	9.87 (±1.68)	<.001

e. $N = 1{,}179$ (300 men, 879 women). All numbers are expressed as means with *SD*s in parentheses. MMSE = Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975).
m the *Hopkins Verbal Learning Test–Revised Professional Manual*, (pp. 12-13), by J. Brandt and R. H .B. Benedict, 2001, Lutz, FL: Psychological Assessment Resources. Copyright
1 by Psychological Assessment Resources, Inc. Reprinted with permission.
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5. Grooved Pegboard

Norms provided by Ruff and Parker 1993 - adjusted for age, gender and education.

Mean Performance of Adults for Grooved Pegboard, by Education, Age, and Gender

	≤Grade 12			>Grade 12		
Age group (Years)	*N*	*M*	*SD*	*N*	*M*	*SD*
Females, Preferred hand						
16-39	30	62.8	8.9	60	57.8	6.2
40-54	14	63.1	4.4	30	63.3	7.4
55-70	15	78.6	11.7	29	75.3	11.3
Females, Non preferred hand						
16-39	29	66.8	10.7	60	65.2	10.3
40-54	14	69.6	6.5	30	70.8	8.9
55-70	13	84.3	15.3	29	82.0	12.5
Males, Preferred hand						
16-39	29	67.8	9.2	60	64.7	10.9
40-54	15	71.9	15.1	30	70.4	10.9
55-70	15	83.7	10.2	30	74.1	13.0
Males, Non preferred hand						
16-39	29	74.5	10.9	59	67.8	10.8
40-54	15	79.1	14.9	30	73.7	9.9
55-70	15	91.0	12.7	28	83.5	13.4

Note: Based on a sample of 357 healthy participants.

Source: From Ruff & Parker, 1993, in Perceptual and Motor Skills 1993. Reprinted in Strauss (p. 1063) with permission.

6. BVRT

The norms in the manual are for 15 – 69 year old population. Table 4.1 from the manual was for a large sample, norms adjusted for age and IQ.

Norms for Administration A Number Correct Score: Adults

Estimated Premorbid IQ Score	Expected Number Correct Score by Age (in Years)		
	15-49	50-59	60-69
110 and above	9	8	7
95 – 109	8	7	6
80-94	7	6	5
70 – 79	6	5	4
60 – 69	4 - 5	3 – 4	2-3
59 and below	3 -4	2 -3	1-2

The examinees obtained score was compared with the expected score adjusted for age and IQ. An obtained score that is 2 points less than the expected score may raise the question or lead to a suspicion of acquired impairment of cog functioning. An obtained score that is 3 points less than the expected score suggests such an impairment. An obtained score that is 4 or more points less than the expected score is a strong indication of such an impairment.

Norms for Administration A Number Error Score: Adults

Estimated Premorbid IQ Score	Expected Number Error Score by Age (in Years)			
	15- 44	45 - 59	60-64	65 - 69
110 and above	1	2	3	4
105 – 109	2	3	4	5
95- 104	3	4	5	6
90 – 94	4	5	6	7
80 – 89	5	6	7	8
70 – 79	6 – 7	7 – 8	8 – 9	9 – 10
60 - 69	7 – 8	8 – 9	9 – 10	10 – 11
59 and below	8 - 9	9 - 10	10 - 11	11 -12

An obtained score that is 3 points greater than the expected score may raise the question or lead to a suspicion of acquired impairment of cog functioning. An obtained score that is 4 points greater than the expected score suggests such an impairment. An obtained score that is 5 or more points less than the expected score is a strong indication of such an impairment.

7. COWA

Ruff et al (1996) published norms based on 360 individuals between the ages of 16 and 70 and in education from 7 to 22 years

TABLE 3
Mean Values for the Controlled Oral Word Association Test, Separately by Gender and Education

	Men $n = 180$		Women $n = 180$		Combined Sex $n = 360$	
Education	Mean	*SD*	Mean	*SD*	Mean	*SD*
12 years or less	36.9[a,b]	9.8	35.9[c,d]	9.6	36.5	9.9
13–15 years	40.5[a]	9.4	39.4[c,e]	10.1	40.0	9.7
16 years and up	41.0[b,f]	9.3	46.5[d,e,f]	11.2	43.8	10.6
All education levels	39.5	9.8	40.6	11.2	40.1	10.5

*$n = 180$ represents a combination of the three educational subgroups.
[a,b]For men, the educational subgroup comparisons were significantly lower for those with up to 12 years of education versus both higher educational groups ($p < .05$).
[c,d,e]For women, all three educational groups were significantly different ($p < .05$) with a higher rate with increasing years of education.
[f]Women achieved a significantly higher fluency rate as compared to men only in the educational subgroup with the highest years of education ($p < .05$).

APPENDIX Q

interpretation of results. This article provides general population and patient with cancer normative data for the FACT-G and its subscales. Interpretation guidelines and examples are provided to aid clinicians and researchers when interpreting the magnitude and meaning of their own results with the FACT-G.

APPENDIX

TABLE A1
Normative Data of General U.S. Adult Population

	Physical Well-Being	*Social/Family Well-Being*	*Emotional Well-Being*	*Functional Well-Being*	*FACT-General*
Total Sample (N = 1075)					
Mean	22.7	19.1	19.9	18.5	80.1
Standard Deviation	5.4	6.8	4.8	6.8	18.1
Percentage at floor	0.2	1.0	0.7	1.8	0.0
Percentage at ceiling	13.2	13.1	32.0	8.8	2.1
Minimum observed score	0.0	0.0	0.0	0.0	15.4
25th percentile	21.0	14.0	18.0	14.0	69.7
50th percentile (Median)	24.5	19.6	21.0	19.6	82.9
75th percentile	26.8	24.5	24.0	23.3	93.1
Maximum observed score	28.0	28.0	24.0	28.0	108.0
Males (n = 516)					
Mean	23.3	18.4	20.5	18.6	80.9
Standard Deviation	5.1	6.7	4.4	6.7	17.4
Percentage at floor	0.2	1.0	0.8	1.6	0.0
Percentage at ceiling	16.1	9.9	34.9	9.1	1.9
Minimum observed score	0.0	0.0	0.0	0.0	17.1
25th percentile	22.2	14.0	18.0	14.0	71.2
50th percentile (Median)	25.7	19.6	22.5	19.8	83.0
75th percentile	26.8	23.8	24.0	23.3	93.2
Maximum observed score	28.0	28.0	24.0	28.0	108.0
Females (n = 544)					
Mean	22.1	19.8	19.4	18.3	79.6
Standard Deviation	5.4	6.8	5.1	6.9	18.6
Percentage at floor	0.0	0.9	0.7	1.8	0.0
Percentage At ceiling	10.5	16.4	28.9	8.6	2.2
Minimum observed score	3.5	0.0	0.0	0.0	15.4
25th percentile	19.8	15.4	18.0	12.8	68.4
50th percentile (Median)	23.3	21.0	21.0	18.7	83.0
75th percentile	25.7	25.2	24.0	23.3	93.2
Maximum observed score	28.0	28.0	24.0	28.0	108.0

SOURCE: Copyright 2004, David Cella, Ph.D.

APPENDIX R

APPENDIX R: LONGITUDINAL RESULTS

Table of Spearman rho correlations between perceived cognitive functioning, HRQoL fatigue and anxiety and depression at T2 for the whole sample

	FACT C						FACIT	HADS	
FACT Cog:	**PWB**	**SWB**	**EWB**	**FWB**	**CCS**	**Total**	**Fatigue**	**Anxiety**	**Depression**
PCI	.564**	0.039	.489**	.518**	.487**	.602**	.672**	-.612**	-.544**
PCA	.415**	-0.014	.429**	.469**	.450**	.528**	. .575**	-.389**	-.408**
QoL	.522**	0.034	.472**	.461**	.392**	.545**	.610**	-.576**	-.582**
Oth	0.215	-0.176	0.199	.250*	.396**	.295**	.341**	-.236*	-.277*

Key: **. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed). FACT Cog subscales: PCI: Perceived Cognitive Impairment; PCA: Perceived Cognitive Ability; QoL: Impact on Quality of Life; Others: Comments from others; FACT C subscales: PWB: Physical wellbeing; SWB: Social wellbeing: EWB: Emotional wellbeing; FWB: Functional wellbeing; CCS: Colorectal symptoms; HADS: Hospital anxiety and depression scale

Table of Spearman rho correlations between perceived cognitive functioning, HRQoL fatigue and anxiety and depression at T2 for each patient group

"Surgery only" group									
	FACT C						FACIT	HADS	
FACT Cog:	PWB	SWB	EWB	FWB	CCS	Total	Fatigue	Anxiety	Depression
PCI	.570**	-.219	.424*	.527*	.286	.486**	-.722**	-.407*	-.0374
PCA	.378	-0.173	.485**	.368	0.244	.427*	.504**	-.193	-.054
QoL	.293	.031	.553**	.262	-0.011	.360	.464*	-.467*	-.306
Oth	.155*	-0.222	.307	.272	.223	.233	.379	-.333	-.081

Chemotherapy group									
	FACT C						FACIT	HADS	
FACT Cog:	PWB	SWB	EWB	FWB	CCS	Total	Fatigue	Anxiety	Depression
PCI	.599**	0.163	.545*	.510*	.587**	.639**	.646**	-.703**	-.566**
PCA	.529**	.011	.427**	.535**	0.521**	.601**	.666**	-.482**	-.489**
QoL	.627**	0.071	.489**	.492**	0.509**	.602**	.655**	-.634**	-.595**
Oth	.239	-0.153	.193	.240	.443**	.317*	.337*	-.199	-.276*

Key: **. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed). CT: Chemotherapy;

Table of Spearman rho correlations between perceived cognitive functioning, HRQoL fatigue and anxiety and depression at T3 for the whole sample

	FACT C						FACIT	HADS	
FACT Cog:	**PWB**	**SWB**	**EWB**	**FWB**	**CCS**	**Total**	**Fatigue**	**Anxiety**	**Depression**
PCI	.604**	0.193	.446**	.445**	.468**	.501**	.707**	-.529**	-.612**
PCA	.447**	0.216	.447**	.448**	.581**	.529**	.629**	-.414**	-.504**
QoL	.500**	.261*	.709**	.541**	.555**	.622**	.652**	-.536**	-.552**
Oth	.409**	0.026	0.201	.318*	.256*	.281*	.521**	-.282*	-.363**

Key: **. Correlation is significant at the 0.01 level (2-tailed).*. Correlation is significant at the 0.05 level (2-tailed).
FACT Cog subscales: PCI: Perceived Cognitive Impairment; PCA: Perceived Cognitive Ability; QoL: Impact on Quality of Life;
Others: Comments from others; FACT C subscales: PWB: Physical wellbeing; SWB: Social wellbeing: EWB: Emotional wellbeing;
FWB: Functional wellbeing; CCS: Colorectal symptoms; HADS: Hospital anxiety and depression scale

Table of Spearman rho correlations between perceived cognitive functioning, HRQoL fatigue and anxiety and depression at T3 for each patient group

"Surgery only" group									
	FACT C						FACIT	HADS	
FACT Cog:	PWB	SWB	EWB	FWB	CCS	Total	Fatigue	Anxiety	Depression
PCI	.657**	0.182	0.379	0.312	0.404	.509*	-.603**	-0.221	-.691**
PCA	.594**	0.049	0.314	0.284	.591**	.525*	.576**	-0.193	-.572**
QoL	.584**	0.044	.638**	0.293	0.414	.492*	.620**	-0.331	-.466*
Oth	0.168	0.000	0.082	0.268	0.330	0.324	.331	0.052	-0.402

Chemotherapy group									
	FACT C						FACIT	HADS	
FACT Cog:	PWB	SWB	EWB	FWB	CCS	Total	Fatigue	Anxiety	Depression
PCI	.607**	0.249	.432**	.513**	.485**	.517**	.764**	-.640**	-.571**
PCA	.459**	0.305	.540**	.526**	.569**	.554**	.664**	-.546**	-.492**
QoL	.511**	.404**	.737**	.672**	.622**	.692**	.662**	-.640**	-.606**
Oth	.501**	0.051	0.221	.346*	0.242	0.287	.592**	-.385*	-.326*

Key: **. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed). CT: Chemotherapy;

APPENDIX S

APPENDIX S: Table of Spearman rho correlations between each deficit/no deficit NP measure (1.5 SD criteria) and HRQoL (as measured by the FACT C) for the whole sample at T2

FACT C Sub-scales	NP Assessment														
	Digit F	Digit B	SDMT written	SDMT oral	TMTA	TMTB	HVLT R recall	HVLT R delay	HVLT R retain	HVLT R rdi	PG Dom	PG Non Dom	COWA	BVRT correct	BVRT error
PWB	-0.010	-0.033	-0.101	-0.138	0.006	0.006	-0.080	-0.089	-0.109	-0.150	-0.209	-0.183	-0.022	-0.110	0.017
SWB	-0.052	-0.157	-0.120	-0.120	-0.188	0.010	-0.117	-0.147	-0.084	0.052	-0.027	-0.041	0.141	0.169	0.153
EWB	-0.116	-0.030	-.245*	-0.150	-0.077	0.042	-0.049	-0.183	-0.211	-0.074	-0.176	-0.087	0.183	-0.033	0.046
FWB	0.112	0.039	-0.183	-0.175	-0.020	0.142	0.119	0.034	-0.113	0.045	-.225*	-0.208	0.101	-0.075	-0.072
CCS	-0.058	-0.016	-0.024	0.013	0.022	0.033	-0.144	-0.166	-0.032	-0.115	0.056	0.130	0.179	-0.044	0.008
Total	-0.027	-0.003	-0.180	-0.146	-0.040	0.094	-0.034	-0.106	-0.109	-0.095	-0.206	-0.124	0.162	-0.081	-0.006

Key: ** red. Correlation is significant at the 0.01 level (2-tailed). *blue. Correlation is significant at the 0.05 level (2-tailed). FACT C subscales:
PWB: Physical wellbeing; SWB: Social wellbeing: EWB: Emotional wellbeing; FWB: Functional wellbeing; CCS: Colorectal symptoms; NP Assessments: Digit F: Digit Span Forwards; Digit B: Digit Span Backwards; SDMT: Symbol Digit Modalities Test; TMT A & B: Trail making test parts A & B; HVLT-R: Hopkins Verbal Learning Test – Revised; recall, delayed recall, retention, recognition; Grooved Pegboard Test, dominant hand; GP non dom: Grooved Pegboard Test, non-dominant hand; BVRT: Benton Visual Retention Test

Table of Spearman rho correlations between each deficit/no deficit NP measure (2 SD criteria) and HRQoL (as measured by the FACT C) for the whole sample at T2

FACT C Sub scales	NP Assessments													
	Digit B	SDMT written	SDMT oral	TMTA	TMTB	HVLT R recall	HVLT R delay	HVLT R retain	HVLTR rdi	PG Dom	PG Non Dom	COWA	BVRT correct	BVRT error
PWB	0.030	-0.207	-0.125	-0.132	-0.073	-0.129	-0.074	-0.058	-0.155	-0.190	-0.190	-0.102	-0.155	0.006
SWB	-0.034	-0.172	-0.082	-0.084	0.006	-0.161	-0.147	-0.095	0.061	-0.058	-0.077	0.010	-0.067	0.153
EWB	0.066	-0.154	-0.079	0.115	0.009	-0.201	-.293**	-0.200	-0.021	-0.219	-0.149	0.057	-0.043	0.039
FWB	0.080	-.251*	-0.186	0.042	0.068	0.038	-0.070	-0.071	-0.036	-.230*	-0.218	-0.003	-0.173	-0.088
CCS	.328**	-0.100	0.061	0.079	-0.007	-0.095	-0.219	-0.121	-0.047	-0.026	0.139	0.171	-0.045	0.011
Total	0.146	-.226*	-0.117	0.017	0.008	-0.106	-0.167	-0.110	-0.058	-.240*	-0.144	0.043	-0.147	-0.024

Key: ** red. Correlation is significant at the 0.01 level (2-tailed). *blue. Correlation is significant at the 0.05 level (2-tailed). FACT C subscales:
PWB: Physical wellbeing; SWB: Social wellbeing: EWB: Emotional wellbeing; FWB: Functional wellbeing; CCS: Colorectal symptoms; NP Assessments: Digit F: Digit Span Forwards; Digit B: Digit Span Backwards; SDMT: Symbol Digit Modalities Test; TMT A & B: Trail making test parts A & B; HVLT-R: Hopkins Verbal Learning Test – Revised; recall, delayed recall, retention, recognition; Grooved Pegboard Test, dominant hand; GP non dom: Grooved Pegboard Test, non-dominant hand; BVRT: Benton Visual Retention Test

Table of Spearman rho correlations between each deficit/no deficit NP measure (1.5 SD criteria) and HRQoL (as measured by the FACT C) for the whole sample at T3

FACT C Sub-scales	NP Assessments												
	Digit F	Digit B	SDMT written	SDMT oral	TMTB	HVLT R recall	HVLT R delay	HVLT R retain	HVLT R rdi	PG Dom	PG Non Dom	COWA	BVRT correct	BVRT error
PWB	-0.222	-0.041	-0.126	-0.113	-0.189	-0.025	-0.011	-0.079	-0.029	-.334**	-0.147	-0.078	0.134	0.037
SWB	-0.220	-0.072	-0.214	-0.068	-0.023	-0.048	-0.174	-0.233	-0.128	-0.080	-0.043	-0.060	-0.113	-0.070
EWB	-0.087	0.011	-0.189	-0.166	-0.068	0.009	-0.114	-0.153	0.101	-.280*	-0.084	0.109	-0.074	-0.202
FWB	-0.091	-0.013	-0.114	0.052	-0.068	-0.001	-0.064	-0.186	0.080	-0.237	-0.058	0.076	-0.014	-0.146
CCS	0.015	0.069	0.103	-0.045	-0.016	-0.160	-0.210	-0.203	-0.054	-0.122	-0.011	0.242	-0.021	-0.191
Total	-0.162	-0.039	-0.161	-0.112	-0.104	-0.081	-0.149	-0.238	-0.037	-0.238	-0.053	0.085	-0.038	-0.166

Key: ** red. Correlation is significant at the 0.01 level (2-tailed). *blue. Correlation is significant at the 0.05 level (2-tailed). FACT C subscales: PWB: Physical wellbeing; SWB: Social wellbeing: EWB: Emotional wellbeing; FWB: Functional wellbeing; CCS: Colorectal symptoms; NP Assessments: Digit F: Digit Span Forwards; Digit B: Digit Span Backwards; SDMT: Symbol Digit Modalities Test; TMT A & B: Trail making test parts A & B; HVLT-R: Hopkins Verbal Learning Test – Revised; recall, delayed recall, retention, recognition; Grooved Pegboard Test, dominant hand; GP non dom: Grooved Pegboard Test, non-dominant hand; BVRT: Benton Visual Retention Test

Table of Spearman rho correlations between each deficit/no deficit NP measure (2 SD criteria) and HRQoL (as measured by the FACT C) for the whole sample at T3

FACT C Sub-scales	NP Assessments										
	SDMT oral	TMTB	HVLT R recall	HVLT R delay	HVLT R retain	HVLT R rdi	PG Dom	PG Non Dom	COWA	BVRT correct	BVRT error
PWB	-0.033	-0.230	-0.087	-0.059	-0.055	-0.029	-0.197	-0.155	-0.072	-0.004	0.157
SWB	0.118	-0.021	-0.043	-.344**	-0.205	-0.128	-0.087	0.002	-0.104	-0.028	-0.110
EWB	-0.044	-0.150	-0.105	-0.211	-0.182	0.101	-0.180	-0.087	0.046	-0.212	-0.066
FWB	0.188	-0.139	0.044	-0.144	-0.164	0.080	-0.123	-0.032	0.068	-0.226	-0.063
CCS	-0.166	-0.128	-0.244	-0.213	-0.247	-0.054	-0.062	0.013	0.198	-0.203	-0.097
Total	0.004	-0.203	-0.163	-.267*	-0.194	-0.037	-0.143	-0.031	0.032	-0.194	-0.065

Key: ** red. Correlation is significant at the 0.01 level (2-tailed). *blue. Correlation is significant at the 0.05 level (2-tailed).
FACT C subscales: PWB: Physical wellbeing; SWB: Social wellbeing: EWB: Emotional wellbeing; FWB: Functional wellbeing;
CCS: Colorectal symptoms; NP Assessments: Digit F: Digit Span Forwards; Digit B: Digit Span Backwards;
SDMT: Symbol Digit Modalities Test; TMT A & B: Trail making test parts A & B;
HVLT-R: Hopkins Verbal Learning Test – Revised; recall, delayed recall, retention, recognition;
Grooved Pegboard Test, dominant hand; GP non dom: Grooved Pegboard Test, non-dominant hand;
BVRT: Benton Visual Retention Test