Cancer in older patients: the impact of global health assessments, measures and outcomes

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A thesis submitted in partial fulfilment of the requirements of the University of Brighton and University of Sussex, for a programme of study undertaken at Brighton and Sussex Medical School, for the degree of Doctor of Medicine (MD).

May 2012

Abstract

Worldwide the population is ageing. Colorectal cancer is the third commonest cancer in Great Britain. In this thesis, the epidemiology of colorectal cancer in patients aged sixty-five and over has been described. Between 1971 and 2006 the number of older people diagnosed with colorectal cancer has increased by nearly an extra ten thousand cases per year reflecting an increasing burden amongst the older patient population in Great Britain. The management of older colorectal cancer patients is challenging. A prospective cohort study, "The assessment and management of older patients with colorectal cancer", was undertaken to investigate the use of a comprehensive geriatric assessment in patients aged sixty-five and over. The ability of specific assessment tools to predict functional decline or death at one year, and if they could predict for severe chemotherapy toxicity in patients receiving adjuvant chemotherapy, was explored. Older patients receiving chemotherapy may be at increased risk of treatment-related toxicity for a variety of reasons. A study, "Global health measures and tolerance of cytotoxic chemotherapy", was undertaken to investigate the predictive ability of three assessment tools in patients aged sixty-five and over receiving chemotherapy. Malnutrition may be an issue in older cancer patients that is not always addressed. The use of three nutritional screening tools in assessing patients with metastatic colorectal cancer has been investigated and the rates of malnutrition in older and younger patients compared. Social networks and support are important in helping cancer patients through treatment. Socially isolated patients may be at higher risk of death compared to those with strong social ties. An observational survey of patients attending an oncology outpatient department was performed and social ties of older and younger patients reported.

In summary, this thesis describes the increasing burden of colorectal cancer in the older population of Great Britain and investigates how specific tools , many commonly used as part of a comprehensive geriatric assessment, may be informative and practical to use in the management of older cancer patients.

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Acknowledgements

Many people have been of significant help in the projects that have been undertaken as part of this thesis. Firstly, I would like to thank my supervisors and particularly Dr Alistair Ring who has introduced me to the specialty of geriatric oncology and sparked an interest in a subject that will continue throughout my career.

Thank you to the Sussex Cancer Fund and the Clinical Investigation and Research unit (CIRU) without whose funding this research would not have been possible. I would like to thank Dr Anjum Menon and Dr Lisa Mohebati, department of Public Health at Brighton and Sussex Medical School who helped with analysis of the statistical data that is presented as part of the "Epidemiology of colorectal cancer in older patients". I am especially appreciative of the assistance of clinical nurse specialists, Anne Alidina, Mark Danieletto, Jenny Gill and Lucinda McKay who helped in confirming patients were suitable to be approached for "The assessment and management of older patients with colorectal cancer" study. They answered my weekly emails promptly and I could not have invited patients to participate without their input. I am also grateful to Lorraine Goodwin, research nurse, who is continuing to recruit patients for the next twelve months and to Dr Raj Sinha who helped with data collection of comorbidity scores for the Global Health Questionnaires study. Much thanks also goes to three medical students who were a pleasure to work with. Jamie Pearce assisted in data entry for the "Global Health questionnaires and cytotoxic chemotherapy" study and Rebecca Smith and Sarah Cappleman helped collect data for the "Malnutrition in patients with metastatic colorectal cancer" study. Thanks also to the reception team, Sussex Cancer Centre, for their assistance in the "Social isolation in patients with cancer" survey.

The oncology secretarial staff at Brighton, Eastbourne and Worthing hospitals were extremely helpful in requesting notes and any additional information that I required and allowed me to use a corner in their office if need be, despite their own heavy workload and time pressures, special thanks goes to Helen, Cathy, Vic and Kate. Christine, Kay and the team on the CIRU received my long list of notes to

be requested in good humour and proceeded to obtain a few hundred notes in an efficient and timely manner. I would like to thank medical statisticians Liz Cheek and Stephanie Goubet for their help and guidance in the data handling and analysis. I must also thank my friends and family for their ongoing support as this thesis has neared its completion.

Finally, I would like to thank the patients who consented to take part in all the research studies. I am grateful to them for giving up their time during a stressful and often uncertain period of their lives. Many expressed the hope that in some small way they could help improve the care of future patients in a similar situation.

Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to these or any other university for a degree and does not incorporate any material already submitted for a degree

Signed

Joanna Stokoe

Chapter One

1. Introduction

1.1. Aims

1. To describe the epidemiology of colorectal cancer in older patients aged sixty-five and over from 1971-2006.
2. To determine the clinical utility of screening and assessment tools, that comprise part of a comprehensive geriatric assessment, in the assessment of older colorectal cancer patients.
3. To ascertain if three specific assessment tools predict for severe toxicities in patients older patients receiving cytotoxic chemotherapy.
4. To ascertain the proportion of patients with metastatic colorectal cancer who are at risk of malnutrition and to compare three nutritional assessment tools.
5. To observe the degree of social isolation amongst oncology outpatients within a cancer centre and to compare social isolation between older and younger cancer patients.

1.2. Ageing population

Worldwide the population is ageing. Over the next forty years, in developed nations the proportion of people aged sixty-five and over is expected to rise from 16% to 26% and in developing countries from 5.8% to 15% (1). In the United Kingdom in 2010, 17% of the population was aged sixty-five and over (10.3 million people) (2). It is expected that by 2035, 23% of the UK population will be aged sixty-five and over (2).

Currently, overall life-expectancy at birth is at its highest ever. In countries with the highest life expectancy rates, if health conditions remain static, three-quarters of babies born in recent years will live to the age of seventy-five (3). The increases seen in overall life-expectancy over the last couple of centuries have occurred due to improvements in various areas such as social living conditions and the discovery of anti-microbial therapies. These developments particularly improved infant and childhood mortality rates (3). However in recent decades, in many countries, there has been a noticeable improvement in the mortality rates of older people and especially those aged eighty and over (3-5). The fastest expanding section of the population is those aged eighty-five and over. This is also the age group that is most likely to suffer from a range of diseases and functional disabilities (3). Over the last twenty five years, their number has nearly doubled to 1.4 million in 2010 and projections to 2035 predict that there will 3.6 million aged eighty-five and over (5% of the total population) in the UK (1). Table 1.1 shows the projected life expectancy for older men and women living in the UK in 2012:

Table 1.1: Life expectancy for men and women in the United Kingdom in 2012. (Office for National Statistics (6))

	65 years old Median survival (years)	70 years old Median survival (years)	80 years old Median survival (years)
Men	18.6	14.9	8.6
Women	21.0	17.0	9.8

An expanding ageing population will have a considerable effect on society as a whole. Many chronic diseases and cancers are prevalent in older people. Disabilities, functional decline and dependence occur more commonly as people enter the latter years of their life. Malnutrition, depression and social isolation are "under-diagnosed" but present in a significant proportion of the elderly.

In an ageing population, geriatricians will have an increasingly important role in the care of older patients. However geriatricians will have to focus their attentions on specific conditions that affect older people and unless there is a planned expansion of geriatricians to meet the growing demand, it will be important for clinicians in all areas of medicine to understand and appreciate the needs of individual older patients. This will particularly be so in the field of cancer medicine. Geriatric oncology is an evolving specialty and continued research into the management of older cancer patients is clinically very relevant and important in order to optimize their care.

There has been much debate around the definition of an "elderly" person and various cutoffs from the age of sixty and above have been used in geriatric oncology. However, the International Society of Geriatric Oncology (SIOG) has agreed patients aged seventy and over should be considered elderly for the purposes of research. At the time of this research study's inception it was decided to approach patients aged sixty-five and above. This was for a number of reasons. In many published research studies involving older cancer patients (particularly studies originating from North America) an older person was defined as aged sixty-five and over. In the UK sixty-five is the male pensionable age. It was also thought that including participants from the age of sixty-five would provide a younger comparative group (sixty-five to seventy years of age). Issues around treatment related toxicity and predictors of toxicity are not unique to older patients and a proportion of younger patients may be less fit.

1.3. Cancer in an ageing population

Cancer is a common disease and in the UK more than one in three people will receive a cancer diagnosis in their lifetime (7). According to recent statistics from Cancer Research UK and Macmillan Cancer Support, 195,000 cancer diagnoses are made in people aged sixty-five and over each year and they comprise 63% of all new cancer cases (8, 9).

The incidence of cancer in older people is projected to continue to increase over the next twenty years in an ageing UK population. Work has been undertaken to model the projected incidence of various cancers up until 2030. The overall incidence of cancer is projected to remain essentially stable, but due to increase in population size and a larger proportion of the population being older, the number of cases of almost all cancer types is likely to increase (10). Mistry et al have reported that in 2007, 67.4% of cancers in men and 58.7% of cancers in women were in people aged sixty-five and over. By 2030, they project that the proportion of men and women aged sixty-five and over diagnosed with cancer will be 76.2% and 67.5% respectively (10). The effects of an ageing population and increase in cancer diagnoses in this expanding section of society will impact on health and social services. The need to improve and optimize the care of older cancer patients should be a priority.

Challenges in the management of cancer in an ageing population

As a greater number of older people are diagnosed with cancer, more will undergo surgery and potentially be considered for cancer treatments in the adjuvant and metastatic setting. There are many challenges in managing older patients with cancer but three principle concerns are:

1. Lack of clinical trial evidence.

The majority of treatment management plans formulated by physicians are created using the most robust evidence available in the medical literature. However, historically older patients have been under-represented in clinical studies (11). Exclusion criteria such as age and certain medical diagnoses (which tend to be

more prevalent in older patients) rendered many patients in their sixties and beyond ineligible for inclusion in trials (12, 13). There may also be a reluctance on the behalf of clinicians to offer clinical trials to patients and a perceived reluctance of older patients to enter clinical trials (14). Moreover, when older patients do enter clinical trials, they are the fit patients and are probably not representative of the older population of patients with cancer. As new treatments and drug regimes have been developed, it has been a challenge for oncologists to extrapolate results from trials on younger patients, mostly free from comorbid illnesses, to an older less-fit patient on a number of medications more commonly sat before them in clinic.

2. Identifying those patients with a good life expectancy who are likely to benefit from treatment.

Older cancer patients are a heterogeneous group. Chronological age alone may not always be a good indicator of fitness for treatment and life expectancy as there may be other competing causes of mortality. Older cancer patients are more likely to suffer from comorbid illnesses than younger cancer patients (15). On average an older patient is likely to have between two and four comorbid diagnoses (16, 17) and the presence of co-morbidities is associated with a worse life expectancy (18, 19). In a review of 6,186 postmenopausal women who took part in the ATAC (Arimidex, Tamoxifen Alone or in Combination) study; of those who had died (after a median follow up of 120 months), 43.7% had died due to other causes and without breast cancer recurrence (19). Older women (≥ seventy years of age) had a significantly increased ten-year risk of death without recurrence (i.e. died due to other causes) compared to women less than seventy years of age, 27.1% versus 7.3% (HR, 4.13; 95% CI 3.53-4.83) (19). The risk of death due to causes other than breast cancer (and without the presence of recurrent disease) increased with increasing comorbidity score (19). However, older women were found to be at increased risk of breast cancer recurrence compared to younger (less than seventy years old) women (19), which indicates the importance of optimizing the treatment of all patients of all ages and not denying older patients certain treatments based on age alone. Overall these data highlight the importance of taking into account competing causes of mortality.

3. Predicting treatment tolerance.

Predicting tolerability of oncological treatments is challenging, especially in older patients. Muss et al compared the rates of toxicities between older and younger women who had taken part in adjuvant breast cancer chemotherapy studies (Cancer and Leukaemia Group B (CALGB) trials). Older patients were found to have higher rates of haematological toxicities and treatment-related death compared to younger patients. However there was no difference in the rate of non-haematological toxicities between older and younger patients (20). A pooled analysis by Sargent et al, of older colon cancer patients who received adjuvant chemotherapy after surgical resection, reported that appropriately selected older patients derived the same benefit from fluorouracil-based adjuvant chemotherapy as younger patients with no significant difference in the incidence of severe toxicities between older and younger patients (21). Analyses of adjuvant regimes containing oxaliplatin have also shown similar benefits and toxicity profiles between older (seventy years old and over) and younger patients (22). The analysis by Goldberg et al reported that older patients had increased incidence of Grade 3 or higher neutropenia and thrombocytopenia compared to younger patients ($p=0.04$) but no significant difference in non-haematological toxicities, overall severe chemotherapy toxicities ($p=0.15$) or 60-day mortality ($p=0.20$) (22). However are patients in clinical trials, from which these conclusions are drawn, representative of all older patients with cancer?

Some clinicians claim that obviously fit or frail patients are easy to identify in clinic (23) but there is few supporting literature for this. Other clinicians would recommend that all older patients undergo a CGA (24). Various studies have shown that fit older patients are able to tolerate standard chemotherapy regimens as well as younger patients (21, 25, 26). The challenge lies in identifying the "potentially vulnerable" and "vulnerable" older cancer patient who may struggle through treatment and whose life expectancy may be shortened by causes other than their cancer diagnosis. Many factors such as physical fitness, functional ability, comorbidities, polypharmacy and psycho-social well-being need to be considered and taken into account when discussing and formulating cancer management plans with patients. Currently, in the field of oncology, traditionally

used scales to measure fitness for treatment or "performance status" do not account for all these factors. An objective assessment process that identifies patients who are likely to be at increased risk of severe chemotherapy side effects or at increased risk of functional decline or death is needed.

1.4. Assessment of older patients in oncology

In the United States, the National Comprehensive Cancer Network (NCCN) produced a document with guidelines for the assessment of older cancer patients (26). Issues specific to managing older cancer patients are summarised. The components of a comprehensive geriatric assessment (CGA) are outlined, as are criteria that can be used to define frailty, functional assessment tools and screening tools such as the Vulnerable Elders Survey (VES-13). The NCCN Clinical Practice Guidelines in Oncology™ Senior Adult Oncology, have stated three questions that need to be considered:
"Is the patient going to die of cancer or with cancer?
Is the patient at risk for the complications of cancer during his/her lifetime?
Is the patient able to tolerate cancer treatment?" (26).

Currently, oncologists use a performance status scale to assess a patient's functional status. The two most commonly used are the Eastern Cooperative Oncology Group (ECOG/WHO) performance status (PS) or Karnofsky Performance Status (KPS) scales (27, 28). Neither of these scales is age dependent and in the older patient the designated score may be an over-estimate of their functional status (29). The ECOG/WHO PS scale has been validated in many cancer patient populations and has been shown to correlate with prognosis and survival (30, 31).

Within our local clinical practice the ECOG/WHO PS scale is used (APPENDIX A). The scale is from zero to five. A score of zero denotes someone who is fit and well and able to carry out all activities that they usually did before a cancer diagnosis with no limitations. A person scores one if they have minimal limitations to their daily activities, such as avoiding heavy lifting/ manual work, but otherwise they

are fully independent and able to work. A score of two applies if a person has some restriction in daily activities but is able to carry out all self-care, is sitting or resting for less than fifty percent of waking hours and is unable to work. A person scores three if they are sitting in a chair or lying in bed for more than fifty percent of waking hours and requires assistance in looking after themselves. If a person is confined to a chair or bed-bound and needs full assistance with personal care they would be rated as an ECOG PS of four. A score of five is allocated when a person has died.

The ECOG PS score has been validated across a wide range of patient populations. In addition, in the assessment of older cancer patients, clinicians take into account many factors from the medical and social history in addition to clinical findings and performance status scores. However, the overall assessment has subjective elements and may not be truly objective. Life expectancy can be calculated using published statistics but these do not take into account a patient's current health status and it is difficult to do so. A comprehensive geriatric assessment (CGA) assesses a patient's functional ability, co morbidities, and nutritional, psychological and social status. A CGA can provide valuable objective scores from a variety of selected assessment tools. The information can be used to help answer the three important questions posed in the NCCN guidelines and assist in further patient management but this is not currently routine practice. Many research studies have evaluated and are evaluating the role of the CGA in managing older oncology patients.

1.5. The Comprehensive Geriatric Assessment

1.5.1. Background

The Comprehensive Geriatric Assessment (CGA) was developed for use in the geriatric population by geriatricians and the wider multidisciplinary team. A CGA provides a more global assessment of an older patient, which routine consultations do not encompass. Domains in which patients are found to be deficient can be detected and interventions employed to improve patients' well-being, quality of life and social situation. The impact of any intervention should be continually

reassessed and adjusted to suit patients' individual needs as they may change over time and during any new treatments that may be initiated.
The assessment tools that comprise a CGA are mainly in the form of questionnaires. Some of these can be self-administered. The process involves a mixture of objective and subjective assessments and can be time consuming. There is debate on what exact domains should be included in a CGA and what tools should be used to assess those domains.

The many assessment tools that constitute a traditional CGA have been validated in elderly patient populations. A large meta-analysis of older patients admitted to hospital reported that those who underwent a CGA were more likely to be alive and living in their own homes one year on following an emergency admission and that this was even more likely if patients had been admitted to the appropriate ward for assessment (32, 33). Research and validation of a CGA in older cancer patient populations is ongoing (29, 34-36). In oncology, the majority of clinicians would prefer to use a screening assessment tool that identified a group of patients requiring further assessment. Performing a full CGA on all older cancer patients is not likely to be practical, feasible or cost-effective. This would mean that a comprehensive CGA is only required in an identified "vulnerable" group of patients. For clinicians treating cancer patients, the ultimate aim would be to identify factors/domains within the CGA process that can predict the likelihood of severe treatment toxicity and mortality and so inform clinical decision making (37).

A comprehensive geriatric assessment encompasses an assessment of an older person's functional status, nutritional status, and cognitive and psychosocial wellbeing in addition to assessment of comorbid illnesses. Many of the tools used to assess the specific domains within a CGA, and within the projects that comprise this thesis, are summarised in Table 1.2. They will be described in more detail in further sections.

Table 1.2: Domains that comprise a CGA and examples of assessment tools

Domain	Examples of assessment tool	Description
Co-morbidity	Charlson Index	Weighted co-morbidity index, score depending on presence or absence of defined co-morbidities. Score >5 considered high
	The Adult Co-morbidity Evaluation (ACE-27)	Severity of co-morbidity measured according to 26 disease systems and each one graded (mild, moderate, severe)
	Cumulative Illness Rating Scale-Geriatric (CIRS-G)	Co-morbidities grouped according to organ system and graded (0-4 severity scale). Higher score associated with poorer prognosis
Function	Activities of Daily Living (ADL)	Assessment of independence in 6 activities (score:0-6)
	Instrumental activities of Daily Living (IADL)	Assessment of independence in 8 activities (score:0-8)
Physical	Hand-grip strength	Measured using hand dynamometer.
	Falls in the last 6 months	
	Timed up and go (TUG)	Time to walk 3 metres and return from sitting in a chair (score: time to complete)
Nutrition	Mini-Nutritional Assessment (MNA)	Questionnaire and anthropometric measurements. Two parts: screening and assessment component Patients defined as normal, at risk of malnutrition or malnourished .
	Malnutrition Universal Screening Tool (MUST)	Nutritional risk calculated based on BMI, recent unplanned weight loss and presence of acute illness. Patients scored as low, medium or high risk.
	Patient Generated- Subjective Global Assessment (PG-SGA)	Two sections – first section can be completed by patient. Second section includes medical history and physical examination. Numerical score 0-35 and patients defined as well nourished, at risk, or severely malnourished
Cognition	Mini-mental state examination (MMSE)	Questionnaire (score: 0-30) Screening tool for dementia
Psychological	Geriatric Depression Score (GDS-15)	Questionnaire. 15 items. (score: 0-15, 0-5 no depression, 6-15 possible depression)
Social situation	Berkman-Syme Social Network Index	Questionnaire. Composite SNI score calculated from:1-4 (socially isolated to highly integrated)
	Medical Outcomes Study Social Support Survey	Self-administered. Includes questions on availability of emotional and instrumental support
Poly-pharmacy	Number of medications	

1.5.2. Screening assessment tools

A full CGA is time consuming and not practical to perform in a busy oncology outpatient clinic. A self-administered assessment tool that can be completed in the waiting room may be useful. The very fit and frail older patients are usually easy to identify but the middle "vulnerable" group may be missed. A number of screening questionnaires have been devised to identify vulnerable (and frail) patients who would benefit from a full CGA. Two screening tools are being used in research studies within this thesis. They are the Vulnerable Elders Survey (also known as VES-13) and the G8 (or ONCODAGE) score (APPENDIX B and C).

The Vulnerable Elders Survey:

The Vulnerable Elders Survey (VES-13) is a 13-item function based scoring system that comprises questions on age, self-rated health status, ability to carry out various physical activities and activities of daily living (38). When it was conceived the aim was to devise a tool that could be used across a number of settings, that was simple to use and easily completed (not requiring a health professional) and also could be completed by the responder. It was hypothesized that basing the survey questions on age and instrumental activities of daily living (IADLs) could identify vulnerable older people as effective as a survey that included or was based on medical comorbidities. The purpose of the VES-13 was to identify vulnerable older (aged sixty five and over) people in the community that were at increased risk of functional decline or death(38).

The predictive ability of the VES-13 survey was explored using the Medicare Current Beneficiary Survey (MCBS) from 1993 and 1995. A representative sample of 6205 community dwelling persons aged sixty-five and over, comprised the study participants and the initial study design consisted of analysis of longitudinal survey data (38). Decline in IADL or activities of daily living (ADL) and death were the two outcomes of interest. IADL/ADL disability was defined as self-reported help from others or an inability to perform an activity of daily living due to a health-related reason. Functional decline was defined as " a change from no IADL or ADL disability to any IADL or ADL disability, an increase of two or more in the

total count of IADL or ADL disabilities, or new admission to a nursing home" (38). In the development of the VES-13 survey a number of scoring systems based on models of functional status and/or medical diagnoses were considered and analysed. It was established that a function-based scoring system was robust. The VES-13 survey design that is now in use consists of questions on age, self-rated health, six physical activities and five IADL/ADL activities (see appendix B). A score of three or greater was found to identify a group of vulnerable older people. The study identified 32% of all participants as being vulnerable (VES-13 score ≥3) and this group had 4.2 times the risk of death or functional decline over a two-year period compared to participants with lower VES-13 scores (38). VES-13 survey has been investigated in various study populations. Initial study populations consisted of older adults living in the community and with no focus on those with a cancer diagnosis. The study by Saliba et al reported that high VES-13 scores (≥3) were predictive of an increased risk of death or functional decline at two years. Their study population consisted of adults aged sixty-five and over who lived in the community setting. Min et al studied 420 vulnerable, older and community dwelling adults and concluded that high VES-13 scores were predictive of an increased risk of functional decline and death in a group of adults previously identified as vulnerable and that a higher score correlated with a higher risk of decline over a shorter follow-up period (mean follow up time was eleven months)(39). However, the robustness of the VES-13 score in different cancer patient populations is not yet fully established and research is ongoing.

There has been limited research so far studying the correlation of VES-13 scores and CGA assessment. A study by Mohile et al, compared VES-13 scores to a CGA in fifty men aged seventy and over with prostate cancer who were receiving androgen ablative therapy in an oncology out-patient setting (40). This pilot study reported that 50% of patients scored ≥3 on the VES-13 questionnaire, that there was correlation with some deficits in CGA domains and overall VES-13 was nearly as good as a CGA in detecting functional impairments in older prostate cancer patients (40). Luciani at al compared VES-13 scores with a number of assessment tools used as part of a CGA, in 419 patients aged seventy and over with a cancer diagnosis. They found that VES-13 scores were predictive of impaired functional

status (as measured by conventional ADL and IADL scores) and concluded that VES-13 could be a useful tool in screening older cancer patients who may require further comprehensive geriatric assessment (41).

G8 screening tool

The G8 score was developed by the French "Institut National du Cancer". It comprises questions on nutritional status (taken from the validated mini-nutritional assessment tool, MNA®), number of prescription medications, self-rated health status and age (see appendix C). A person can score from 0-17 and a score of fourteen or less has been shown, in exploratory work, to be predictive of failing a comprehensive geriatric assessment (42) . Further prospective work into the usefulness of the G8 screening tool and its validation, in an older cancer patient population, has been ongoing as part of a large multi-centre study called ONCODAGE (43). In this large multi-centre prospective study, the results reported to date have confirmed the cut off value of fourteen as being the optimal value. (sensitivity of 76.6%, specificity of 64.4%). The G8 score was compared to the VES-13 assessment tool in ONCODAGE and the G8 was more sensitive than VES-13 (76.6% v 68.7%). However the specificity was lower for G8 compared to VES-13 (64.4% v 74.3%) (43).

The VES-13 and G8 scales are both explored in studies in this thesis.

1.5.3. Functional assessment

In geriatrics, activities of daily living (ADLs) and instrumental activities of daily living (IADLs) assessment scores are used to measure an individual's functional abilities. ADL scores assess basic self care activities such as washing, dressing, feeding, continence, going to the toilet and transferring between bed and chair which are essential for a certain level of independence (44) (APPENDIX D). IADL scores assess activities such as using the telephone, shopping, meal preparation, house-keeping, laundry, driving or the use of public transport, ability to take medications unsupervised and manage financial matters (45) (APPENDIX E). IADLs are essential for independence within the wider community setting and are usually more relevant than ADLs when assessing patients in an outpatient setting. However, ADL and IADL scores provide additional information about a patient over and above a traditional performance status score and are used within the CGA process. They are both simple and quick to complete. On initial presentation, around 20% of older cancer patients have an ECOG PS of 2 but over half require help in some IADLs (29, 46-49) In the geriatric cancer population, studies assessing functional status scores have shown that they are an independent predictor for morbidity (chemotherapy toxicity and post operative morbidity) and mortality (47, 50, 51). Various studies have shown that IADL scores (not ADLs) have some correlation with reduced performance status and worse outcomes (29, 47).

Direct measurement of functional status can be carried out using tests such as the "Timed Up and Go" test and the six-minute walk test (52, 53). Studies have shown that questionnaire-based assessments (such as ADL/IADL scores) only partly correlate with direct measurements of functional ability and some groups researching comprehensive geriatric assessment in older cancer patients include both objective and subjective tests of functional status (29). Further work is required to investigate the prognostic usefulness of such direct functional measurements and their correlation with ADL and IADL scores (29).

Hand-grip strength is a direct and objective functional measurement that could be included in a comprehensive geriatric assessment. Measurement of hand-grip strength in middle-aged and elderly people is a good assessment of general muscle strength (54). A large Japanese study of nearly five thousand men and women (without cancer) aged 35 to 74 years old found that hand grip strength was a predictor of all-cause mortality (54). Similar results have been reported in other studies of older people (55-58). In a study of men and women aged 65 and over, grip strength was found to be a long-term predictor of mortality from all causes including cancer in men (58). Grip strength has also been shown to be associated with more markers of frailty than age alone in a study population aged 64 to 74 (59).

A minimum dataset was chosen to comprise a modified CGA in our research. Functional status is an important component of a CGA. In this thesis ADL, IADL and hand-grip strength were chosen to determine functional status in study participants. Whilst recognizing the value of physical tests of functional ability such as the "Timed Up and Go (TUG)" test, we questioned their feasibility in the oncology clinic setting. The TUG test was felt not to be practical in a busy outpatient environment but we recognized the importance of including a tool that measured physical strength. Hand-grip strength was felt to be more practical to measure and a potential applicable assessment tool.

1.5.4. Comorbidity assessment

Older cancer patients are more likely to have comorbid medical conditions and the prevalence of comorbidities increases with increasing age (18). Additional medical conditions and medications can have an effect on an older patient's ability to tolerate various treatment modalities used to manage cancer such as surgery, radiotherapy and systemic therapies.

Chemotherapy causes side effects in patients of all ages. The presence of comorbidities can exacerbate side effects. In older patients the impact of side effects on functional status, quality of life and overall well-being is variable and not

always predictable. In addition, many chemotherapy agents undergo renal and hepatic metabolism. Impaired renal and liver function may be more prevalent in older patients and affect drug metabolism and drug clearance (60, 61). Bone marrow function and reserve may also be reduced which additionally affects older patients' ability to withstand the side effects of many chemotherapy drugs (61).

In cancer patients, certain comorbid medical conditions may be life-limiting. The key issue here is whether a patient is likely to die from their cancer or from a competing cause of mortality. For example, it may be difficult to predict whether an individual patient is more likely to die from a recurrence of their cancer or whether their ischaemic heart disease will precipitate a fatal myocardial infarction first. In the adjuvant treatment setting, the benefit of chemotherapy is often small and measured in terms of a five-year survival benefit. In a review of women who took part in the ATAC study, older women with higher comorbidity scores had a higher risk of death without breast cancer recurrence and the risk of death increased as the comorbidity score increased (19). Measuring comorbidities formally in older cancer patients and as part of a CGA may help clinicians in stratifying treatment options This will inform consultations with individual patients and assist both the clinician and patient as they decide whether the benefits of treatment out-weighs the risks.

A number of comorbidity scales such as the Charlson Comorbidity Index and Cumulative Illness Rating Scale-Geriatrics (CIRS-G) have been devised to measure co morbidity (62, 63). They have their limitations and the usefulness of various comorbidity scales as part of an oncological CGA is being studied.

Charlson Comorbidity Index

The Charlson Comorbidity Index is a comorbidity scale used by health professionals in various medical specialties. It has been validated as a predictor of mortality risk in a number of conditions including some cancers (64). It does not include some comorbidities that may affect the use of cancer therapies (15) but it has been adopted as the comorbidity scale for use in the EORTC Elderly Minimum Data Set as part of the assessment of older cancer patients' global health (65). This

data set has been designed and recommended for use in future research in the field of geriatric oncology and will facilitate meaningful and useful comparisons between studies in the future (65).

The Charlson Comorbidity Index was designed in 1987 following a study which involved looking at the case notes and medical records of medical inpatients in an American institution, recording one year mortality and analyzing the impact of various comorbidities on the risk of death at one year. The index lists nineteen medical conditions, each weighted with a score of one to six (APPENDIX F). Another scoring option was devised some years later where for each patient who is aged fifty and over, one point is added for each additional decade of age (i.e. one point if aged 50-59, two points if aged 60-69, three points if aged 70- 79 and so on)(66).

There are limitations of using the Charlson score in oncology patients. It does not include the primary cancer diagnosis in the overall score. It does not contain/score some conditions that cancer clinicians take into account when considering treatment options, such as the presence of certain haematological disorders, neurological disorders and moderate renal impairment (64). In cancer patients the scores recorded using this index tend to be highly skewed and the overall range of scores is very small (64). Overall, studies have focused on the ability of the Charlson score to predict mortality (67).

Adult Comorbidity Evaluation 27 (ACE-27)

The Adult Comorbidity Evaluation 27 (ACE-27) is an adaption of the Kaplan Feinstein index (described later) and has been validated for use in cancer patients (APPENDIX G)(68, 69). The ACE-27 score was devised in 2000 in the United States of America and has not been widely used in the United Kingdom. It grades specific conditions, within different organ systems, into one of four levels (0= no comorbidity, then 1=mild, 2=moderate, 3= severe). Once the comorbidity score has been assigned the ACE-27 score overall is based on the highest ranked single condition (68). The exception to this is, if there are two "moderate=grade 2" scores in two separate organ systems, the overall ACE-27 score is classified as severe

(score=3). Paleri et al investigated the scoring of comorbidities, through a retrospective review of medical records in UK head and neck cancer patients, and compared the Charlson and ACE-27 scores (70). They found that scoring comorbidities using both tools was feasible, although medical records may be incomplete and this may affect the ability to score the ACE-27 score more than the Charlson (70).

Examples of other comorbidity scales included in a CGA:

Cumulative Illness Rating Scale (CIRS)

The CIRS was originally designed in 1968 and takes into account all the medical conditions of the patient being assessed (71). Diseases were grouped by organ system and rated according to severity on a scale of 0 to 4 and in subsequent years modifications have been made (64). Miller at el adapted the score for use in an older patient population and renamed the scale: Cumulative Illness Rating Scale-Geriatric (CIRS-G) (63).

The CIRS-G has been validated in older cancer patients (72) and has good inter-rater and good test- retest reliability (64) (67). As diseases need to be graded according to severity, more training is required to use the CIRS-G than that needed to use the Charlson score (64).

Index of Coexistent Disease (ICED)

The ICED was devised by a team in 1987 based on review of the medical records of a group of older breast cancer patients. This comorbidity score was designed to take into account the effect of comorbid diseases on cancer management plans (73). It comprises two scales measuring physical and functional status. The physical scale grades the severity of comorbidities from 0 to 4 and then reallocates the conditions into 14 categorical groups. Functional ability is measured by 12 domains and graded from 0 to 2. The physical and functional scores are then combined and re-graded to give an overall severity score from 0 to 3 (64). To use the ICED some prior medical knowledge is needed and the rater would need to refer to a scoring guide.

Kaplan Feinstein Index

The Kaplan Feinstein Index score was devised in 1974 to assess comorbidity in diabetic patients (74). A list of medical conditions are grouped into twelve categories and assigned a severity rating of 0-3. The number of diseases and the severity scores are combined to give an overall comorbidity score from 0 to 3 (64, 74). Kaplan-Feinstein index scores have correlated with mortality in various cancer patient groups. Results from certain studies support predictive validity (62, 74, 75). The score rating is easier than the CIRS and ICED indices and inter-rater reliability is good (64).

Summary

The routine practice of formally scoring comorbidities (using a validated co-morbidity scale) may help inform clinical decision making, particularly in the management of older cancer patients. The Charlson Comorbidity Index was chosen for use in this thesis as it has been validated in a number of cancer patient populations and was felt to be easy and practical to use. It has been adopted as the co-morbidity scale of choice in the EORTC minimum dataset (76) . Additionally, the ACE-27 score was compared with the Charlson score in the "Global health and tolerance of cytotoxic chemotherapy" study (chapter 4). The ACE-27 score was chosen as it is not widely used in the UK and the NCIN has invited projects to explore the feasibility of using ACE-27 to measure co-morbidity (77).

1.5.5. Nutritional Assessment

Malnutrition

Malnutrition is an independent risk factor for increased length of hospital stay, morbidity and mortality (78). Within the community setting the rates of malnutrition in the elderly are estimated to be between 5 and 20% and within the institutionalized or hospitalized elderly this ranges from 23 to 85% (79, 80). A large European study, carried out over a ten year period, showed that weight loss in a group of older people living independently is associated with a significant increase in mortality compared with those of stable or marginally increased weight (81).

Cancer patients are at greater risk of malnutrition (82). This may be due a variety of reasons including their premorbid nutritional state, the co-existence of other illnesses, the type and stage of cancer diagnosed, and anti-cancer treatments used. The assessment of malnutrition in older cancer patients is therefore important before, during and after all modalities of treatment.

There are various definitions of malnutrition in the medical literature. One definition of malnutrition is, "a state of nutrition in which a deficiency, excess or imbalance of energy, protein and other nutrients causes measurable adverse effects on tissue (shape, size, composition), function and clinical outcome" (83) NICE guidelines published in 2006 defined a malnourished person as someone who had a body mass index (BMI) of less than 18.5 kg/m^2 , or an unintentional weight loss of greater than ten percent in the past three to six months or someone with a BMI of less than 20 kg/m^2 and an unintentional weight loss of greater than five percent in the past three to six months (84).

Nutritional assessment tools:

Many assessment tools have been developed over the years to assess nutritional status. The following section describes the three assessment tools that are used in projects undertaken as part of this thesis.

Mini Nutritional Assessment tool

The Mini Nutritional Assessment or MNA® is an assessment tool that was originally developed to assess the nutritional status of elderly people living in a nursing home environment (85) Its development was prompted by the recognition that, at the time of its inception, nutritional status was not routinely assessed as part of a comprehensive geriatric assessment (CGA) despite the knowledge that under-nutrition was prevalent in many elderly patients resident in nursing homes and hospitals (86). It was first published in 1994. Initially the MNA tool was developed and tested on a small population (n=155) of elderly people who had either been admitted to a geriatric unit or lived in the community (87). Further

validation was carried out on two patient populations in France and Mexico (86, 88). A number of studies have since evaluated the MNA in various elderly populations and its sensitivity and specificity has been extensively studied, published and validated.

A shortened version of the MNA was published in 2001 (89). It was developed to identify individuals at risk of malnutrition, who then should undergo a second stage of assessment. The screening questions shorten the time taken to assess all patients to under five minutes and are used in combination with the full assessment, in individuals identified as "at risk", to obtain an overall score (89). Following further validation, since 2005, the MNA has been published as a two-step screening tool (89-91) (APPENDIX H). The short form (MNA-SF) consists of six questions and only if the score identifies the patient to be at risk of malnutrition should the full assessment be undertaken (which takes around 15 minutes to complete). The screening questions ask about appetite, weight loss, mobility, psychological stress/acute disease and measures BMI. The full assessment includes questions about social situation, number of prescription medications, presence of pressure sores/skin ulcers, number of meals eaten in a day, food types/groups consumed, fluid intake, mode of feeding, self-rated health status and anthropometric measurements.

Malnutrition Universal Screening Tool (MUST)

The Malnutrition Universal Screening Tool (MUST) was developed by the British Association for Parental and Enteral Nutrition (BAPEN) in 2003 (83)(APPENDIX I). It was designed to assess patients of all ages in all health care settings and was evaluated in various environments such as inpatient wards and outpatient clinics in secondary care, primary care, care homes and in the community. Its aim is to primarily identify adult patients who are under-weight and at risk of malnutrition as well as over-weight/obese patients (92, 93). The score is calculated based on three criteria. Firstly, a patient's body mass index (BMI) is calculated and scored according to its value. Secondly, unplanned weight loss is assessed. Any unplanned weight loss (and its amount) in the preceeding three to six months is recorded and

scored. Thirdly the presence of acute disease and whether it has caused the patient to have had no nutritional intake over the previous five days (or the likelihood that the patient will be unable to eat over the following five days) is recorded. Depending on scores obtained in the three assessment criteria, patients are allocated to one of three risk groups – low risk (score=0), medium risk (score=1) or high risk (score ≥2). Guidelines regarding further patient management, according to risk group, accompany the MUST literature (83) The MUST assessment is quick and easy to use. NICE has approved and recommended its use as a nutritional screening tool (84) and many healthcare institutions have adopted it as their screening tool of choice.

Patient Generated Subjective Global Assessment (PG-SGA)

The Patient-Generated Subjective Global Assessment (PG-SGA) was developed in Toronto and is based on the subjective global assessment (SGA) (94). It consists of two sections. The first section is completed by the patient and consists of questions on weight loss, food intake, and symptoms that impact on nutritional status and activity level/functional status. The second section is completed by a health professional and includes a clinical examination. Patients are scored on scale of 0-35 and are also defined as well nourished (A rating), moderately nourished or at risk of developing malnutrition (B) or severely malnourished (C). A high numerical score indicates higher risk and aids the health professional in assessing the urgency of dietetic intervention. The PG-SGA has been validated in numerous studies (95) and has been validated in several cancer patient populations (96-98).
The PG-SGA is considered the gold standard to screen for nutritional status in cancer patients (82) . However, it requires training and as a physical examination is required to score patients, only certain health professionals may be able to use it. This therefore limits its usefulness in many health care settings due to time, training and cost implications. The Abridged PG-SGA consists of only the patient generated questions (four questions in the first section of the PG-SGA, APPENDIX J). It can be self-completed and is quick to use. It has not been fully validated as a tool on its own and its use as a nutritional screening tool is explored in this thesis (chapter 4).

1.5.6. Cognitive function and assessment

Cognitive function can decline with age and impairment can affect a cancer patient on many levels. It may affect their ability to make decisions about their treatment and to give informed consent. Good cognitive function is vital to ensure patients are compliant in taking medications correctly when at home such as anti-emetics and some oral chemotherapy treatments. They need to be able to seek medical help when they become unwell due to treatment-related toxicity. Those patients that have a degree of cognitive impairment may need to rely on carers and family members for additional support in order to successfully and safely navigate their way through a course of treatment.

In older people, a diagnosis of dementia is an independent predictor of mortality and has a detrimental impact on survival (99, 100). Studies have shown that patients with a diagnosis of dementia were less likely to have a histological diagnosis of their cancer, were less likely to undergo curative treatment (including surgical resection and adjuvant treatments) and their survival was reduced (101, 102). In a study where patients with cognitive impairment were treated in a geriatric oncology unit and received the appropriate treatment for their stage of disease, their survival was much reduced compared patients with no cognitive dysfunction and comparable stage of disease (29).

Many tools exist to measure cognitive function and assess for dementia. One of the tools most frequently used within a CGA is the Mini Mental State Examination (MMSE) (103) (APPENDIX K). The MMSE was devised in the 1970s. The test is in two parts. The first section tests orientation, memory and attention and the second section tests the ability to name objects, follow verbal and written commands, write a sentence and copy a polygon (103). The MMSE is one of commonest tools used in primary and secondary care to screen for dementia. Other screening tools that are often used include the Mini-Cog test and the "Clock Drawing Test" (104, 105). Subtle changes in cognition may not be apparent or detected in a routine consultation especially if a patient is accompanied by a relative or carer who asks and answers a lot of questions on the patient's behalf. In studies that assessed

cognitive function using a screening tool, such as the Mini Mental State examination as part of a CGA, 25 to 50% of older cancer patients had results that required further assessment (29).

1.5.7. Psychological assessment

In certain areas psychological assessment is viewed as a core component of a CGA and is included in assessment of older cancer patients (106, 107). Depression is common in the geriatric population and in patients diagnosed with cancer (108-110). Therefore, prevalence of depression in older cancer patients is high and may be under-diagnosed. A diagnosis of depression is made if patients have symptoms that meet the criteria as defined by the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition) (111). Symptoms of low mood, loss of interest or enjoyment in all activities should have been present for at least two weeks or have come back repeatedly for a few days at a time. Patients should also have a minimum number of other symptoms which include: sleep disturbance (difficulty sleeping, waking early or sleeping more); tiredness; lacking energy; change in appetite (eating more or less); tearfulness; poor memory; reduced concentration; irritability; lacking self-confidence; low self-esteem; preoccupied with negative thoughts; helplessness; suicidal thoughts. Diagnosing depression in patients with physical illnesses such as cancer can be challenging as some of the symptoms of depression overlap with those of the illness or treatment side-effects (112).

Studies using geriatric assessments containing screening tools for depression, have shown that the prevalence of depression in older people varies from 14% to 40% (29). A large study of breast cancer patients showed that patients with a recent diagnosis of depression were less likely to receive curative treatment and survival rates were worse. The differences in treatment did not account for the poorer survival rate in the group with a recent diagnosis of depression (113). Commonly used screening tools for depression include the Geriatric Depression Scale (GDS) and the Hospital Anxiety and Depression Scale (HADS) (114, 115). The Geriatric Depression Scale (GDS) was devised as a thirty-item questionnaire with yes/no responses (114). A shorter, fifteen-item version of the GDS was created that is

quicker to use and is often included as an assessment tool of depression in a CGA. The HADS score is a 14-item self-completion tool containing seven questions on depression and seven on anxiety. Patients indicate their level of distress over the previous week on a four point scale and the two subscales are scored separately (115). Both the GDS and HADS score are used as screening tools in many healthcare settings. A review of a number of validated depression instruments, including GDS-15 and HADS, specific to geriatric oncology patients concluded that evidence of their validity in older cancer patients is "lacking" (116). Some symptoms indicating depression in older cancer patients may not be detected. Further research regarding validating depression assessment tools for use in older cancer patient populations and therefore the most appropriate tool to include in a CGA would be informative (116).

1.5.8. Social network assessment

Social isolation or lack of social ties is an important consideration in the management of a patient with cancer. Social support is likely to act as a buffer against some of the physical and psychological effects of treatment and have an impact on quality on life (37, 117). Socially isolated people have two to four times the risk of all-cause mortality compared to people with good social ties and networks (118). Social isolation has been shown to be an independent predictor of mortality in the geriatric population (119). In a large study of women with breast cancer, social isolation was shown to be an independent predictor of mortality (120). Social isolation is considered to be a significant problem for one in ten older people in Britain (121) and so may be a particular issue in older patients with cancer and it may be a factor that determines whether a patient accepts the treatment that is offered to them. The Berkman-Syme Social Network Index (SNI) (APPENDIX L) and the Medical Outcomes Survey social support study (MOS-SSS) are two assessment tools that are used to measure social networks and social isolation (122, 123).

The Berkman-Syme Social Network Index was devised in the 1970s following a large study of 6,928 community dwelling adults in a California, United States of America (122). This large study reported an association between social ties and risk of death. Participants with fewer reported social and community contacts had an increased risk of death during the nine year follow up period, compared to participants with many social ties (122). The association of a low SNI score with increased risk of mortality was found to exist independently of a number of factors including physical health, social class, smoking, alcohol intake and obesity (122). In the study, four domains of social contacts were examined: marriage; contacts with close friends and relatives; religious group membership; community social group membership (formal and informal). Further analysis of the results led to the development and creation of the Berkman-Syme SNI. The overall SNI score is calculated from answers to questions covering four domains of social contact and answers are weighted according to the number, frequency and relative importance. The final SNI score ranges from one to four, a lower score reflecting few social ties and social isolation. Subsequent studies using the Berkman-Syme SNI have shown an association between social isolation (low SNI score) and increased risk of death (118, 119, 124).

The MOS Social Support Survey (MOS-SSS) was devised for participants in the Medical Outcomes Study which was a longitudinal study of patients with chronic conditions (123). It is a 19-item survey including various facets of support such as emotional, affectionate, informational, structural, functional and perceived availability of social support (123). The survey can be self-completed and patients rate their answers to questions on a scale of one to five. The MOS-SSS has been used widely in many different patient populations and has been used to assess social support and networks in cancer patient populations (117, 125).

In this thesis we chose to use the Berkman-Syme SNI to assess social networks in a cancer patient population (chapter 6). The SNI has been used as an assessment of social networks in a cancer patient population and as a questionnaire was thought to be simple for patients to self-complete. It was felt that the MOS-SSS may take longer for patients to self-complete and that certain questions, particularly

concerning emotional and affectionate support, may cause distress in some patients.

1.6. Outline of thesis aims

Five closely related projects have been undertaken to achieve the aims stated in section 1.1 and form the basis of this thesis:

1. Epidemiology of colorectal cancer in older patients
2. The assessment and management of older patients with colorectal cancer
3. Global health questionnaires and cytotoxic chemotherapy
4. Malnutrition in patients with metastatic colorectal cancer
5. Social isolation in patients with cancer.

The incidence of colorectal cancer in people aged 65 and over in Great Britain from 1971-2006 is described, including trends in incidence and contemporary disease site distribution in older patients.

Older patients with Stage I-III colorectal cancer have been recruited to a study to assess their general health and fitness using a modified CGA. The primary aim is to ascertain if a screening tool (Vulnerable Elders Survey, VES-13) predicts for functional decline or death at one year. Secondary aims include whether other components of a CGA predict for functional decline or death at one year and whether patients experienced severe chemotherapy toxicities in patients' who received adjuvant chemotherapy.

Over five hundred patients of all ages and cancer diagnoses have been recruited to the "Global health questionnaires and cytotoxic chemotherapy study". In this thesis, patients aged sixty-five and over will be presented. An analysis has been conducted, exploring whether patient-reported measures of performance status and VES-13 and G8 screening tool scores predict those patients that experience severe chemotherapy toxicities.

Patients with metastatic colorectal cancer have been recruited to a study assessing the use of three nutritional screening tools. The aim has been to establish the proportion of patients who are at risk of malnutrition, according to the Mini-nutritional assessment (MNA) and compare the frequency in older and younger patients. Other aims include comparing the sensitivity and specificity of two other screening tools with the MNA.

Finally, a survey has been conducted of patients attending a cancer centre outpatient clinic. The purpose of the survey was to measure the degree of social isolation in this group of cancer patients and compare older and younger patients.

Chapter Two

2. Epidemiology of colorectal cancer in the 65s and over in Great Britain 1970-2006

2.1. Introduction

Colorectal cancer is the third most common cancer in the UK after breast and lung cancer, with 41,142 new cases diagnosed in the UK in 2009 (126). Colorectal cancer is common in older people. In the United Kingdom, an average of seventy-two percent of bowel cancer diagnoses were recorded in those aged sixty-five and over between 2007 and 2009 (126). In a number of countries, including the United Kingdom, the population is ageing and this issue has been discussed in chapter one of this thesis. There are therefore likely to be large increases in the number of older patients diagnosed with colorectal cancer. This will have significant implications for:

(i) Resource allocation and the provision of curative treatments including surgery, chemotherapy and radiotherapy.

(ii) Bowel cancer screening programmes.

(iii) Research priorities – as the older population are under-represented in clinical trials at present.

An understanding of the scale of the potential disease burden will be essential for all of these reasons.

In this analysis cancer registry data was examined to achieve following aims:

(i) describe case numbers of colorectal cancer

(ii) describe changes in incidence of colorectal cancer in the elderly aged 65+ years in Great Britain during the period 1971-2006

(iii) describe histological morphology and topography (site of disease) in the most recently available population of patients aged 65+ years in Great Britain

2.2. Methods

Cancer registration in England and Wales is conducted by 12 population-based regional cancer registries, and in Scotland by the central Scottish Cancer Registry. Individual records of primary colorectal cancer registrations (ICD-10 codes: C18.0-18.9; C19; C20) for men and women aged 65+ years at diagnosis for the period 1971-2006 were obtained from the Office for National Statistics (ONS) (for England), Welsh Cancer Intelligence & Surveillance Unit, and Information Services Division Scotland (ISD) (Scottish Cancer Registry). For each case of colorectal cancer, the dataset included information on: year of birth, gender, ethnicity (for 1993-2006), age at first diagnosis (65+ years), year of diagnosis, topography (ICD-10 codes), morphology (ICD-O-3 codes), most valid basis of diagnosis (1993-2006), and type of treatment (1993-2006). Details of the mid-year population aged 65+ years for England, Wales, and Scotland were obtained in 5-year age and sex subgroups for the years 1971-2006 from the ONS and ISD Scotland. Crude age- and sex-specific average annual incidence rates (per 100 000 persons) of colorectal cancer were calculated for each 5-year age group (65-69, 70-74, 75-79, 80-84, 85+) and time period (1971-75, 1976-80, 1981-85, 1986-90, 1991-95, 1996-2000, 2001-06) ; truncated (age 65+ years) average annual age-standardised incidence rates were calculated using the European standard population. Join point statistical analysis is a methodology used to examine and characterize population trends. Join point regression analysis (National Cancer Institute, 2010) was conducted to examine trends in age-standardised incidence rates of colorectal cancer during the period 1971 to 2006. The magnitude and direction of trend(s) was determined by calculating the annual percent change (APC) and average annual percent change (AAPC) during a fixed predetermined period. A maximum number of four join points were used in the analysis to identify changes in the linear trends of colorectal cancer incidence rates based on regression models with 0, 1, 2, 3, and 4 join points. All data management and analyses were conducted using the Excel, SPSS and STATA programmes.

2.3. Results

2.3.1. Cases

During the 36-year period, 1971-2006, a total of 777,086 cases of colorectal cancer among the elderly aged 65+ years were registered in Great Britain; 48.4% males, 51.6% females. Table 2.1 shows the distribution of cases according to age group.

Table 2.1. Characteristics of elderly (age 65+ years) patients diagnosed with colorectal cancer in Great Britain, 1971-2006

	Great Britain	
	n	%
	777,086	100.0%
Age (years)		
65-69	155,284	20.0%
70-74	182,439	23.5%
75-79	181,846	23.4%
80-84	142,674	18.4%
85+	114,843	14.8%
Gender		
Male	376,294	48.4%
Female	400,792	51.6%

Table 2.2 shows the number of cases for each five year time period (1971-2006 inclusive) for England and Wales combined and Scotland.

In England and Wales, there was a 61.9% increase in the average annual number of colorectal cancer cases during the study period (from 14,313 in 1971-75 to 23,114 in 2001-06) . Similarly, in Scotland there was a 58.9% increase in the average annual number of cases (from 1,479 in 1971-75 to 2,511 in 2001-2006.)

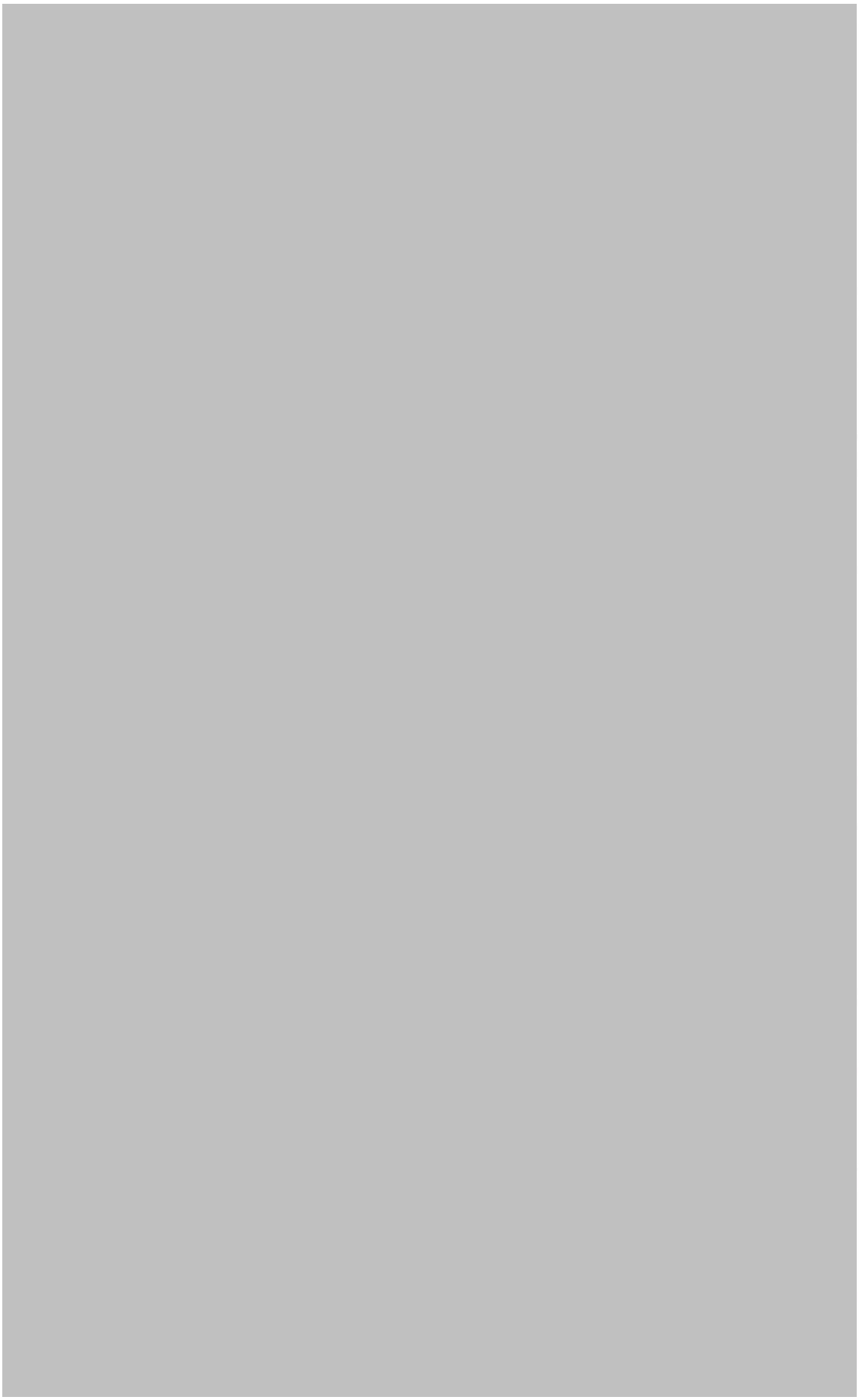
Table 2.2 Number of elderly (age 65+ years) patients diagnosed with colorectal cancer in Great Britain, 1971-2006

Year of diagnosis	England & Wales	Avg. No. Cases/Year	Scotland	Avg. No. Cases/Year
1971-1975	71,563	14,313	7,395	1,479
1976-1980	81,497	16,299	8,988	1,798
1981-1985	91,194	18,239	9,697	1,939
1986-1990	98,951	19,790	10,462	2,092
1991-1995	106,181	21,236	11,449	2,290
1996-2000	113,368	22,674	12,593	2,519
2001-2006	138,684	23,114	15,064	2,511

2.3.2. Incidence

Table 2.3, shows the average annual incidence rates (per 100,000) of colorectal cancer among the elderly aged 65+ years in Great Britain during the 36 year time period, 1971-2006. Figures are shown for men and women in each five year time period and for age groups 65-69, 70-74, 75-79, 80-84 and 85+.

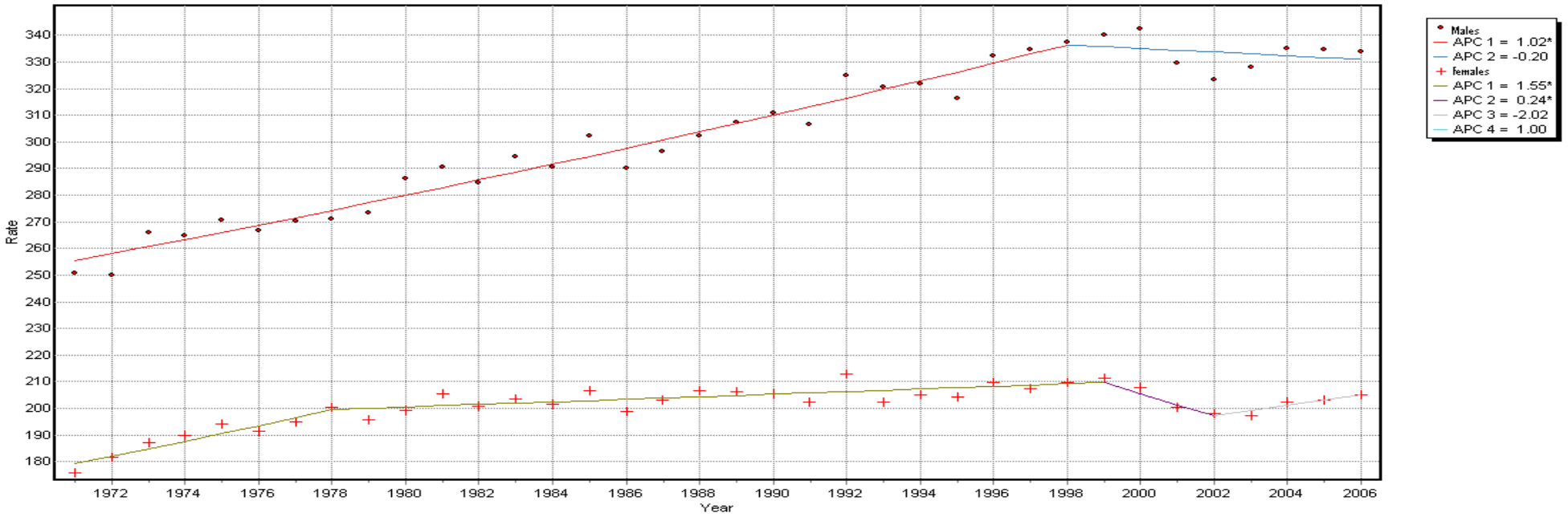
- The average annual incidence rates increase with increasing age in both sexes and this is seen through all the time periods shown. For example, in men in 2001-2006 the annual incidence rate increased from 224 in the 65-69 age group, to 494.7 in the 85+ age group, in women over the same time period the annual incidence rate increased from 131.6 in the 65-69 years old to 332.1 in those aged 85 and over.
- The incidence of colorectal cancer in all age groups aged 65 and over, in both men and women, has increased over the last thirty-five years, with the exception of the final time period studied (2001-2006). The incidence rate was 244.2 in men and 189.8 in women in 1971-1975 and increased to 342.8 and 225.5 in men and women respectively, in 2001-2006.



The graph (Figure 2.1) shows the fitted annual trends in age-standardised incidence rates (per 100,000) of colorectal cancer in the elderly based on join point analyses. The breakdown of the join point analyses is shown in the accompanying table (Table 2.4).

For males, during the time period 1971-1998 the increase incidence rate of 1% per year was statistically significant. From 1998 to 2006 the incidence rate tailed off but the reduction in incidence rate over this time period was not found to be of statistical significance. In females the increased incidence rate of 1.6% per year during 1971-1978 time period was statistically significant. From 1978-1999 the incidence rate rose at a statistically significant slower rate of 0.2% per year. From 1999-2006 the decreases and increases seen in the time periods 1999-2002 and 2002-2006 respectively were not found to be statistically significant and the incidence rate in older women has remained fairly static over the 1999-2006 period. In summary, the graph (figure2.1) shows a rise in the incidence of colorectal cancer from 1971-2006 in both sexes and the rise in incidence is greater in older men compared to older women.

Figure 2.1. Fitted annual trends (based on joinpoint regression analysis) in age-standardised (Europe) incidence rates (per 100 000) of colorectal cancer in the elderly (age 65+ years) in Great Britain, 1971-2006 (• male, + female)



* The estimated annual percentage change (APC) is significantly different from zero.

Table 2.4. Trends in age-standardised (Europe) incidence rates (per 100 000) of colorectal cancer in the elderly (age 65+ years) in Great Britain, 1971-2006 (based on joinpoint regression analysis)

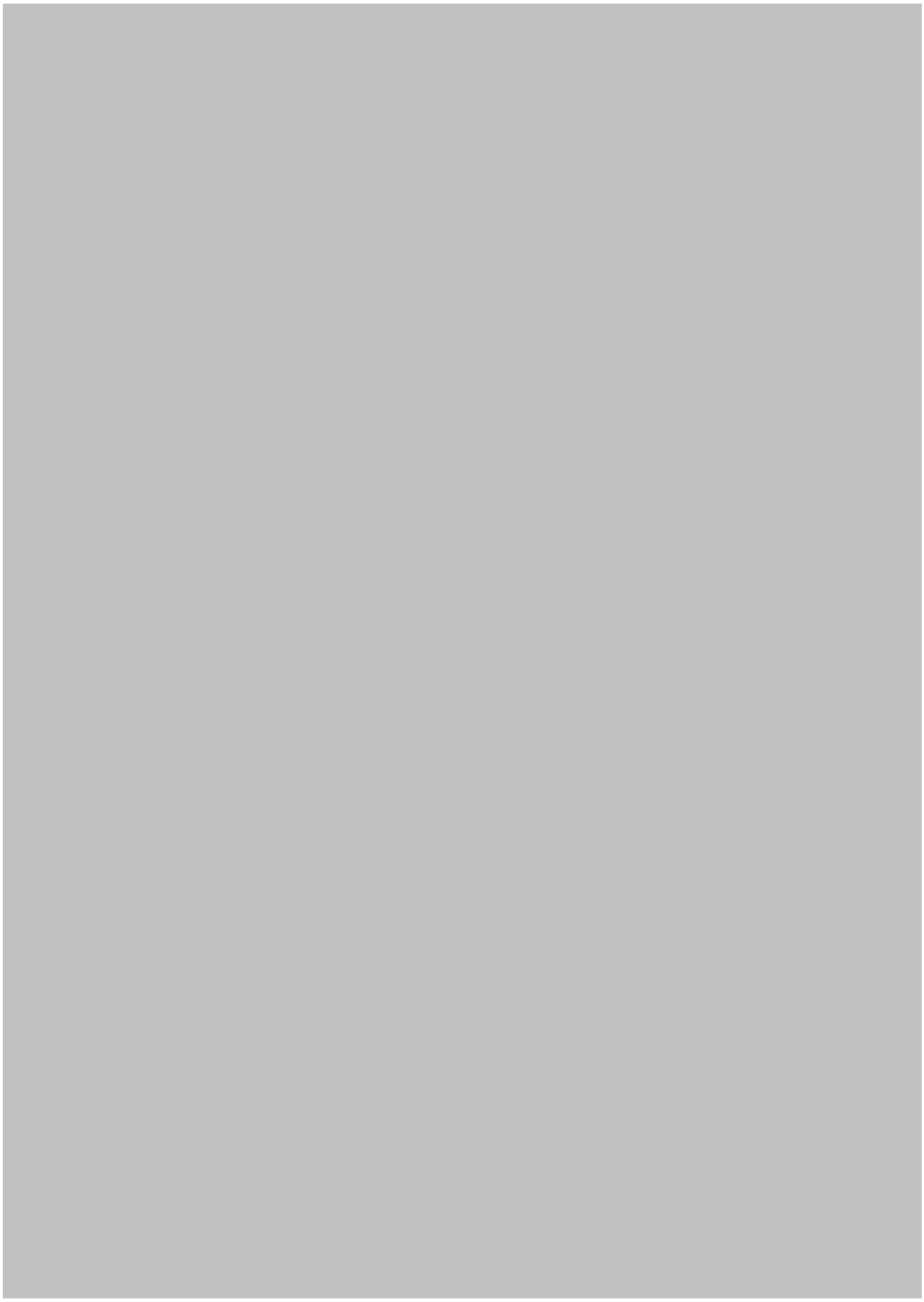
	Joinpoint Analyses (1971-2006)									
	Trend 1		Trend 2		Trend 3		Trend 4		AAPC (95% CI)	
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	1971-2000	1971-2006
Males	1971-1998	1.0* (0.9 to 1.1)	1998-2006	-0.2 (-0.7 to 0.3)					0.9* (0.8 to 1.0)	0.7* (0.6 to 0.9)
Females	1971-1978	1.6* (0.9 to 2.2)	1978-1999	0.2* (0.1 to 0.4)	1999-2002	-2.0 (-6.0 to 2.2)	2002-2006	1.0 (-0.3 to 2.3)	0.5* (0.3 to 0.7)	0.4 (-0.0 to 0.8)

APC, annual percent change. APC is based on truncated age-standardised (Europe) incidence rates per 100 000.
AAPC, average annual percent change. AAPC is the weighted average of the APCs calculated by Joinpoint regression analysis.
*Statistically significantly different from zero.

2.3.3. Morphology and topography

Morphology and topography of colorectal cancers in the elderly for the last ten years (1997-2006) in Great Britain was also reviewed. Overall, 81.0% of cases were adenocarcinomas, and 13.6% were carcinoma of other types or carcinoma not-specified as shown in Table 2.5.

Information on the site of colorectal cancer tumours in older men and women for the ten year time period 1997-2006 is shown in Table 2.6. Information for England, Wales and Scotland are shown and then combined in the final column to give overall statistics for Great Britain. Over half of colorectal cancer diagnoses occurred in the rectum, recto sigmoid junction and sigmoid colon. The differences in tumour site between the sexes were explored. A two-sample test of proportion (z-test) confirmed that the proportion of cancers in the recto sigmoid junction and rectum were significantly greater for elderly males than elderly females (38.6 v 30.1%, $p<0.0001$) and that the proportion of cases located in the caecum were significantly greater for elderly females than for elderly males (18.0 vs., 12.5%, $p<0.0001$).



2.4 Discussion

The average annual number of colorectal cancer cases in men and women in Great Britain aged sixty-five and over has increased by 61.6% over the time period 1971-2006. This was found to be due partly due to increasing incidence and any increases seen in excess of this are likely to be due to increases in size of the susceptible population.

Cases/registrations

From 1971-1975 time period until 1996-2000, the rising number of total cases and incidence rates of colorectal cancer in all age groups was observed. From the time period 1996-2000 to 2001-2006 the total number of cases continued to increase but the age-standardised incidence rate fell for the first time. The excess of cases is probably due to the increase in the size of the population and particularly an expansion in numbers of older people who are more likely to develop colorectal cancer (126).

Incidence

We found that the incidence of colorectal cancer was higher in elderly men compared to women and incidence in men has increased at a greater rate compared to women, over the last thirty-six years. However, the incidence of colorectal cancer in both sexes has stabilised over the time period 2001-2006 and the reason for this is not clear

The increase in incidence might be explained by:

(i) changes in aetiological factors associated with bowel cancer such as high red and processed meat consumption, obesity and sedentary lifestyle. In western and developed countries the availability and consumption of red meat and processed meats has increased over the years. A number of studies and meta-analyses have shown that eating red and processed meat is associated with an increased risk of bowel cancer and that the risk of developing colorectal cancer, increases if larger amounts are consumed (127-130). UK Government guidelines now recommend that we consume less red and processed meat to reduce our cancer risk. Over the last thirty years our lifestyles have become more sedentary. A meta-analysis

performed by Samad et al showed that physical activity is associated with a reduced risk of colon cancer in men and women (131). Further studies have shown that the higher the level of physical activity, the lower the risk of colorectal cancer (132) and this has led the World Cancer Research Fund to conclude that "the evidence that physical activity protects against colon cancer is convincing" (133) . Alongside our more sedentary lifestyle, the incidence of obesity has increased over the years. For example statistics, published on rates of obesity in England from 1993 to 2010, report that the proportion of obese adults has increased. For men 13.2% were obese in 1993 and 26.2% were obese in 2010, over the same time period the percentage of obese women increased from 16.4% to 26.1% (134). An increase in body mass index also increases an individual's cancer risk (135, 136). A meta-analysis by Moghaddam et al concluded that "obesity has a direct and independent relationship with colorectal cancer" (137) and that there was evidence that as BMI and waist circumference increases, risk of colorectal cancer increases (137). Worldwide differences in incidence are mainly related to diet (138). Over time, colorectal cancer incidence is increasing in countries where diet is becoming more "Westernised" (e.g. Japan) and incidence is increasing/ remaining static in Northern and Western Europe and decreasing in North America (138, 139).

(ii) Cancer awareness: in patients and clinicians. An increase in incidence may occur because of improved cancer awareness and therefore an increased likelihood that patients will present with symptoms and be diagnosed. Over time clinician attitudes and behaviours may also change, such that contemporary clinicians may be more likely to investigate possible cancers in older patients because co-morbidities are better controlled, more (potentially less toxic) treatments are available, or because local or national guidelines oblige them to do so.

Morphology and topography

The majority of colorectal cancers are adenocarcinomas. In our analysis of morphology and topographical data, 81.0% of cases were adenocarcinomas, and 13.6% were carcinoma of other types or carcinoma not-specified. The percentage of cases coded in our analysis as adenocarcinomas is less than is generally

reported – over 90% of bowel cancers are adenocarcinomas (140). This difference may be due to a variety of factors including incorrect coding at the time of data entry and improvements in accuracy and reliability of histological reporting over the last thirty-five years.

The site of colorectal tumours presenting in the older British population is comparable with known patterns of disease, with over two-thirds of older patients presenting with distal colon or rectal tumours. However, it is interesting to observe that over the last ten years (1997-2006) there was a significant difference in some of the sites of colorectal cancer tumours recorded between older men and women. The proportion of tumours in the recto sigmoid junction and rectum were significantly greater for elderly men compared to women (38.6 vs. 30.1%, $p<0.0001$). The percentage of caecal tumours in older women was significantly greater when compared to older men (18.0 vs. 12.5%, $p<0.0001$). The reasons for these observed differences between the sexes are unclear.

Implications

The substantial increase in the number of older patients diagnosed with colorectal cancer, amounting to almost an extra 10,000 cases per year compared to the early 1970s, clearly has many implications. The management of older patients with colorectal cancer is complex, and needs to take into account pre-existing co-morbidities, frailty, likely tolerance of treatment, and all of the psychological and social variables, which can impact on the holistic care of older patients with cancer. The successful management of such patients is likely to need more specialised training of health professionals, better management of co-morbidities, clinical trials sensitive to the needs of older patients with cancer, and more objective assessments of fitness for treatment. All of these developments will have resource implications.

The National Bowel Screening programme was commenced in England in 2006 and achieved nationwide coverage by 2010. Currently, all men and women aged sixty to seventy-five are sent a faecal occult blood (FOB) test kit every two years (the upper age limit was extended from sixty-nine to seventy-five in 2010 and is being rolled out across the UK). If patients have an abnormal FOB test they are seen for further investigation and usually would undergo a colonoscopy. FOB testing has been calculated to reduce mortality by up to 25% in those who undergo

screening (141). In 2011, in England patients aged between sixty and seventy-five are invited to undergo FOB screening every 2 years, Scotland invites patients aged fifty to seventy-four. The use of flexible sigmoidoscopy in colorectal cancer prevention has been studied and a large UK multicentre trial has reported that once-only flexible sigmoidoscopy in persons aged fifty-five to sixty-four years reduces their incidence of and mortality from colorectal cancer (142, 143). There are now plans to roll out an additional screening programme of once-only flexible sigmoidoscopy to people when they turn fifty-five years old. They would still undergo FOB screening from the age of sixty. The impact of bowel screening programme on colorectal cancer incidence is awaited, and our data suggest that in patients aged 65 or over, flexible sigmoidoscopy alone would miss at least 12.5% of cancers in men and 18% of cancer in women (because they are right-sided).

We have described the increasing incidence of colorectal cancer over the last thirty-six years in the older population of Great Britain. This increase impacts on many areas of the National Health Service such as the bowel screening programme, diagnostic services, surgical and cancer services. Adequate resources will need to be allocated to enable early and efficient diagnosis, which will improve survival rates. Public education will be required to maximise uptake of the current screening programme and to ensure patients are also aware of symptoms that should be discussed with a health professional promptly. However, many older people do present late with advanced disease or are unfit due to comorbidities and it is important that they have access to local palliative care services.

Summary

The number of older patients diagnosed with colorectal cancer in Great Britain, over the last thirty-six years has increased. In recent years there have been an extra ten thousand patients diagnosed compared to over thirty years ago. It is likely that numbers will continue to increase as our population ages. Individualised management plans for older patients will be essential in ensuring that they receive appropriate treatment for their stage of cancer. All of these factors will have implications in health service costs in terms of screening, diagnosis, treatments and palliative care.

Chapter Three

3. Assessment and post-surgical management of older patients with colorectal cancer

3.1. Introduction

3.1.1. Background

Colorectal cancer is the third commonest cancer in the UK. It is affects older men and women and in recent years an average of 72% of cases were diagnosed in patients aged sixty-five and over (144). Locally, within the Sussex Cancer Network, at least two-thirds of patients diagnosed with colorectal cancer are over the age of seventy (145). Early stage colorectal cancers, stage I and the majority of stage II tumours, are usually cured by surgery alone. Recent data published by the National Cancer Intelligence Network (NCIN) report that, in England, the five-year relative survival of patients with stage I colorectal cancer is 93.2%, however for patients who are diagnosed with stage III disease it is 47.7% (146).

3.1.2. Adjuvant chemotherapy in colorectal cancer

Evidence from large randomized trials have shown that patients with stage III colorectal cancer derive benefit from adjuvant chemotherapy, following surgery. Early trials demonstrated an improved survival benefit with adjuvant fluorouracil-based chemotherapy (147). Further trials have investigated combination regimens. The MOSAIC study was a large study comparing adjuvant 5-Fluorouracil and oxaliplatin (FOLFOX) versus infusional 5-Fluorouracil alone in patients with stage II or III colorectal cancer. Results from the MOSAIC trial and other studies have shown that the addition of oxaliplatin confers an additional disease-free and overall survival benefit (148-151).

3.1.3. Evidence for adjuvant chemotherapy in older colorectal cancer patients

Studies demonstrating the benefit of adjuvant chemotherapy in high-risk colorectal cancer patients tended to exclude older patients or include small numbers of older patients. In 2001, a pooled analysis by Sargent et al looked at data from seven phase three trials (studying adjuvant fluorouracil) and concluded that in selected patients aged over seventy, the same benefits in terms of overall survival and disease free survival can be achieved compared to younger patients with no significant increase in treatment-related toxicity (21).

In the MOSAIC study the median age of patients in the two treatment groups was sixty and sixty one years of age (148). Older patients benefited from the addition of oxaliplatin but "older" patients were not older than seventy-five years of age and were likely to have been quite fit to be eligible for trial entry (22, 148, 152). A pooled analysis of four trials investigating the use of FOLFOX included three thousand seven hundred and forty two colorectal cancer patients of which 16.4% were aged seventy years old and over (but none older than seventy five years of age) (22). The analysis found that older patients (seventy years and older) were more likely to experience haematological (grade three or higher neutropenia or thrombocytopenia) toxicity compared to younger patients but that there was no difference in progression or recurrence-free survival and overall survival between older and younger patients. They concluded that FOLFOX could be used safely and with equal efficacy in "selected elderly patients" (22).

3.1.4. Post-surgical management of older colorectal cancer patients

Older colorectal cancer patients are a heterogenous group and (with advancing age) they tend to present later with more advanced disease, they are more likely to undergo fewer staging investigations and less likely to have curative elective surgery (153) . With increasing age, older patients may be less likely to be referred for and receive adjuvant chemotherapy (154) and older patients may be denied further treatment on the basis of factors such as co-morbidities, perceived frailty, impaired organ function (152) . However, there is evidence that older fit patients

have similar outcomes as younger patients when managed optimally (152). A large retrospective review of patients with stage III colon cancer found that older patients were less likely to receive adjuvant chemotherapy but that the overall survival benefit achieved in older patients was comparable to those in younger age groups (155).

In patients undergoing curative surgery, adjuvant chemotherapy may be considered to reduce the risk of recurrence. As described previously, for oncologists, the evidence for the benefit of chemotherapy in older patients, particularly those aged seventy and over, has been sparse. Physicians may extrapolate the evidence obtained from younger, healthy patients and apply it to older patients who may have other factors that need to be taken into account. Alternatively, due to lack of evidence, older colorectal cancer patients may be denied adjuvant treatment on the basis of age alone.

In order to benefit from adjuvant treatment, the patient's life expectancy irrespective of their cancer has to be sufficiently good to accept the side effects and risks of treatment. The analysis by Sargent et al showed, perhaps unsurprisingly, that the probability of older patients dying without disease recurrence was greater compared to younger patients. Patients aged fifty years old and younger had a 2% chance of death without disease recurrence compared to a 13% risk in patients aged seventy and over (21, 152). As older patients are more likely to die due to causes other than their primary cancer diagnosis it is important to assess patients' fitness for treatment and consider other potential competing causes of mortality. Age alone is a poor predictor of life expectancy and tolerance of treatment. However, assessment of a number of different factors may help predict these outcomes. These include assessments of functional status, co-morbid medical conditions, nutritional status, and blood parameters (156). A number of validated assessment tools have been devised to assess these parameters in various patient populations. However, the applicability and usefulness of these surveys in older colorectal cancer patients has not been fully investigated.

It is hypothesized that some parameters measured, as part of a modified CGA or alternative assessment tool such as VES-13 or G8 score, may predict functional decline or death in older patients with localised colorectal cancer. In turn, these tools may help better predict those older patients who are more able to tolerate and benefit from adjuvant chemotherapy.

3.2. Study Aims

Primary Aim

To ascertain if the Vulnerable Elders Survey (VES-13) score predicts for functional decline or death in patients aged sixty-five and over, with stage I-III colorectal cancer, who have undergone surgery.

Secondary Aims

In the study population:

(i) To ascertain if the VES-13 score predicts for severe chemotherapy toxicity.

(ii) To ascertain if G8 score, ECOG-PS, age, Charlson co-morbidity index, MNA, or grip strength predict for functional decline or death at one year.

(iii) To ascertain if G8 score, ECOG-PS, age, Charlson co-morbidity index, MNA, or grip strength predict for severe chemotherapy toxicity.

3.3. Methods

Study Design

Prospective Cohort Study

Study Population

Patients aged sixty-five years old and over, newly diagnosed with stage I-III colorectal cancer within the Sussex Cancer network hospitals: Brighton and Sussex University Hospitals, Eastbourne District General Hospital and Worthing District General Hospital.

Inclusion criteria

Patients aged sixty-five years old and older.
Diagnosed with stage I-III colorectal cancer following primary surgical resection. (Patients who had undergone neoadjuvant treatment (e.g. chemotherapy or long course chemo radiation) prior to surgical resection were also eligible.)
Capacity to provide written informed consent.

Exclusion criteria

Patients unable to give informed consent.
Life expectancy less than three months.
Patient presenting with metastatic (Stage IV) disease at diagnosis.
Patients who have already commenced adjuvant treatment e.g. chemotherapy.

Study conduct

All patients with a new cancer diagnosis are discussed in a multi-disciplinary meeting (MDM). Eligible patients for this study were identified through the colorectal MDMs held in within the Sussex Cancer Network Hospitals. The patient's clinical nurse specialist was consulted to ensure that the patient was appropriate to contact. Eligible patients were sent a letter in the post offering them the opportunity to become involved in the research study. The letter included a patient information sheet and a consent form (APPENDIX M).

Patients who did not respond to the initial letter were sent a reminder letter, after 6 weeks. Thereafter, no further contact was attempted.

Patients who replied were contacted by telephone to establish that they understood what their involvement in the study entailed and to answer any questions. Arrangements were made to meet and carry out the baseline assessment. This occurred at a place and time that was convenient for the patient. With the patient's consent, their GP was informed of their involvement in the study.

Further medical information, regarding the tumour type, grade, stage, and further details regarding co-morbidities were ascertained from the medical records.

The aim was to perform the baseline assessment within 3 months of the operation date and the information collection is detailed as follows:

i) Patient demographics. Tumour histology, staging, date and type of operation performed.

ii) At interview:
a) Height and weight.
b) ECOG/WHO performance status (27).
c) Vulnerable Elder Survey (VES-13) (38).
d) G8 score (42).

e) Charlson comorbidity index (62).
f) Activities of daily living (ADL) and Instrumental activities of daily living (IADL) (44, 45).
g) Mini Nutritional Assessment (MNA) (87).
h) Hand-grip strength (26, 54)
i) Mini Mental State Examination (MMSE-30) (103)(See appendices A-F,H,K).

In assessing hand-grip strength, four measurements were taken (alternating between the right and left hand). The highest reading of the four attempts was used to assign participants into either a frail or non-frail group, based on patient sex, age, body mass index and hand-grip strength. The calculation was based on a table published in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Senior Adult Oncology 2005 (26):

Table 3.1: Cut-off groups for frailty according to grip strength(kg), adjusted for sex and body mass index (26).

		Cutoff for grip strength (Kg) criterion for frailty:	
Men	Women	Men	Women
BMI ≤ 24	BMI ≤ 23	≤ 29	≤ 17
BMI 24.1-26	BM1 23.1-26	≤ 30	≤ 17.3
BMI 26.1-28	BMI 26.1-29	≤ 30	≤ 18
BMI >28	BMI >29	≤ 32	≤ 21

In addition a blood sample was taken to measure full blood count, renal and liver function, bone profile, CRP, B12, folate, thyroid function and vitamin D levels.

The cohort comprised two groups: One group of patients were referred to an oncologist and were to receive adjuvant chemotherapy. The second group consisted of patient deemed appropriate for routine surgical follow up only.

The baseline questionnaires were to be completed within three months of surgery and before the first cycle of chemotherapy in those patients having adjuvant chemotherapy.

Data regarding adverse outcomes and chemotherapy toxicity was recorded from the electronic prescribing system, the medical records and patient interview when the end of chemotherapy assessment was undertaken. Severe chemotherapy toxicity was defined as grade III/IV toxicity (CTCAE version 3.0 criteria (157)), dose delays/reductions, unplanned hospitalization, treatment discontinuation or death within 30 days of treatment.

Table 3.2: Timetable of assessments:

Assessments	At diagnosis	End of Chemotherapy[1]	1, 2 & 5 years
Demographics	Standard Variables		
Tumour Data	Standard pathological variables		
Screening	G8		
Performance status	ECOG-PS	ECOG-PS	ECOG-PS
Functional status	ADL IADL VES-13	ADL IADL VES-13	ADL IADL VES-13
Co-morbidities	Charlson c-morbidity index		
Nutrition	MNA (screening)		
Physical strength	Handgrip by digital dynamometer[2]		
Cognitive status	MMSE-30		
Biomarkers	Blood collection[3]		
Chemotherapy toxicity		Grade III/IV toxicity, dose reductions etc	

[1] In patients who have had adjuvant chemotherapy – usually at 12-24 weeks depending on regimen given

[2] In kg, frail vs. not frail according to sex and BMI

[3]Routine bloods collected tested for: Haemoglobin, urea, creatinine, Na, K, Ca, Phosphate, albumin, Vit B12, Folate, TFTs, 25(OH) Vit D, CRP.

Follow-up

At the time of completion of chemotherapy treatment, individual patients were contacted by telephone. Functional status was re-assessed by completing performance status (PS), ADL and IADL scores. VES-13 score was also repeated. Patients were asked about their treatment and toxicities and additional information regarding the progress of their treatment was obtained from their medical records.

In both cohorts, functional status was repeated at one year from the baseline assessment. Ethical approval has been obtained for follow up to continue at two and five years from baseline assessment. Before contacting the patient, it was established that the patient was alive or dead through looking at their local hospital records and /or contacting the GP practice.

Current place of residence and social situation was recorded and WHO-PS, IADL/ADL and VES-13 scores were completed via a telephone call to the patient. Functional decline will be defined as a change from no IADL/ADL disability to any ADL/IADL disability, an increase of 2 or more IADL/ADL disabilities or nursing home admission (38). In patients who died, cause of death was recorded from the death certificate or medical records.

Statistical analysis and sample size

This study is an exploratory study and patient recruitment was intended to be undertaken over a period of at least ten months (November 2009- August 2010). Across the Sussex Cancer Network there are approximately eight new older patients discussed in the colorectal MDMs each week. Therefore over a ten month period a possible maximum of 400 eligible patients may be identified. It was hoped that up to 150 patients would agree to take part in the study.

Due to the exploratory nature of the study, formal power calculations were not possible. The VES-13 score distribution is not known in this patient population and neither has one year follow up data been obtained before.

The primary input variable of VES-13 score has been used to drive sample size calculations. (In a previous study older patients (without cancer) with a VES-13

score of more than 3 had a fourfold higher risk of functional decline or death than those with score of less than 3 (38). From this existing data, it is assumed that the proportion of patients with VES-13 scores ≥3 and <3 will be 32% and 68%, and that the proportion of those who die or functionally decline in the <3 group will be 11.8% (38). For the purposes of this study an increase in risk of functional decline or death of 20% was defined as clinically important (11.8 to 31.8%). Power calculations were then based on a test of a comparison between two proportions using a two-sided 0.05 significance level. A sample size of 153 would have 80% power in detecting an increase in risk of 20%, at the 5% level of significance.

The other six input variables: G8 score, Age, Performance status, Charlson score, MNA score, and grip strength will be tested together in a multiple regression model. Using six input variables in a multiple logistic regression model: sixty events would be needed (158). Assuming an event rate of 24% (38), 250 patients would be needed. If the sample size in this study is small, the study may not be powered to assess some of the secondary endpoints (that is, if any of the other scores predict for functional decline or death).

Data Handling

(i) Distribution of VES-13 (<3 vs ≥ 3), ADL (0-6), IADL (0-8), G8 (0-17), WHO performance status (0-4), Charlson comorbidity score (0-30), MNA (0,1,> 2), Grip strength (frail versus not frail),will be presented. These results will also be presented stratified for age (65-69,70-74,75-79,80-84,≥85). The differences in these variables between the different age groups will be analysed using chi-squared tests.

(ii) Twelve month rates of death and functional decline (defined as a change from no IADL or ADL disability to any IADL or ADL disability, an increase of two or more in the total count of IADL or ADL disabilities, or new admission to a nursing home) will be presented.

(iii) Multiple logistic regression will be used to assess whether any of the input variables (G8, VES-13, WHO performance status, Charlson comorbidity, MNA score,

age and grip strength) predict death, functional decline or the compound outcome (death and functional decline). Logistic regression will give adjusted odds ratios for each potential predictor variable, allowing their relative weights to be assessed.

(iv) In those patients receiving chemotherapy exploratory analyses will be conducted to investigate whether any of the input variables (above) predict severe chemotherapy toxicity. The latter will be defined as grade III/IV toxicity (CTCAE version 3 criteria), dose reduction, unplanned hospitalization, treatment discontinuation, or death within 30 days of treatment.

Unplanned analysis

An analysis was undertaken to explore whether the G8 score predicted for failure of a CGA. We defined having "failed" a CGA if patients had a deficit in any of ADL, IADL, nutrition or grip-strength domains. If they were dependent in any ADL domain, and or dependent in any IADL domain, and or at risk of malnutrition/malnourished according to MNA assessment, and or frail (according to grip-strength) then they had failed our CGA.

Ethics approval

Ethical approval for this study, "The assessment and management of older patients with colorectal cancer", was obtained from a local ethics committee (REC reference number 09/H1109/75).

3.4. Results

One hundred and eighty one invitation letters, including study information sheets and consent forms, were posted to potentially eligible patients over a twelve month period (October 2009 to October 2010).

One hundred and seventeen patients returned signed consent forms, indicating that they were willing to be involved in the study. Overall response rate was 64.6%. Of the positive responses, five patients were ineligible: two patients had metastatic colorectal cancer; two patients replied after the time period in which they had to be seen and one patient replied after they had started adjuvant chemotherapy.

On receiving the returned consent forms, the patients were contacted by telephone to enquire whether they had any further questions and to establish that they understood what their participation in the study involved. The initial assessment was carried out at the most convenient place and time for the patient, either their local hospital or within their own home.

One hundred and thirteen patients were seen and underwent the baseline assessment. One patient was found to have metastatic disease on subsequent review of the histopathology report (metastatic peritoneal deposits) and was not included in the final analysis due to ineligibility. Therefore, one hundred and twelve study participants' results have been analysed.

3.4.1. Patient demographics

Demographic details of patients recruited are shown in table 3.3. Fifty seven (50.9%) of the participants were female, fifty five (49.1%) were male. The mean age was 74.7 years old (range 65-90 years, standard deviation 6.305). Seventy four (66.1%) participants were married or lived with a partner, twenty (17.9%) were widowed. Twenty five participants (22.3%) lived alone and five (4.5%) lived in sheltered housing or warden assisted accommodation

Table 3.3: Patient demographics

Patient Characteristics	Number of patients	Percent
Patients assessed	112	100
Age, years		
65-69	24	21.4
70-74	35	31.3
75-79	29	25.9
80-84	16	14.3
≥ 85	8	7.1
Sex		
Female	57	50.9
Male	55	49.1
Marital status		
Married/lives with partner	74	66.1
Widowed	20	17.9
Single	8	7.1
Divorced/separated/other	10	8.9
Household status		
Lives alone	25	22.3
Lives with spouse/relative/partner	87	77.7
Accommodation		
Lives in own home	106	94.6
Lives with relative	1	0.9
Sheltered/Warden-assisted housing	5	4.5

3.4.2. Tumour demographics

Sixty seven (59.8%) patients underwent an elective laparoscopic resection and of these, 8 cases were converted to open procedures. Forty five (40.2%) patients underwent an open procedure and of these seven were emergency cases.

The most common sites of disease were rectum (24.1%), sigmoid colon (22.3%), caecum (21.4%) and recto-sigmoid (10.7%). The majority of tumours were adenocarcinomas. Details of tumour characteristics are shown in Table 3.4.

Post-surgical management plan

All new colorectal cancer patients were discussed in a multidisciplinary team (MDM) meeting. The management decision following surgery was recorded for each patient. Sixty seven patients (59.8%) were for routine surgical follow up alone. Forty five patients (40.2%) were referred for an oncological opinion. Following an oncology outpatient consultation, thirty patients (66.7% of patients referred, 26.8% of the entire study cohort,) were commenced on adjuvant chemotherapy. Fifteen patients referred for an oncological opinion did not receive chemotherapy. Their medical records were reviewed and reasons given were recorded.

Table 3.4. Colorectal tumour characteristics & surgical procedure

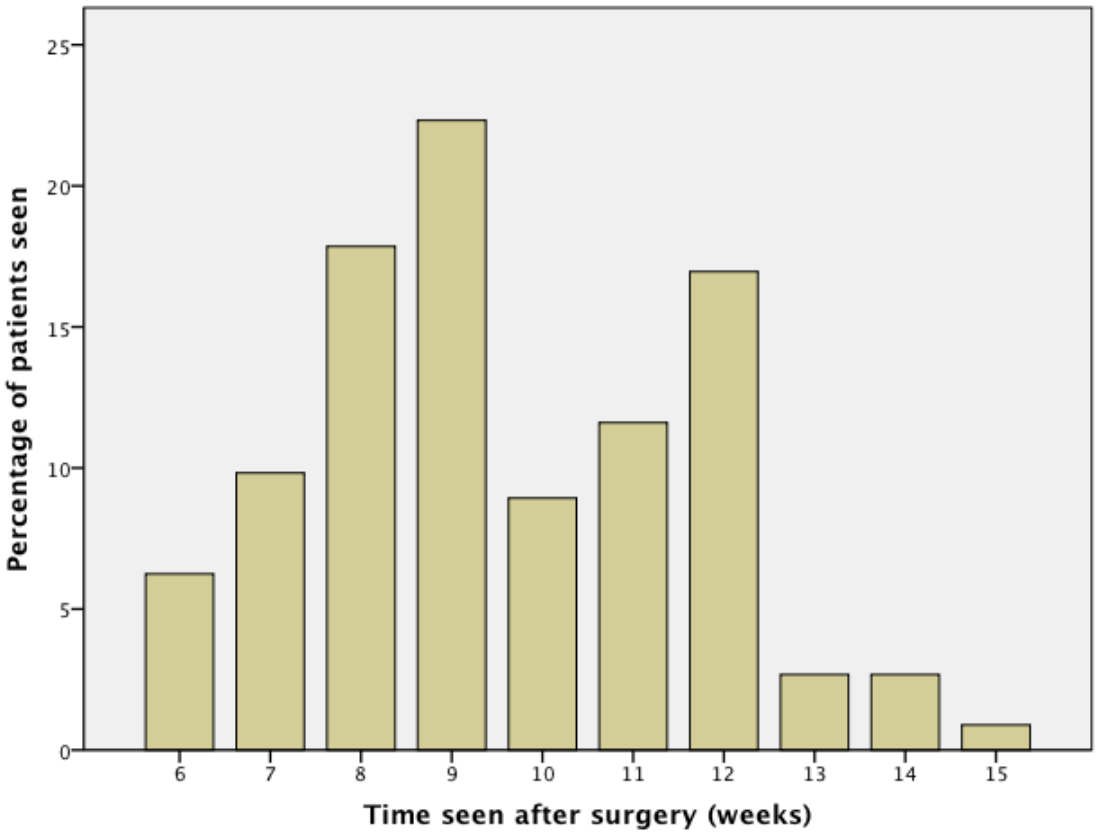
Tumour characteristics	Number of patients (Total n=112) (%)
Site	
Rectum	27 (24.1)
Recto-sigmoid	12 (10.7)
Sigmoid	25 (22.3)
Descending colon	1 (0.9)
Splenic flexure	3 (2.7)
Transverse colon	5 (4.5)
Hepatic flexure	3 (2.7)
Ascending colon	7 (6.3)
Caecum	24 (21.4)
Other	5 (4.5)
Histology	
Adenocarcinoma	103 (92.0)
Mucinous adenocarcinoma	8 (7.1)
Carcinoma	1 (0.9)
Differentiation	
Well	7 (6.3)
Moderate	87 (77.7)
Poor	18 (16.1)
Lymphovascular invasion	
Present	22 (19.6)
Suspicious	1 (0.9)
Absent	86 (76.8)
Unknown	3 (2.7)
UICC staging	
Stage I	21 (18.8)
Stage II	48 (42.9)
Stage III	43 (38.4)

Surgical procedure	Number of patients (%)
Elective	
Laparoscopic	59 (52.7)
Laparoscopic converted to open	8 (7.1)
Open	38 (33.9)
Emergency	
Open	7 (6.2)
Total	112 (100)

Time of baseline assessment

The aim of the study was to see patients for their baseline assessment from six to twelve weeks after their date of operation. The time at which patients were seen after surgery is shown in Figure 3.1.

Figure 3.1: A graph displaying the time (weeks) at which study patients were assessed after their operation date.



The median time from surgery when patients were assessed was 9 weeks (range 6 to 15 weeks). Seven patients were seen after the planned 12 weeks from surgery.

3.4.3. Baseline assessment results

In addition to a modified comprehensive geriatric assessment, ECOG performance status, VES-13 and G8 scores were also measured. A summary of the baseline assessment scores is displayed in Table 3.5 and 3.6:

Table 3.5: Study participants' Performance status, VES-13 and G8 scores at baseline assessment

Assessment tool	Number of patients	Percent %
Patients assessed	112	100
Performance status		
0	35	31.3
1	50	44.6
2	21	18.8
3	6	5.4
VES-13 score*		
<3	74	66.1
≥3	38	33.9
G8 score*		
>14	43	38.4
≤14	69	61.6

Note:

*VES-13 score ≥3 : increased risk of functional decline/death at two years (38).

*G8 score ≤14: predictive of failing a CGA (42).

Table 3.6: Study participants' scores in comprehensive geriatric assessment domains at baseline assessment

Assessment domain	Number of patients (Total n=112)	Percent% (100)
ADL		
ADL Dependent	16	14.3
No. dependent domains:		
1	12	10.7
≥2	4	3.6
ADL Independent	96	85.7
IADL		
IADL Dependent	39	34.8
No. dependent domains:		
1	16	14.3
2	12	10.7
≥3	11	9.9
IADL Independent	73	65.2
MNA		
At risk of malnutrition	47	42.0
Malnourished	2	1.8
No nutritional problems	63	56.3
Charlson score		
0	76	67.9
1	22	19.6
2	7	6.3
≥3	7	6.3
Frail		
Yes -frail	35	31.3
No-not frail	77	68.8
MMSE		
>25	109	97.3
≤25	3	2.7

Overall the numbers of patients in the five age groups (65-69, 70-74, 75-79, 80-84, ≥85) were small and too small to meet the criteria for statistical tests comparing test scores between the five age groups. Due to the small numbers, results are presented and analysed in two age groups – 65-69 years old and ≥ 70 years old.

Performance status scores:

Performance status (PS), as measured using the ECOG performance status scale (27) was recorded. Performance status was measured taking into account the patient's view on which defined score was most reflective of their activity levels and also the physician 's (JS) assessment. Therefore, it was a joint assessment on the part of the patient and assessor.

Performance status	<70 years old n=24 (%)	≥ 70 years old n=88 (%)	Total n=122 (%)
0	10 (41.7)	25 (28.4)	35 (28.7)
1	12 (50.0)	38 (43.1)	50 (44.6)
2	2 (8.3)	19 (21.6)	21 (18.6)
3	0 (0)	6 (6.8)	6 (5.4)

Table 3.7: Participants' PS scores at baseline, comparing 65-69 year old and ≥70 year old age groups.

PS scores were divided in two groups, those scoring PS 0 or 1 and those scoring PS ≥ 2. Cross tabulation between the two age groups and PS groups showed that a greater proportion of patients aged 70 and over (28.4%) scored a PS of 2 or greater compared to those aged under 70 years of age (8.3%). The chi-square statistic showed this to be statistically significant : $\chi 2 = 4.154$, p=0.042.

Vulnerable Elders Survey (VES-13) scores:

The distribution of scores across the study population is shown in Figure 3.2. The mean VES-13 score was 2.43, median 1.00 (range 0-10, SD 2.72).

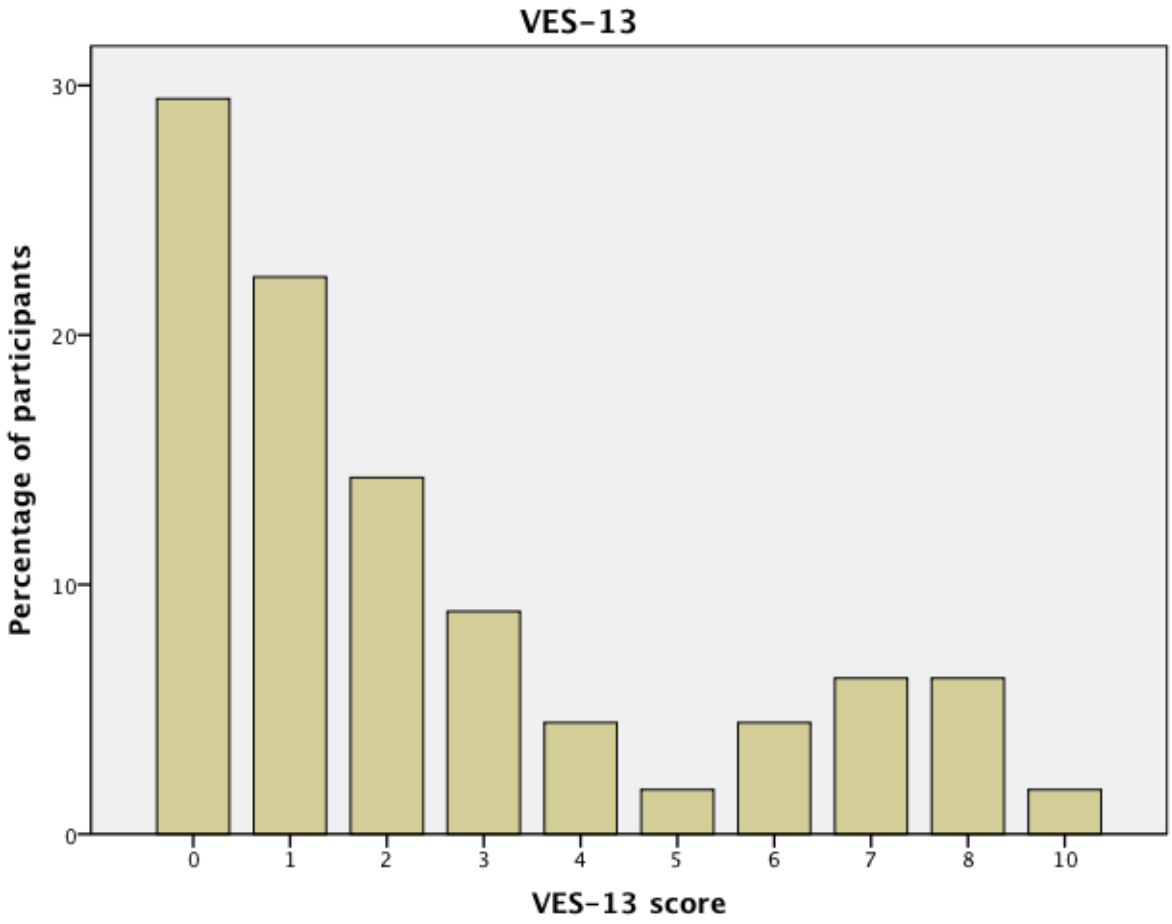


Figure 3.2: A graph displaying the range of VES-13 scores recorded in study participants.

Cross tabulation between patients 65 to 69 years of age and patients aged 70 and over, and the VES-13 cut-off scores showed that a greater proportion of participants aged 70 and over scored a VES-13 score of ≥ 3 compared to younger participants (40.9% v 8.3% respectively). The chi-square statistic showed this to be statistically significant: $\chi 2 = 8.927$, $p=0.03$.

G8 score:

The distribution of G8 scores across the study population is shown in figure 3.3. The mean G8 score was 13.24, median 13.25 (range 8-17, SD 2.23).

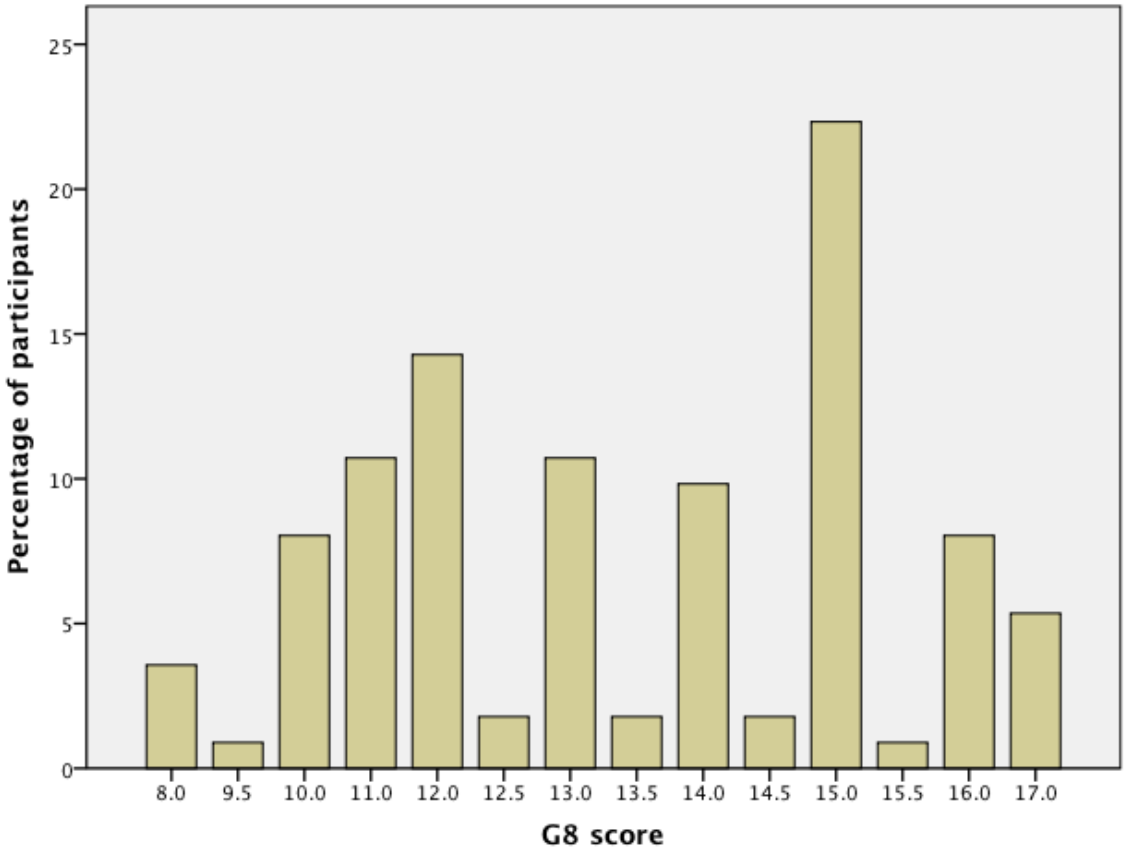


Figure 3.3: A graph displaying the range of G8 scores recorded in study participants

Comparing G8 cut-off scores between participants aged 65 to 69 years old and 70 and over, showed no statistically significant difference between the two age groups. 54.2% of participants aged under 70 scored a G8 score of 14 or less compared to 63.6% aged 70 and over ($\chi 2$= 0.715, p=0.398).

Modified comprehensive geriatric assessment:

A summary of the modified CGA scores is displayed in Table 3.6 (page 75).

Functional status:

ADL scores

Ninety-six (85.7%) of study participants were independent of all activities of daily living (ADL). Twelve participants (10.7%) were dependent in one ADL domain, three participants (2.7%) in two ADL domains and one participant (0.9%) was dependent in three ADL domains at initial assessment (Table 3.6).

Of the sixteen participants who were dependent on one or more ADL domain, fifteen were aged 70 or over. Overall, 95.8% of those aged under 70 were independent in all ADLs compared to 83.0% of participants aged 70 and over. Numbers in the groups were too small to enable valid statistical comparison.

IADL scores

Seventy-three participants (65.2%) were independent in all IADLs at baseline. Sixteen (14.3%) were dependent in one IADL domain, twenty-three (20.5%) were dependent in two or more IADL domains. A greater proportion of older participants (≥ 70 years old) were dependent on one or more IADL domain compared to younger participants: 39.8% aged 70 and over were IADL dependent; 16.7% aged under 70 were IADL dependent. The difference in IADL dependency between the age groups was statistically significant: $\chi 2= 4.436$, p=0.035.

Hand-grip strength

Thirty-five participants (31.3%) were classified as frail according to hand-grip strength. Cross tabulation comparing older and younger participants revealed a greater proportion of older participants (≥70 years old) were classed as frail compared to those under 70 years of age: 35.2% v 16.7% but the observed difference did not reach statistical significance ($\chi 2= 3.024$, p= 0.082).

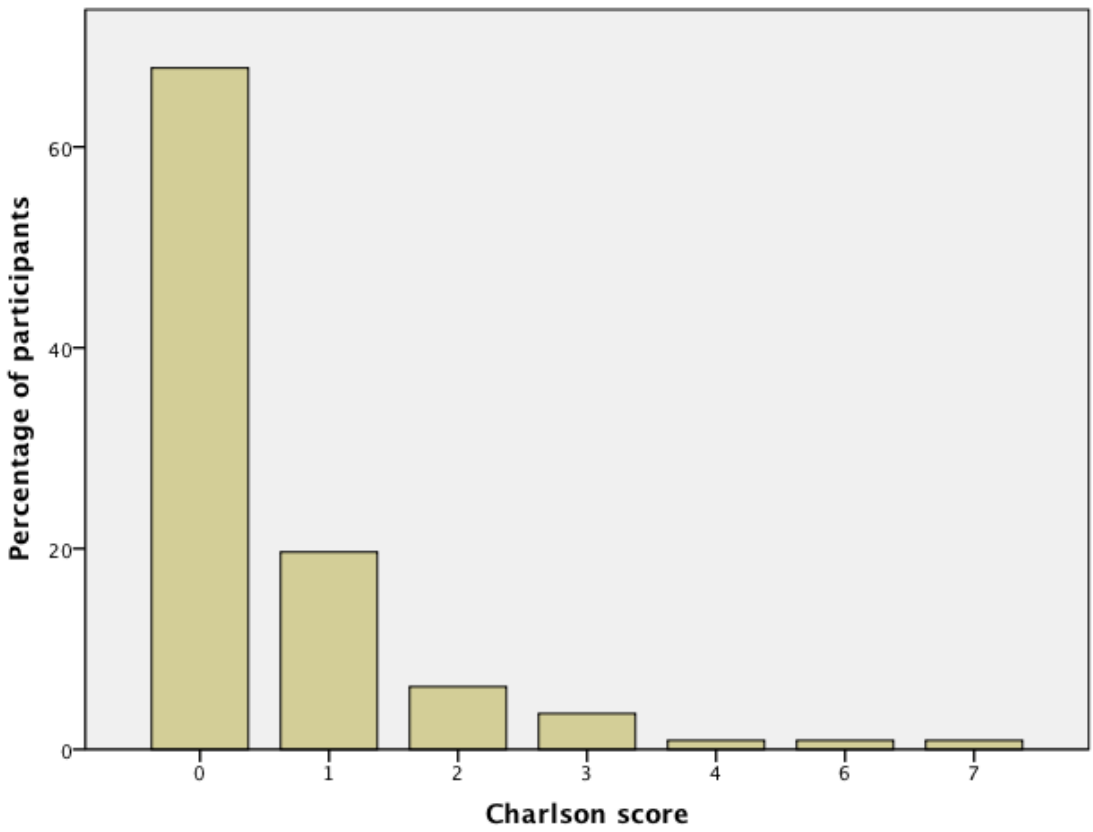
Nutritional status:

Patients' height and weight were measured and body mass index (BMI) calculated. Mean BMI was 27.1 (range 19.2-46.1, SD 4.567). The percentage of study participants classified as overweight or obese was 70.5%. The Mini-nutritional assessment tool (MNA®) measured nutritional status. 56.3% (63/112) of participants had no nutritional concerns, 42.0% (47/112) were identified as "at risk of malnutrition" and 1.8% (2/112) were malnourished according to MNA scores. A comparison of older and younger participants who were "at risk of malnutrition/ malnourished" to those with "no nutritional concerns" showed no significant difference between the two age groups ($\chi 2=0.054$, p= 0.816).

Charlson comorbidity score:

The presence of comorbidities was measured using the Charlson comorbidity score. The range of scores was 0-7 (mean 0.58, median 0.00, SD 1.160). The distribution of scores was skewed (figure 3.4).

Figure 3.4: The range of Charlson comorbidity scores in study participants



Seventy-six participants (67.9%) scored zero, twenty-two (19.6%) scored one and fourteen (12.5%) had a Charlson score of two or greater. A greater proportion of participants aged 70 and over had a Charlson score of ≥ 1 compared to those under 70 years of age (36.4% versus 16.7%) however the observed difference in Charlson score between the two age groups did not reach statistical significance ($\chi 2=3.354$, p=0.067).

Prescription medications:

The number of prescription medications was recorded as part of the G8 score. The median number of medications that study participants were prescribed was four (mean 3.86, range 0-17, SD 2.913).

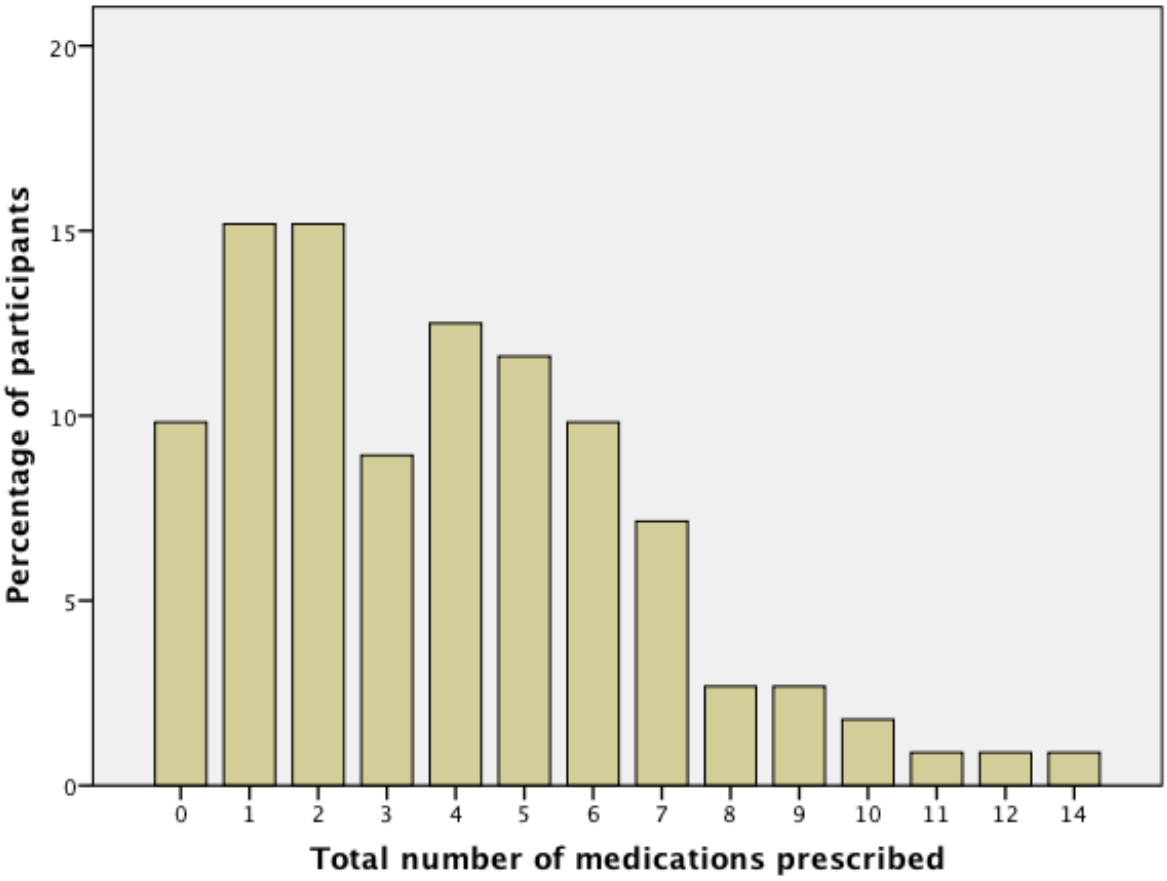


Figure 3.5: A graph displaying the number of prescription medications taken by study participants

Cognition:

The Mini-Mental State Examination (MMSE) scores ranged from 20.5 to the maximum score of 30. The distribution of MMSE scores was skewed and the median score was 30.0 (mean 29.268, SD 1.336).

Blood results:

Participants consented to having a sample of blood taken and the following blood tests were performed: Full blood count; Renal function; Liver function; B12 and folate; Thyroid function tests; Vitamin D levels and CRP.

Participants were recruited from three hospitals and all hospitals had slightly different normal ranges for each parameter measured. For comparison purposes, each blood result was coded into low, normal or high according to the normal range of the hospital laboratory that the sample was processed in.

A summary of the results is shown in Table 3.8

Fifty-eight patients (51.8%) had a haemaglobin (Hb) level that was below the normal range. The range of Hb results was 8.9 to 15.9 (Mean 12.3, SD 1.498)

Ninety patients (80.4%) had a serum creatinine that was within the normal range, fourteen patients (12.5%) had a raised serum creatinine. One hundred and six patients (94.6%) had normal liver function (ALT and ALP) and one hundred and ten patients (98.2%) had a serum albumin level within the normal range.

Thyroid function (as indicated by serum TSH levels) was normal in one hundred and three patients (92.0%). Four patients (3.6%) had low TSH levels and five patients (4.5%) had a TSH level above the normal range.

Serum B12 levels were within the normal range in one hundred and two (91.1%) patients and low in seven (6.3%) patients. Serum folate levels were normal in ninety-eight (87.5%) patients and low in two (1.8%) patients. Vitamin D levels

were normal in fifty-eight (51.8%) patients and below the normal range in fifty-four (48.2%) patients.

Table 3.8. Study participants' haematology and serum biochemistry blood results.

Blood test	n=112(%)			
	Normal	Low	High	Unknown/Missing
Haemaglobin	54 (48.2)	58 (51.8)	-	-
Total WBC*	105 (93.8)	3 (2.7)	4 (3.6)	-
Neutrophil	104 (92.9)	4 (3.6)	3 (2.7)	1 (0.9)
Lymphocyte	95 (84.8)	16 (14.3)	1 (0.9)	-
Creatinine	90 (80.4)	8 (7.1)	14 (12.5)	-
Albumin	110 (98.2)	-	2 (1.8)	-
ALT*	106 (94.6)	2 (1.8)	3 (2.7)	1 (0.9)
ALP*	106 (94.6)	-	6 (5.4)	-
CRP*	90 (80.4)	-	22(19.6)	-
TSH*	103 (92.0)	4 (3.6)	5 (4.5)	-
Calcium	103 (92.0)	8 (7.1)	1 (0.9)	-
Phosphate	102 (91.1)	5 (4.5)	5 (4.5)	-
B12	102 (91.1)	7 (6.3)	2 (1.8)	1 (0.9)
Folate	98 (87.5)	2 (1.8)	11 (9.8)	1 (0.9)
Vitamin D	58 (51.8)	54 (48.2)	-	-

*WBC= White Blood cell count, ALT= Alanine Transferase, ALP= Alkaline Phosphatase, CRP= C Reactive Protein, TSH= Thyroid Stimulating Hormone

Confounding factors

It was thought that operation type and the time at which patients were seen could be potential confounding factors.

Operation type:

Cross tabulation of the seven input variables to be used in the logistic regression model was performed versus operation type (open v laparoscopic). No statistical differences between the assessment score groups and the operation type were observed. The p values were as follows:

1. VES-13 group (<3 or ≥3) vs laparoscopic or open surgery, p=0.228
2. G8 group (>14, or ≤14) vs laparoscopic or open surgery, p=0.892
3. PS group (0,1 or ≥ 2) vs laparoscopic or open surgery, p=0.325
4. MNA group (at risk or not) vs laparoscopic or open surgery, p=0.489
5. Frail group (yes or no) vs laparoscopic or open surgery, p=0.818
6. Charlson score (0 or ≥1) vs laparoscopic or open surgery, p=0.426
7. Age group(<70 or ≥ 70) vs laparoscopic or open surgery, p=0.869

Timing of baseline assessment following surgery:

The input variables (VES-13 group, G8 group, PS group, MNA group (at risk of malnutrition/not at risk), Frail group (yes/no according to grip-strength), Charlson score and age group were each plotted against "time seen since operation" to explore whether there were any differences in distribution of scores. Box and whisker plots did not show any marked differences in distributions of the scores (within the two groups for each variable) according to the time at which patients were assessed following surgery.

(see tables and figures in APPENDIX N for reference).

3.4.4. Adjuvant chemotherapy patients

Following discussion at the colorectal multi-disciplinary meetings, sixty-seven study participants were for routine surgical follow up alone and forty-five participants were referred to an oncologist for consideration of adjuvant treatment. Thirty study participants, 26.8% of the total study population, went on to commence adjuvant chemotherapy. Fifteen patients referred to an oncologist did not receive adjuvant chemotherapy. The baseline assessment scores of these three groups of patients are shown in Table 3.9.

Medical records of the fifteen participants who did not receive adjuvant therapy were reviewed. In six cases, it was a joint decision between the patient and doctor to not undertake adjuvant chemotherapy. In three cases it was the patients' choice, in a further three cases it was the doctors' decision based on a documented overall minimal benefit of adjuvant treatment. Three patients were deemed unfit to undergo treatment based on the presence of co-morbid illnesses (two patients) or frailty (one patient).

The age range of the thirty patients who commenced adjuvant chemotherapy was from 65-80 years of age (mean 70.97, median 71.00, SD 4.255). Seventeen (56.7%) were female, thirteen (43.3%) were male. Four (13.3%) lived alone. Three patients (10%) had stage II and twenty-seven (90%) had stage III colorectal cancer.

Initially, twenty (66.7%) patients were commenced on Capecitabine and Oxaliplatin, nine (26.7%) on Capecitabine and one (3.3%) on Raltitrexed and Oxaliplatin. At the end of chemotherapy treatment the final regimen that patients were receiving, differed in a number of patients. Eleven (36.7%) patients were still receiving Capecitabine and Oxaliplatin. fifteen (50%) were receiving Capecitabine alone. Two (6.7%) patients were prescribed Raltitrexed and Oxaliplatin, one (3.3%) was on Raltitrexed alone and one had stopped Capecitabine after 5 days of treatment. This one patient did not continue treatment due to toxicity and

Table 3.9. Baseline assessment scores of study patients(N=112) who were for surgical follow up (n=67) or who were referred for and either received (n=30) or did not receive (n=15) adjuvant chemotherapy.

Assessment domain	Routine follow up only n=67 (%)	Received adjuvant chemotherapy n=30 (%)	Referred ,but did not receive adj. chemo n=15 (%)
Performance status			
0	21 (31.3)	8 (26.7)	6 (40.0)
1	28 (41.8)	17 (56.7)	5 (33.3)
2	17 (25.4)	4 (13.3)	0 (0.0)
3	1 (1.5)	1 (3.3)	4 (26.7)
VES-13 score			
<3	40 (59.7)	25 (83.3)	9 (60.0)
≥3	27 (40.3)	5 (16.7)	6 (40.0)
G8 score			
>14	20 (29.9)	15 (50.0)	8 (53.3)
≤14	27 (70.1)	15 (50.0)	7 (46.7)
ADL			
Dependent	7 (10.4)	6 (20.0)	3 (20.0)
Independent	60 (89.6)	24 (80.0)	12 (80.0)
IADL			
Dependent	25 (37.3)	8 (26.7)	6 (40.0)
Independent	42 (62.7)	22 (73.3)	9 (60.0)
MNA			
At risk of malnutrition	32 (47.8)	13 (43.3)	4 (26.7)
Not at risk	35 (52.2)	17 (56.7)	11 (73.3)
Charlson score			
0	46 (68.7)	23 (76.7)	7 (46.7)
1	13 (19.4)	5 (16.7)	4 (26.7)
2	4 (6.0)	1 (3.3)	2 (13.3)
≥3	4 (6.0)	1 (3.3)	2 (13.3)
Frail (handgrip)			
Yes-frail	26 (38.8)	5 (16.7)	4 (26.7)
No- not frail	41 (61.2)	25 (83.3)	11 (73.3)
MMSE			
≥26	66 (98.5)	29 (96.7)	14 (93.3)
<26	1 (1.5)	1 (3.3)	1 (6.7)
Age group			
<70 years	14 (20.9)	10 (33.3)	0 (0.0)
≥70 years	53 (79.1)	20 (66.7)	15 (100.0)
CRC Stage			
I	21 (31.3)	0 (0.0)	0 (0.0)
II	38 (56.7)	3 (10.0)	7 (46.7)
III	8 (11.9)	27(90.0)	8 (53.3)

stopped treatment herself. End of chemotherapy assessment scores were not obtained from this patient.

Seventeen (56.7%) patients did not complete the intended chemotherapy regimen. The reasons for stopping chemotherapy early or switching to an alternative regimen (eg if on Capecitabine and Oxaliplatin and continuing with Capecitabine alone) were due to toxicity of treatment. Details of chemotherapy regimens are displayed in Table 3.10.

At the end of chemotherapy treatment (within four weeks of administration of the last chemotherapy cycle), functional status was reassessed via telephone interview. Performance status, ADL and IADL scores were recorded and VES-13 score repeated. Results are displayed in Table 3.11 alongside baseline and year one scores.

In the study design, severe chemotherapy toxicity was defined as any of: grade III/IV toxicity (CTCAE version 3 criteria), dose reduction, unplanned hospitalization, treatment discontinuation or death within 30 days of treatment. According to this definition twenty-seven (90%) of patients experienced defined severe chemotherapy toxicity. The sample size is too small to analyse statistically whether any of the input variables (PS, VES-13, G8, Charlson co-morbidity, MNA score, age, grip strength) predict defined severe chemotherapy toxicity. Further recruitment is in progress and it is hoped that an increased sample size will enable further analysis to be undertaken.

Table 3.10 Chemotherapy regimens received and incidence of treatment completion, dose reductions and severe treatment-related toxicities

Details of chemotherapy treatment	Patient number (Total n=30)	Percent (Total=100%)
Initial regimen		
Capecitabine/Oxaliplatin	20	66.7
Capecitabine	9	26.7
Raltitrexed/Oxaliplatin	1	3.3
Regimen at end of treatment		
Capecitabine/Oxaliplatin	11	36.7
Capecitabine	15	50.0
Raltitrexed/Oxaliplatin	2	6.7
Raltitrexed	1	3.3
Stopped Cape after 5 days	1	3.3
Completed planned regimen		
Yes	13	43.3
No	17	56.7
Dose modification		
Yes	25	83.3
No	4	13.3
Missing	1	3.3
Treatment delay		
Yes	17	56.7
No	12	40.0
Missing	1	3.3
Grade 3/4 toxicities		
Yes	17	56.7
No	12	40.0
Missing	1	3.3
Unplanned hospital admission		
Yes	3	10.0
No	25	83.3
Missing/Unknown	2	6.7
Death within 30 days of treatment		
None	30	100
Study defined severe treatment-related toxicity		
Yes	27	90
No	3	10

Table 3.11 Functional assessment scores of patients who received chemotherapy at baseline, end of treatment and at one year

Assessment domain	Baseline assessment n=30 (%)	End of chemotherapy assessment scores n=30 (%)	Year One scores n=30 (%)
Performance status			
0	8 (26.7)	4 (13.3)	14 (46.7)
1	17 (56.7)	13 (43.3)	9 (30.0)
2	4 (13.3)	10 (33.3)	3 (10.0)
3	1 (3.3)	2 (6.7)	1 (3.3)
Missing	-	1 (3.3)	3 (10.0)
VES-13 score			
<3	25 (83.3)	16 (53.4)	19 (63.3)
≥3	5 (17.7)	13 (43.3)	8 (26.7)
Missing	-	1 (3.3)	3 (10.0)
ADL			
Dependent	6 (20.0)	2 (6.7)	4 (13.3)
Independent	24 (80.0)	27 (90.0)	23 (76.7)
Missing	-	1 (3.3)	3 (10.0)
IADL			
Dependent	8 (26.7)	11 (36.7)	8 (26.7)
Independent	22 (73.3)	18 (60.0)	19 (63.3)
Missing	-	1 (3.3)	3 (10.0)
Year One status			
Alive			28 (93.3)
Deceased			2 (6.7)
Functional decline or death at one year			
Yes			6 (20.0)
No			23 (76.7)
Missing			1 (3.3)

3.4.5. Year one follow up results

All patients were contacted one year on from baseline assessment. Patient and disease status, functional status (ADL/IADL scores), ECOG performance status, VES-13 scores and then rates of death and functional decline were recorded.

Patient and disease status

One hundred and six (94.6%) participants were alive (one of these was lost to follow up, no assessments could be undertaken as he was not contactable, but was known to be alive). Five participants (4.5%) had died. One participant (0.9%) was lost to follow up – he had moved out of the area and details on his current status were unknown. Ninety-seven (86.6%) of study participants were disease free at one year.

Five patients died within the first year. Three patients died due to colorectal cancer. Causes of death on the death certificate were: "carcinomatosis of the bowel"; "carcinomatosis of the caecum" and "bowel cancer". Two died at home, one in a hospice.
Two patients died due to cardiac causes. Cause of death on the death certificate were: "1a Left ventricular failure, Ib Left ventricular hypertrophy, Ic Ischaemic heart disease and hypertension"; "Ia Heart failure, Ib Aortic Stenosis, 2 Bowel cancer". One had died at home suddenly, one died in hospital.

Seven patients had documented recurrence of colorectal cancer. One patient had progressive metastatic prostate cancer.

Functional decline
Overall twenty three (20.5%) participants had functionally declined or died at one year. Eighteen had functional decline as defined previously, five had died.

Results are summarized in Table 3.12:

Table 3.12: Rates of functional decline, death and disease recurrence at one year follow up

Year One Results	Number of patients (Total n=112)	Percent %
Functional decline		
Yes (Functionally declined (Died	23 18) 5)	20.5
No	87	77.7
Lost to follow up	2	1.8
Disease Status		
Disease free	97	86.6
Recurrent colorectal cancer	7	6.3
Metastatic prostate cancer	1	0.9
Deceased	5	4.5
Lost to follow up	2	1.8

3.4.6. Data analysis

Primary Aim:

Does the VES-13 score predict functional decline or death, at one year, in older colorectal cancer patients?

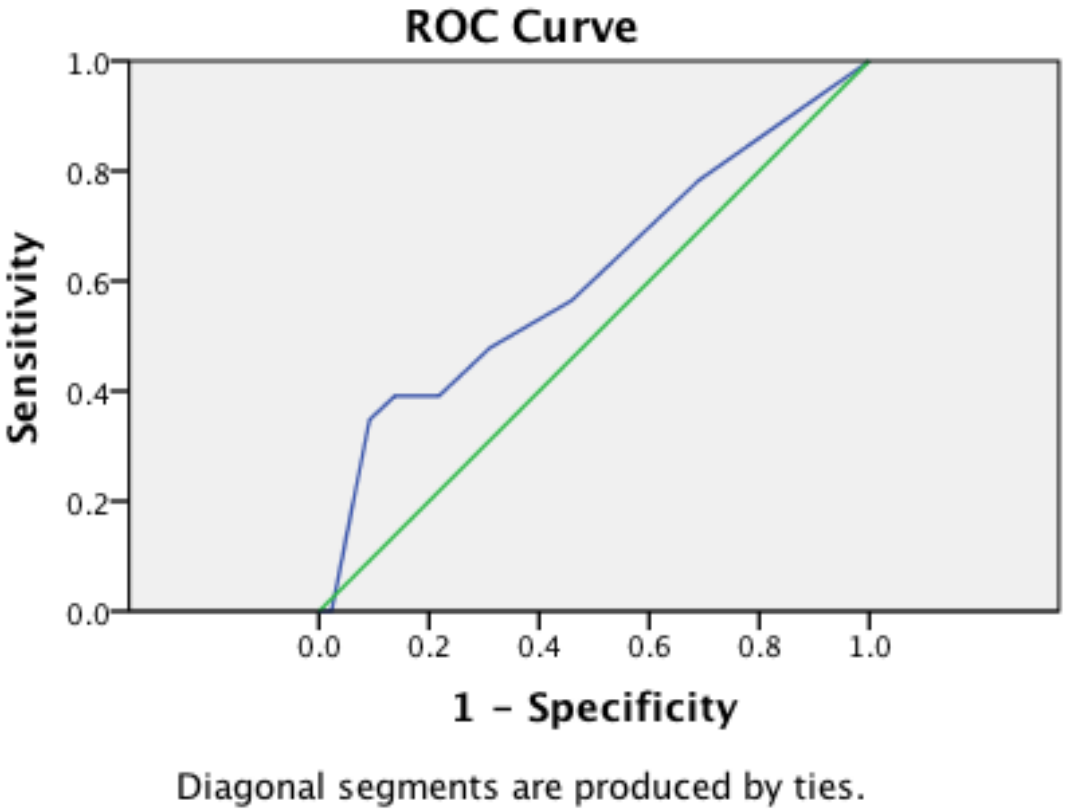
Of the one hundred and twelve study participants, twenty-three (20.5%) had functionally declined or died at one year. Crosstabulation of VES-13 score in the cut off groups (<3 and ≥3) and functional decline/death at one year is shown:

Table 3.13: Crosstabulation of VES-13 scores (<3 versus ≥3) versus functional decline at one year

	Functional decline or death at one year		
	No	Yes	Total
VES-13 <3	60	12	72
VES-13 ≥3	27	11	38
Total	87	23	110

A greater proportion of patients with a VES-13 score of ≥3, functionally declined or died at one year compared to the proportion of patients with a lower VES-13 score (28.9% versus 16.6%) . However the difference between the two groups did not reach statistical significance (χ^2 =2.268, p=0.132)

Figure 3.6: Receiver operating characteristic (ROC) curve to show VES-13 scores versus functional decline/death at one year



The area under the curve is 0.610 (95% CI 0.471-0.749).

Secondary Aims:

1. Does the VES-13 score predict for severe chemotherapy toxicity?

The number of patients who received adjuvant chemotherapy was small (n=30) and not adequate to perform a Chi-Squared test. The result of Fisher's Exact test was 1.000. Therefore, we were unable to reject the null hypothesis of no difference. Crosstabulation of VES-13 scores within the cut-off groups and severe chemotherapy toxicity is shown:

Table 3.14: Crosstabulation of VES-13 score groups (<3 vs ≥3) versus severe chemotherapy toxicity

	Severe chemotherapy toxicity		
	No	Yes	Total
VES-13 <3	3	22	25
VES-13 ≥3	0	5	5
Total	3	27	30

All patients with VES-13 scores ≥3 experienced severe chemotherapy toxicity compared to 88% of patients with VES-13 scores <3.

2. To ascertain if G8 score, PS, Age, Charlson co-morbidity index, MNA or grip strength predict for severe chemotherapy toxicity.

Due to the small sample size of patients receiving adjuvant chemotherapy it was not possible to undertake formal statistical analysis to investigate whether any of the above input variable predict for severe chemotherapy toxicity. However overall, twenty-seven patients (90%) experienced severe chemotherapy toxicity and observations which can be made are:

An almost equal proportion of patients with G8 scores above and below the cut off value of 14, experienced severe chemotherapy toxicity. All five patients who were of PS 2 or greater experienced severe chemotherapy toxicity. All six patients who were ADL dependent and all eight patients who were IADL dependent, experienced severe chemotherapy toxicity. Six out of seven patients with a Charlson score of 1 or greater and eleven out of thirteen patients who were at risk of malnutrition, developed severe toxicity. All five patients who were frail according to grip strength experienced severe chemotherapy toxicity.

The three patients who did not have any adverse side effects during chemotherapy were all under seventy years of age. They were all of PS 0 or 1, had VES-13 scores of < 3 and were independent of ADLs and IADLs.

3. To ascertain if G8 score, PS, age, Charlson co-morbidity index, MNA, or grip strength predict for functional decline or death at one year.

Firstly, logistic regression was carried out entering seven variables (VES-13, G8, PS, Age, Charlson score, MNA and Grip strength) in the model to predict the composite outcome of functional decline or death at one year. Five input variables were coded into binary outcomes with the "unfit" state coded as 1, the healthier state coded as 0.
i.e: VES-13: <3 or ≥3 (0 v 1), G8: >14 or ≤ 14 (0 v 1), Charlson score: 0 or ≥1 (0 v 1) , MNA: not at risk of malnutrition v at risk/malnourished (0 v 1), Grip strength: not frail v frail (0v 1). Age and PS were entered as continuous scale variables.

The results obtained are shown in Table 3.15

Table 3.15. Results of logistic regression model exploring if assessment scores are predictive of functional decline/death at one year (seven input variables)

Logistic regression – 7 input variables:

Variable	p-value	Odds Ratio (OR)	95% CI for OR Lower	Upper
Age	0.938	0.996	0.911	1.090
VES-13 Group	0.416	0.557	0.136	2.283
G8 Group	0.452	1.754	0.406	7.573
Charlson Group	0.203	1.992	0.689	5.760
Nutrition Group	0.762	0.812	0.211	3.127
Frail group	0.585	1.383	0.431	4.438
PS	0.027	2.339	1.104	4.956
Constant	0.466	0.086		

The sample size (n=112) is smaller than had been envisaged when the initial data analysis was planned. As age is measured in some way in both the VES-13 and G8 scores, it was decided to remove age as one of the input variables. The G8 score contains many of the questions that make up the MNA screening tool and so it was decided to omit the Nutrition group. Logistic regression was repeated with five variables (VES-13, G8, PS, Charlson and Grip strength). Four scores were recoded as binary variables as before, except PS which remained a continuous variable. The results obtained are shown in table 3.16.

Table 3.16 Results of logistic regression model exploring if assessment scores are predictive of functional decline/death at one year (five input variables)

Logistic regression- 5 input variables:

Variable	p-value	Odds Ratio (OR)	95% CI for OR Lower	Upper
VES-13 Group	0.352	0.529	0.139	2.021
G8 Group	0.471	1.514	0.491	4.670
Charlson Group	0.208	1.975	0.685	5.697
Frail Group	0.616	0.749	0.242	2.317
PS	0.023	2.370	1.124	4.999
Constant	0.270	0.149		

Table 3.16 shows that the only input variable that was predictive of the composite outcome of functional decline and death was performance status (PS), p=0.023 (95% CI 1.124-4.999)

Unplanned analysis:

1. Does the G8 score predict for failing a CGA?

Table 3.17: Crosstabulation of G8 scores (>14 vs ≤14) versus failure of a CGA (defined as a deficit in any ADL, IADL, nutrition or hand-grip strength domain)

	Failed CGA overall		
	Yes	No	Total
G8 score >14	16	27	43
G8 score ≤14	57	12	69
Total	73	39	112

A greater proportion of patients with a G8 score of ≤ 14 had deficits within the CGA compared to the proportion of patients with higher G8 scores (>14), 82.6% v 37.2%) and the difference between the groups was statistically significant, (χ^2 = 24.057 p=0.000).

3.5. Discussion

In the United Kingdom the use of a comprehensive geriatric assessment (CGA) in any format in oncology practice is not current standard practice. However, the majority of cancer patients are older and in an increasingly ageing population, the numbers are forecast to increase considerably over the coming years. This study has investigated the use of certain assessment and screening tools such as the VES-13 survey and G8 questionnaire in addition to other previously validated assessments already used within a geriatric assessment, in an older population of colorectal cancer patients.

One hundred and twelve patients who had undergone surgery for localized colorectal cancer were assessed and the positive response rate to postal invitations to the study was good (64.6%). The number recruited in the study time period was less than had been hoped and so the sample size did not reach the figure required from the statistical power calculations for the primary study aim, however interesting observations can be made from the results and further recruitment is ongoing.

Colorectal cancer is common in both men and women, the overall male: female ratio in the UK is 11:10 (144). In this study an almost equal number of men and women participated. The age range of study participants was wide – sixty-five to ninety years old. The majority (78.6%) were aged seventy and over and 21.4% were aged eighty or older. The study population was felt to be representative of older colorectal cancer patients. Most people lived in their own home, two-thirds were married and twenty-five participants (22.3%) lived alone.

Surgical resections of bowel tumours were predominately performed electively, 6.2% of patients had emergency procedures. Older patients tend to present late and the incidence of emergency surgery is often higher in older patients compared to younger patients at presentation (153). The availability of laparoscopic procedures varied across our cancer network at the time of recruitment, and so the rate of laparoscopic resections recorded is less than may otherwise be expected.

Adenocarcinoma is the commonest histopathological sub-type of colorectal cancers and 92% of study participants were diagnosed with colorectal adenocarcinomas and over three-quarters of all tumours (77.7%) were graded as moderately differentiated. The most common stage at diagnosis was Stage 2 (42.9%) followed by Stage 3 (38.4%) and Stage 1 (18.8%).

After patients had consented to take part in the study, the baseline assessment was undertaken at a time and place that was convenient for the patient. The study aim stated that patients would be assessed within three months of the date of their operation. The median time of assessment was in the ninth week. In seven cases, due to patient choice or re-scheduling due to adverse weather, the baseline assessment occurred after the planned twelve weeks. Ideally, all patients would have undergone the assessment within a similar time period.

The operation type and the time at which patients underwent the baseline assessment were identified as potential confounding factors. Patients who underwent laparoscopic surgery may have shorter recovery times and functional scores may be better compared to patients who have had an open procedure and for example, those seen at eleven weeks post-op may be fitter and functionally better than those seen at seven weeks post-op. Cross tabulation of the seven baseline input variables used in the logistic regression model (VES-13, G8, PS, MNA, Grip strength, Charlson score, and age group) did not reveal any statistical difference between assessment score groups and the operation type (laparoscopic v open). There was also no difference in the distribution of assessment scores between cut-off groups, according to time seen since surgery, i.e. it did not follow those patients seen after longer time interval since surgery scored better.

Baseline assessment scores:

In clinical practice, oncologists assess patients' performance status (PS) and use this to inform their decision making process. In older patients, the performance status scales commonly used, may provide an over estimate of their functional status (29). In this study, performance status was measured taking into account patients' self-assessment (i.e. which definition of PS they felt best applied to them)

and the assessor's own assessment. Three-quarters of study subjects were of good PS i.e. zero or one. The proportion of patients who scored a PS of two or greater was greater in those aged seventy or older and the difference between the two age groups was found to be statistically significant (p= 0.042).

In studies of the VES-13 survey, a cut-off score of 3 or greater has been shown to be predictive of functional decline or death at 2 years (38). In this study population, 33.9% participants recorded a VES-13 score of ≥ 3. Cross tabulation of scores between the two age groups showed there to be a significant difference in scores between participants aged sixty-five to sixty-nine years and over seventy years old (p=0.03). However, the VES-13 score includes a score for age (one point if 75-84 years old, three points if ≥85 years old) and this may contribute to the difference in scores between the two age groups.

Exploratory studies have proposed that a G8 score of 14 or less is predictive of failing a comprehensive geriatric assessment (42, 43) In this study; sixty-nine participants (61.6%) scored a G8 score of 14 or less. Age is also taken into account in the G8 score (two points if < 80 years old, one point if 80-85 years old and zero points in >85 years old). However, when comparing scores between those under and over seventy years old, no significant difference in G8 scores was seen between the two age groups (p=0.398). This finding was surprising, given the median age of the study population.

Functional status was assessed through measuring activities of daily living (ADL), instrumental activities of daily living (IADL) scores and hand-grip strength. The ADL score assesses basic functions such as washing, dressing, eating and toileting and is a more useful score in the inpatient setting. In the outpatient setting, the majority of oncology patients are likely to be independent in all ADLs and this was reflected in the results seen in this study population where 85.7% of participants were independent in all ADLs.

The IADL score measures eight activities: shopping, housekeeping, meal preparation, laundry, transport use, prescription medication use, managing of personal finances and using the telephone. All these activities are important to lead

an independent life in the community. The IADL score was designed in the 1960s and is commonly used to assess older patients' functional ability in geriatrics (45). In oncology, some of these questions may be asked when determining a patient's performance status but the IADL score is not formally recorded. Care needs to be taken when recording the IADL score as some subjects, particularly men, could be "over scored" as dependant, if they were married and relied on their wife to do many of the IADL tasks. In this study, participants were scored as dependent in an IADL domain if they were dependent for health-related reasons. If participants were in a couple, some of the IADL domains were shared between the couple and this was particularly so if the study participant was male. For example, on questioning male participants, the laundry domain and meal preparation was often not relevant as "the wife does all that". However, on further questioning, it was not because they were not capable and often they would undertake specific housekeeping tasks or other jobs such as upkeep of the garden instead. Many would also indicate that they could do a specific IADL activity if they "had to". One of the domains relates to the administration of medication. If a participant was not on any medication, they could be inadvertently scored as "dependent" as none of the responses were appropriate. Therefore, if only a total IADL score out of 8 was recorded, many participants could be deemed, incorrectly, to be IADL dependent. It was decided to score patients only on relevant IADL domains, record if they were dependent in any relevant IADL domain (yes/no) and the total number of dependent IADL domains.

Hand-grip strength was assessed as an objective measure of participants' fitness and functional ability. Nearly one-third (31.3%) were classed as frail when their highest hand-grip score was adjusted for age, sex and body mass index (26). Hand-grip strength was used as it was easy and quick to measure alongside the other assessments and prior research in non-cancer populations has shown it to be predictive of all-cause mortality (54) .

Nutritional status was measured using the Mini-nutritional assessment tool (MNA) as this tool has been validated in elderly patient populations in many studies. Body mass index (BMI) was measured, as part of the MNA assessment and BMI is included in the G8 score. Obesity is a risk factor for many cancers, including

colorectal cancer, and the percentage of patients in this study classified as overweight or obese was 70.5%. In cancers of the gastrointestinal tract, due to symptoms and during the post-operative recovery period, food intake and absorption may be impaired. Within three months of curative surgery, 42.0% of participants were identified as being at risk of malnutrition and two participants (1.8%) were malnourished. Nutritional status may not be formally assessed, especially in overweight patients, but it is important to advise patients accordingly as this will help aid their recovery and benefit their future health.

The presence of comorbidities was measured using the Charlson comorbidity score. The distribution of scores was highly skewed, with around two-thirds of patients scoring zero. Similar distributions of Charlson comorbidity scores have been recorded in others studies of cancer patients (64). Oncologists use information on comorbid illnesses from patients' past medical histories to inform decision-making. Only specific illnesses and criteria are scored in the Charlson co-morbidity index and some factors which oncologists perceive to be important in enabling patients to tolerate systemic therapies are not scored. This may mean that the Charlson score is not as informative and helpful as a comorbidity score could be. In this study population, patients had been deemed fit to undergo surgery and so very frail patients with significant co-morbidities would have not been included in potentially eligible participants.

The number of prescription medications was incorporated in the G8 score (a score (zero) was attributed if a patient was taking more than three medications) and so a record of the total number of prescriptions medications that study participants were prescribed was collated. The median number of medications was four which is considerable and many patients were taking a larger number than this. This was not reflected in the co-morbidity score, as common conditions such as hypertension and hypercholesterolaemia were not included. Polypharmacy may affect renal and hepatic function reserve and potential interactions with cytotoxic chemotherapy may need to be considered, particularly in the older cancer patient population (159).

Cognition scores recorded in the mini-mental state examination (MMSE) were high. This is unsurprising as patients were approached by letter and had to be able to read, understand and return a signed consent form independently, to indicate that they were willing to take part in the study. This would require a certain level of mental ability and patients with poor literacy skills or lower mental ability may be over-represented in non-participants.

Chemotherapy patients

Thirty study participants (26.8%) commenced adjuvant chemotherapy. The numbers are small and so one should be cautious when comparing groups, but as might be expected, their assessment scores were more favourable compared to the remaining study population. A higher proportion of patients were of good performance status (0 or 1) and below the cut-off scores for VES-13 and G8 scores. Functional scores were also generally better but a slightly higher proportion of patients were ADL dependent in the chemotherapy group (6/30 chemotherapy patients) compared to the participants who were for surgical follow up only (7/67 patients) which is surprising (see table 3.9). In the six patients receiving chemotherapy who were ADL dependent, five of them were dependent due to incontinence alone. After measuring hand-grip strength, a larger proportion of chemotherapy patients were classed as not frail (83.3%) compared to patients who were referred but did not receive chemotherapy (73.3%) and patients on routine follow up alone (61.2%) Nutrition and cognition scores were comparable and overall comorbidity scores were lower in the chemotherapy group.

Twenty-five (83.3%) patients required a dose modification, seventeen (56.7%) had at a treatment delay and the same number did not complete the intended chemotherapy course. Seventeen (56.7%) had a severe (Grade3/4) chemotherapy toxicity, three (10.0%) had an unplanned hospital admission whilst on treatment. There were no deaths within thirty days of chemotherapy treatment. Overall 90% of patients experienced the study's definition of severe chemotherapy toxicity. The majority of older patients who received adjuvant chemotherapy for their colorectal cancer required a medical intervention (dose reduction, alteration to drug

combination), over half experienced a severe side effect and three patients (10%) required admission to hospital during the treatment period.

Within four weeks of the last cycle (day one) of chemotherapy, functional assessment was reassessed and scores are shown in table 3.11. Patients' performance status scores tended to increase (ie worsen), IADL dependency increased marginally and a greater proportion of patients had VES-13 scores ≥3 compared to baseline. Interestingly, ADL scores improved with four patients becoming independent in ADLs by the end of chemotherapy treatment. In one patient, the assessment was undertaken twelve weeks after the last cycle of chemotherapy. Chemotherapy had been stopped early due to severe side effects, but the computer chemotherapy prescribing system indicated that the patient was still receiving chemotherapy. (This patient's functional scores would have been much worse if they had been recorded within four weeks of the last (second) cycle of treatment as they experienced severe side effects and required hospital admission).

Overall, forty-five patients were referred for an oncological opinion of which fifteen did not proceed with treatment for a variety of reasons. The benefit of chemotherapy in stage II colorectal cancer patients is small and evidence not conclusive for older patients (149, 160, 161) and so this may explain the higher proportion of stage II patients in the group that did not receive treatment. In the majority of cases the decision not to proceed with treatment was based on the minimal benefit that would be achieved and this was agreed jointly between the patient and doctor. In three cases, there was clear documentation that the patient's poor general fitness was the reason for declining chemotherapy.

Year one follow up

At one year, 94.6% of study participants were alive. Two patients were un-contactable and so follow-up assessments could not be completed (one patient was confirmed to be alive and one patient had moved out of the area). Five patients had died. In three cases the cause of death was colorectal cancer and two patients died due to cardiac causes. Functional decline was defined as " a change from no IADL

or ADL disability to any IADL or ADL disability, an increase of two or more in the total count of IADL or ADL disabilities, or new admission to a nursing home" (38). Eighteen patients had functionally declined at one year. The rate of the composite outcome of functional decline and death at one year was 20.5% (23/112 patients).

The primary aim of the study was to ascertain whether the VES-13 score predicted for functional decline or death at one year in older colorectal cancer patients. A greater proportion of patients with a VES-13 score above the cut-off value, functionally declined or died compared to patients with a favourable VES-13 score but the difference between the groups was not statistically significant (p=0.132). Saliba et al determined that older (aged sixty five and over) community dwelling people with a VES-13 score of three or greater had 4.2 times the risk of functional decline or death over a two-year period. The VES-13 score has not been validated for predicting functional decline at one year and this study was unable to establish this. This may be for a number of reasons which include an insufficient sample size (the study is currently underpowered) and that the VES-13 score may not be able to be used to accurately predict functional decline at one year (instead of the validated two year time period).

Secondary aims included whether VES-13 and other assessment tools could predict severe chemotherapy toxicity and whether a combination of baseline assessment scores could predict functional decline at one year. As the number of patients who received adjuvant chemotherapy was small, formal statistical analysis was not possible. It was noted all five out of the thirty patients in the chemotherapy group who had VES-13 scores ≥3, all experienced severe chemotherapy toxicity. However, the overall rate of defined treatment-related toxicity was high at 90% and many patients with low VES-13 scores also experienced severe toxicity. It was noted that many chemotherapy patients with poorer baseline assessment scores experienced severe chemotherapy-related toxicity. The three patients who did not experience any of the treatment-related adverse events were all under seventy years of age, of PS 0 or 1, VES-13 score <3 and independent in all ADLs and IADLs. In this discussion, patterns have been commented on but a larger sample size would help establish if any specific one or

combination of assessment tools may be informative in predicting the likelihood of patients experiencing adverse events whilst on chemotherapy treatment.

Logistic regression was performed as part of the planned data analysis to explore if any of the seven input variables of VES-13, G8, performance status, Charlson score, MNA score, grip strength and age predict for functional decline at one year. In this model, the performance status score was significant (p=0.027) and for every one point increase in performance status score, the risk of functional decline increases by 2.34 (95% CI 1.10-4.96).
It was thought that there were a large number of input variables for the sample size. Age is taken into account in the VES-13 and G8 scores and many questions in the MNA are included in the G8 score. Logistic regression was repeated with age and nutrition group removed. A similar result was obtained and performance status was found to be the only positive predictor of functional decline in this study population p=0.23, Odds ratio= 2.37 (95% CI 1.12-4.99).

An unplanned analysis was performed to explore whether the G8 score was predictive of patients failing a CGA. Patients were defined as having "failed" a CGA if they had recorded deficits in any of these four domains: ADL (dependent v independent); IADL (dependent v independent); Nutritional assessment according to MNA (at risk of malnutrition/malnourished v no nutritional concerns) and hand-grip strength (frail v not frail). Crosstabulation of the G8 score in cut-off groups (>14 or ≤14) versus CGA failure showed that a significantly greater proportion of patients with low (≤14) G8 scores had failed a CGA compared to those with G8 scores >14, 82.6% v 37.2%, and the difference was statistically significant, p=0.000.

Study limitations

There were limitations in this study, some of which have already been alluded to in previous sections. Patients were approached via postal invite. This may have prevented patients with literacy problems or certain disabilities from having the opportunity to take part. Eligible patients were only sent a letter if the researcher (JS) had confirmed with the key worker that the patient was suitable to approach.

This was to ensure that only patients who knew their diagnosis were approached, so as not to cause distress, and therefore "eligible" patients were not sent invites if this fact could not be confirmed. After consultation with key workers, some potential patients were not approached if they suffered from severe dementia, had had a stormy post-operative recovery or if the key worker felt that that particular patient would be unduly distressed by being sent a study invite. The time that patients were seen after surgery for the baseline assessment was variable and this was in part due to the time taken to establish patients' final diagnosis. Post-operative pathology and final staging were discussed within the multi-disciplinary meetings and the time when this review occurred varied across the three hospitals. In some cases invite letters could not be sent out until patients had been seen for their follow up outpatient appointment. This made it impossible to plan to see and assess all patients at the same time point after surgery.

If resources had allowed, many of these issues could have been addressed if the study researcher had approached patients pre-operatively, or if members of the team looking after the patients had discussed the study and given written information to be considered on discharge from the hospital. A full comprehensive geriatric assessment can take up to two hours and so a selection of tools were chosen to cover as many assessment domains as possible in a reasonable amount of time. In the study, the assessment process could be completed in half an hour but in frailer patients it would take longer. Some domains were not formally assessed. Depression is prevalent in the older population and this could have been formally assessed using a tool such as the geriatric depression scale (GDS). Cognition was measured using the MMSE and subtle deficits may not have been detected. Alternative tests of cognition may have been more informative but would have increased the total assessment time considerably.

The number of patients who received adjuvant chemotherapy was smaller than expected (n=30) and the rate of defined severe chemotherapy toxicity was high (90%). This may be representative of older patients who receive chemotherapy or the definition of severe chemotherapy toxicity may have been too broad and a more specific definition should be explored.

The sample size of one hundred and twelve was not large enough to satisfy power calculations for the study aim. Recruitment is continuing and further statistical analysis will be repeated when the target recruitment number is achieved.

3.6. Summary and areas for future work

Presently, the use of a comprehensive geriatric assessment (CGA) in oncology practice is not standard practice. A full CGA is time-consuming and not feasible for oncologists to incorporate into an already time-pressured clinic (35). A CGA assessment can take up to 2 hours (162) with additional time required for interventions. If patients were able to complete the majority of questionnaires themselves, with minimal assistance from health professionals, that would reduce cost and assessment time and this could be explored in other research studies.

Performance status is a quick assessment tool that many oncologists use. In this study population, a higher performance status score was associated with an increased risk of functional decline at one year. If scored by the patient and physician together, performance status may be sufficient. The performance status scale does not formally assess important domains such as nutritional concerns or instrumental activities of daily living. Deficits in these domains affect patients' ability to tolerate and complete cancer treatments. If deficits were identified in areas assessed as part of a CGA, in geriatrics, interventions would be employed to address the deficits and support the patient. The assessment process would then be repeated after a time to assess the effectiveness of the intervention(s). The feasibility and usefulness of this approach could be explored in a population of cancer patients. However, a screening tool that identifies vulnerable older patients who require further assessment, who are likely to be at high-risk of experiencing severe treatment-related toxicities and who may benefit from specific interventions, would be useful and more feasible to implement in an oncology environment. In this study population the G8 score looks to be promising. It takes less than five minutes to score (JS experience). The G8 screening score was found to be predictive of patients failing a CGA, and who would require a full CGA assessment. Further studies are needed to validate the tool and to explore whether it could identify patients who are more likely to develop treatment-related toxicities.

Chapter Four

4. Global health measures and tolerance of cytotoxic chemotherapy

4.1. Introduction

Oncologists often have the difficult challenge of weighing up the risks versus the benefits when planning the chemotherapy treatment of cancer patients. Chemotherapy regimens for various tumour types, particularly in the adjuvant setting, confer small overall survival benefits. In the palliative setting, the response rates of some chemotherapy regimens are variable. In many situations, the risks of significant treatment-related toxicity may be deemed to outweigh the benefits of treatment by the treating physician and/or the patient.

In terms of chemotherapy toxicities, it is difficult to predict which patients are likely to get side-effects, and this is a significant issue in the older population who are particularly vulnerable to treatment-related toxicity (including treatment-related death). Presently, the decision to proceed with cytotoxic treatment is based on the physician's assessment of risk taking into account patient factors such as co-morbid illnesses, performance status, age and disease factors such as high- risk pathological features and tumour stage. These factors should be discussed with individual patients and a management plan agreed. The process can be subjective and decisions made can vary according to the treating oncologist and individual patients' views and perceptions of risk and benefit.

Older patients may be at particular risk of developing treatment related toxicities compared to younger patients for a variety of reasons:

1.**Comorbidities**: Co-morbid illnesses are more common in people aged sixty five and over. On average this age group have three diagnosed medical conditions (17). The presence of co-morbidities may affect their fitness to undergo cancer therapies.

2. **Polypharmacy:** Older patients with comorbidities are likely to be prescribed a number of medications for primary and secondary prevention. The risk of adverse drug reactions increases with increasing number of medications taken (163). Older

cancer patients are also more likely to require medications to treat side effects of other drugs (159).

3. **Physiological reserve:** Physiologically older patients also differ compared to younger patients. Their bone marrow reserve is often reduced, renal function may be impaired and hepatic enzyme function altered (164). Age-related changes in body composition, drug absorption, metabolism and excretion may affect drug pharmacokinetics (164). Older patients' ability to tolerate stressors such as chemotherapy may therefore be reduced. Some of these factors can be measured and identified in pre-treatment blood tests but it is not possible to identify or predict those patients who have "normal" baseline blood parameters but reduced reserve and so are vulnerable to developing a range of side effects.

4. Functional status: Functional status is another factor that one might hypothesize affects older patients' ability to cope with treatment. A cancer diagnosis has been associated with increased presence of functional limitations (dependency in ADLs and IADLs), vulnerability and frailty (165).

Whilst in some cases the existence of such factors which may predict poor tolerance is obvious, this is not always the case. The objective assessment of health status may be useful in predicting risk of toxicity. A number of assessment tools have been developed by geriatricians in order to provide global measures of health in older patients, but the domains included (such as nutrition and functional status) are also likely to be relevant to all patients with cancer, irrespective of age. In an ideal world one could consider conducting a full CGA, but this may not be practical in day to day clinical practice. A CGA requires the supervision of a health professional and a shorter assessment process using specific questionnaires that rely on patient self-completion would be advantageous.

Potential alternative assessment tools are explored in this study. The G8 score (0-17) measures functional status, nutrition and symptomatology. A G8 score of </= 14 has been shown to be predictive of failing a comprehensive geriatric assessment (42, 43) The VES-13 is a questionnaire that measures functional capacity. The 13-item scoring system covers age, self-rated health, limitations in physical function, and functional disabilities, and a score of 3 or greater is

predictive of death and functional decline in older patients (38). The ECOG/WH0 performance status is a 5 point scale (0-4) describing day to day levels of activity, and is routinely used in oncology clinical practice (27) (see chapter 1).

We hypothesized that these abbreviated global measures of health and fitness may also be predictors of how well patients tolerate chemotherapy. If so, one or more of these tools may provide a subjective measurement that helps inform the physician and patient decision-making process. If it were possible for patients to complete these questionnaires themselves, it would be an added advantage in a time pressured outpatient environment.

4.2. Aims

Primary:

To ascertain if the G8 score predicts severe chemotherapy toxicity defined as: grade III/IV toxicity (CTCAE version 3.0 criteria (157)), dose reduction, unplanned hospitalization, treatment discontinuation, or death within 30 days of treatment.

Secondary:

(i) To ascertain if the VES-13 score (≤ 3 vs >3) or WHO PS (0,1 vs >/=2) predict severe chemotherapy toxicity (defined as above).

(ii) To compare the sensitivity and specificity of G8, VES-13 and WHO PS scores as diagnostic tests in predicting risk of chemotherapy toxicity.

(iii) To measure patient co-morbidities using two assessment tools (Charlson Comorbidity Index and ACE-27 score) and to ascertain if either score predicts severe chemotherapy toxicity.

4.3. Methods

Study Design

Prospective cohort study

Study population

Patients referred for cytotoxic chemotherapy at the hospitals of the Sussex Cancer Network: Brighton and Sussex University Hospital, Worthing and Eastbourne District General Hospitals. The recruitment target was of five hundred patients, aged eighteen and over, with a minimum of one hundred patients aged seventy or over. In this thesis, data on older patients (aged sixty-five and over) has been analysed. A number of studies use the age of seventy and over as a cut-off age for older patients so the data from this study has been analysed in two age groups, sixty-five to sixty-nine years old versus seventy years old and over.

Inclusion criteria

Patients aged eighteen years old and over.
Diagnosed with cancer.
Planned to be treated with a new course of cytotoxic chemotherapy, in any treatment setting.
Patients able to provide informed consent.

Exclusion criteria

Patients unable to give informed consent.
Patients with a life expectancy of less than eight weeks.
Patients due to receive targeted (non-cytotoxic) therapy.
Patients who are part way through a chemotherapy course.

Study conduct:

Patients who were attending prior to commencement of a new course of chemotherapy were given a letter of invitation (Appendix O). This was posted with the information for their chemotherapy information session that they attend with

the nurses prior to commencing the first cycle. Patients who were interested could then open the study envelope which contained the patient information sheet (Appendix O) Those interested were asked to sign a consent form (Appendix O) and patients who provided written informed consent were asked to fill in baseline questionnaires: ECOG performance status, VES-13 and G8 (APPENDIX P). They returned completed forms in an envelope to the cancer department.

Patients then received chemotherapy as part of normal care. Height and weight and other baseline tumour and demographic data were recorded from the chemotherapy records and patient notes. Data regarding adverse outcomes were recorded from the electronic chemotherapy prescribing system, supplemented by review of the medical records. Severe chemotherapy toxicity was pre-defined as any of the following: toxicity (grade III/IV by CTCAE version 3.0 criteria), treatment delay, chemotherapy dose reductions, death within thirty days of chemotherapy administration and unplanned hospitalization.

In the G8 score, one of the questions asks about mental well-being and whether the patient suffers from mild or severe depression or dementia. This question was not included in the questionnaires posted out as it was felt that the question may distress some patients. Details regarding patients' mental status were obtained from medical records in order to calculate the total G8 score. Comorbidity scores were recorded from the patient's medical records using the Charlson and ACE-27 comorbidity scales (APPENDICES F,G). The patient's GP was informed of their involvement in the study.

Ethical approval was obtained from the local ethics committee, REC reference number 09/H1107/60. Data was recorded and analysed using Microscoft Excel and Access Databases and statistical package SPSS Version 18.0.

4.4. Results

Seven hundred and fifty questionnaires were sent out to patients of all ages receiving chemotherapy; of these five hundred and thirty three were returned (response rate 71.1%). At the time of data analysis for this thesis, five hundred and six replies had been received and of these two hundred and two were from patients aged sixty-five and over. Of the responses from patients aged sixty-five and over, seventeen patients' questionnaires were excluded from data analysis. They did not meet study inclusion criteria as patients were on targeted, non-cytotoxic chemotherapy or completed study questionnaires mid-way through chemotherapy (as indicated by the date on the consent form and the date of chemotherapy administration on their medical records). Therefore, a total of one hundred and eighty five questionnaires, from patients aged sixty-five and over, have been included in this analysis.

4.4.1. Patient demographics

Baseline patient demographics are displayed in Table 4.1. Ninety three (50.3%) of study participants were female, ninety two (49.7%) were male. The mean age of respondents was 71.25 years, the age range was 65-84 years old (median 70.00, SD 4.778). Patients had a range of cancer diagnoses. The commonest tumour sites were colorectal, lung and breast (27.5%, 16.7% and 12.4% respectively). The majority of patients had Stage 3 (38.4) or 4 (40.4%) disease and 47.6% were commenced on chemotherapy treatment with palliative intent.

Table 4.1 Patient characteristics

	Number of patients (Total n=185)	Percent %
Sex		
Female	93	50.3
Male	92	49.7
Age (years)		
65-69	83	44.9
70-74	61	33.0
75-59	30	16.2
≥ 80	11	5.9
<70	83	44.9
≥70	102	55.1
Diagnosis		
Lower Gastrointestinal	51	27.5
Lung	31	16.7
Breast	23	12.4
Gynaecological	21	11.3
Urological	20	10.8
Upper Gastrointestinal	17	9.1
Lymphoma	11	5.9
Other	11	5.9
Stage		
I	6	3.2
II	22	11.9
III	71	38.4
IV	74	40.4
Other	12	6.5
Treatment intent		
Palliative	88	47.6
Adjuvant	45	24.3
Neoadjuvant	34	18.4
Primary/Radical	18	9.7

Table notes
Diagnosis: Lower Gastrointestinal cancers include (number of patients in brackets) colon (33), rectal (17) and anal. (1) Lung cancer: non small cell (23) small cell (3) and mesothelioma (5). Gynaecological: Ovarian (15), Cervical (2), Endometrial (3), Fallopian tube (1). Urological: Bladder (10), Prostate (10). Lower Gastrointestinal: Oesophageal (11), Gastric (3), Pancreatic (2), Cholangiocarcioma (1). Other includes Brain, Head and Neck, Melanoma and Primary peritoneal.
Stage: "Other " includes staging for certain tumours types such as lung and brain.

4.4.2. Completion of self-assessments

1. Performance status

All patients were able to self-complete the performance status score question.

2. VES-13

Twenty three patients (12.4%) did not complete the questions comprising the VES-13 score sufficiently for a total score to be calculated. 15/23 (65.3%) of patients with missing VES-13 scores had severe chemotherapy toxicity.

(Results for reference are in APPENDIX Q).

3. G8

Twenty patients (10.8%) did not complete the questions comprising the G8 score adequately for a total score to be calculated. 16/20 (80%) of patients with missing G8 scores had severe chemotherapy toxicity.

(Results for reference are in APPENDIX Q).

Table 4.2: Summary results from study questionnaires

Assessment score	Number of patients (Total n=185)	Percent %
Patient assigned:		
1. Performance Status		
0	77	41.6
1	58	31.4
2	43	23.2
3	7	3.8
2. VES-13		
<3	124	67.0
≥3	38	20.5
Missing	23	12.4
3. G8		
>14	65	35.1
≤14	100	54.1
Missing	20	10.8
Medical records:		
Charlson score		
0	102	55.1
1	42	22.7
2	24	13.0
≥3	9	4.9
Missing*	8	4.3
ACE-27 score		
0	61	33.0
1	76	41.1
2	34	18.4
3	6	3.2
Missing*	8	4.3

***** Insufficient medical records available for co-morbidity assessment to be possible

Performance status scores:

Performance status (PS) scores are displayed in Table 4.2.

Comparison of performance status scores (0,1 versus ≥2) according to age group (65-69 years old and 70 years old and over) showed no statistically significant difference in the proportion of scores according to age (χ^2 =0.272, p=0.602).

Vulnerable Elders Survey (VES-13) scores

A number of questionnaires were returned with incomplete answers to the VES-13 component questions. Completed VES-13 total scores that could be included in the analysis were 162 (87.6%). The mean VES-13 score was 1.71, range 0 to 8 (median 1.00, SD 2.449). A cut off score of 3 or greater has been determined to be predictive of functional decline or death at two years (38). In this study population, thirty eight patients (20.5%) had a VES-13 score of 3 or greater. Figure 4.1 shows the range of VES-13 scores recorded:

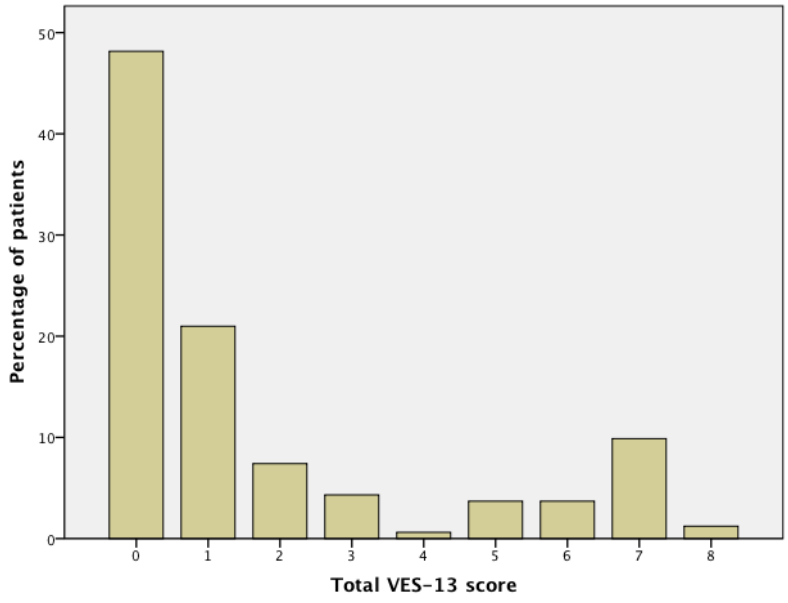


Figure 4.1: A graph displaying the range of VES-13 scores in older cancer patients receiving chemotherapy.

Comparison of VES-13 scores (<3 versus ≥3) according to age group (65-69 years old versus 70 years old and over) showed no statistically significant difference in the proportion of scores according to age (χ^2 = 1.355, p=0.244).

G8 scores

Completed G8 total scores that could be included in the analysis were one hundred and sixty five (89.2%). The mean G8 score was 13.45, range 8 to17 (median 14.0, SD 2.329). A cut-off value of 14 has been has been proposed as being predictive of patients failing a CGA (42). In this study population, one hundred patients (54.1%) had a G8 score of 14 or less.

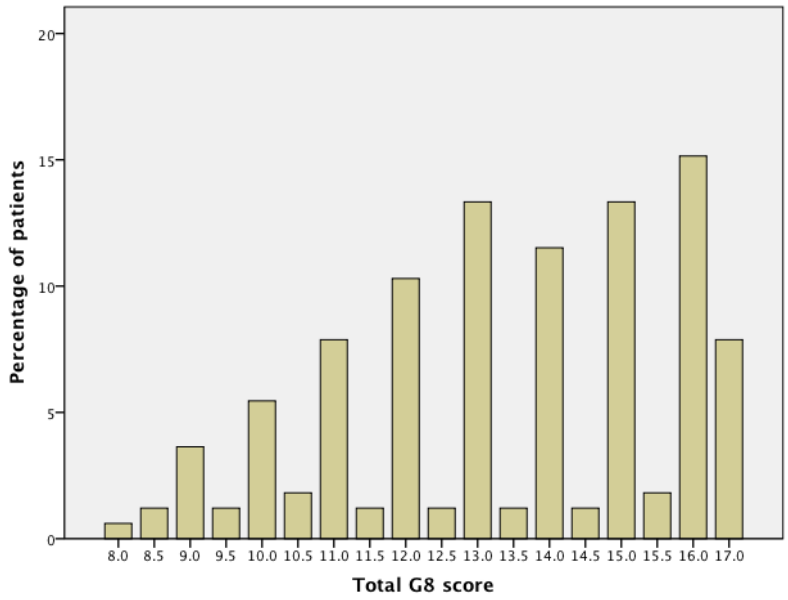


Figure 4.2: The range of G8 scores in older cancer patients receiving chemotherapy.

Comparison of G8 scores (≤ 14 versus >14) according to age group (65-69 years old and 70 years old and over) showed a statistically significant difference in the proportion of scores according to age (χ^2 = 7.698, p=0.006).

Table 4.3: Crosstabulation of G8 score group and age group

	Age Group		
	65-69 years old	≥ 70 years old	**Total**
G8 score			
0-14	35	65	100
14.5-17	37	28	65
Total	72	93	165

4.4.3. Comorbidity scores

The distribution of Charlson and ACE-27 comorbidity scores are displayed in figures 4.3 and 4.4:

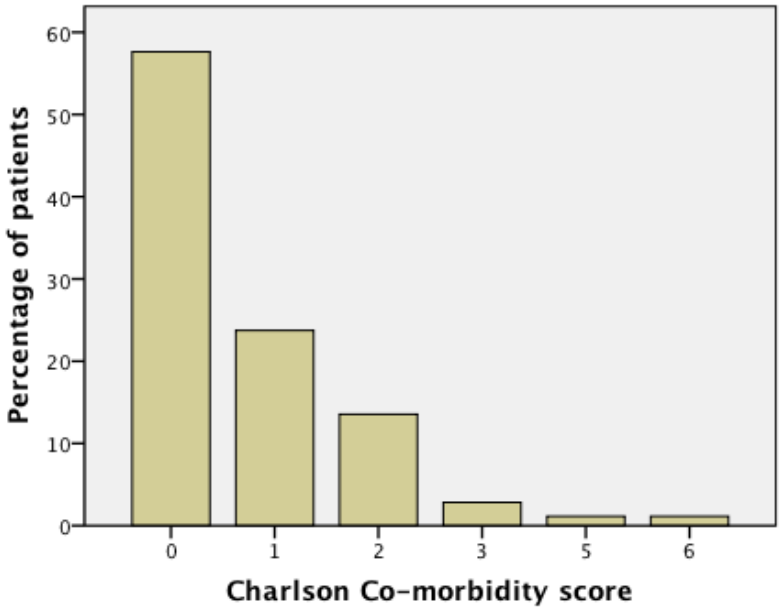


Figure 4.3: Distribution of Charlson comorbidity Index scores n=177

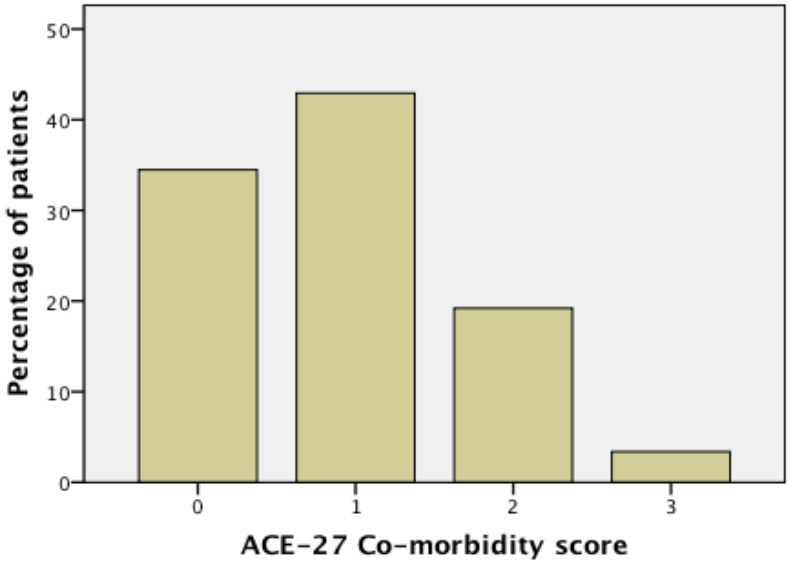


Figure 4.4: Distribution of comorbidity scores with the ACE-27 scale, n=177

4.4.4. Chemotherapy toxicity

Severe chemotherapy toxicity in this study was pre-defined as grade III/IV toxicity (CTCAE version 3.0 criteria), dose reduction, unplanned hospitalization, treatment discontinuation, or death within thirty days of treatment. Chemotherapy details are displayed in Table 4.4.

One hundred and fifty three patients (82.7%) were commenced on full dose chemotherapy. Documented reasons for an initial dose reduction included poor renal function, age, hepatic function, previous chemotherapy and poor performance status.

Dose reductions (after initiation of treatment) were noted in sixty two patients (33.5%). Reasons for dose modifications that were recorded included haematological, renal and hepatic dysfunction. Gastrointestinal, skin, neurotoxicity were other cited reasons for dose reductions. Forty seven patients (25.4%) had a delay in a planned cycle of chemotherapy treatment. The commonest reason was due to a haematological cause such as reduced white cell count.

Grade III/IV toxicities were documented in forty nine patients (26.5%). Unplanned admission to hospital whilst receiving chemotherapy occurred in forty three patients (23.2%). Treatment was stopped early in 33.0% (61/185) of patients and reasons included disease progression, no response to treatment, hospital admission, toxicities due to chemotherapy and patient request. There were eight (4.3%) deaths within thirty days of the last chemotherapy cycle.

The proportion of patients who developed the pre-defined severe chemotherapy toxicity was 59.5% (110/185). (Further details of these results are displayed in APPENDIX R).

Table 4.4 Details of chemotherapy regimens, modifications and treatment-related toxicities

	Number (n=185)	Percent %
Chemotherapy regimens		
Fluoropyrimidine + oxaliplatin	37	20.0
Gemcitabine + platinum	29	15.7
Anthracycline/taxane regimen	18	9.7
Carboplatin +/- taxane	18	9.7
Fluoropyrimidine alone	13	7.0
Chemo concomitant with radiotherapy	13	7.0
Docetaxel alone	12	6.5
Etoposide+platinum+capecitabine	11	5.9
Platinum+etoposide/pemetrexed	10	5.4
Other regimens*	24	13.0
Initial chemotherapy dose (%)		
100%	153	82.7
75-85%	21	11.4
50-70%	7	3.9
Unknown	1	0.5
Day 8 Gemcitabine cut	3	1.6
Chemotherapy stopped early?		
Yes	61	33.0
No	123	66.5
Missing	1	0.5
Dose modification		
Yes	62	33.5
No	122	65.9
Missing	1	0.5
Treatment delay		
Yes	47	25.4
No	136	73.5
Missing	2	1.1
Grade III/IV toxicity		
Yes	49	26.5
No	132	71.4
Missing	4	2.2
Unplanned hospital admission		
Yes	43	23.2
No	141	76.2
Missing	1	0.5
Death within 30 days		
Yes	8	4.3
No	177	95.7
Pre-defined severe chemotherapy toxicity		
Yes	110	59.5
No	73	39.5
Missing	2	1.1

*Other chemotherapy regimens include: irinotecan, rituximab combination regimens (lymphoma), mitoxantrone, dacarbazine, gemcitabine, liposomal doxorubicin

4.4.5. Data analysis

Primary aim:

Does the G8 score predict severe chemotherapy toxicity?

Our hypothesis was that a low G8 score (≤ 14), previously associated with a high probability of failing a CGA, would identify and predict a population of patients who are at risk of severe chemotherapy toxicity. Cross tabulation between G8 group scores and the presence of severe (pre-defined) chemotherapy toxicity showed that a greater proportion of patients with a G8 score below the cut off value of 14 experienced severe toxicity, 64.6%, compared to 46.9% with a score of 14.5-17. The chi-square statistic showed this difference to be statistically significant: χ^2 = 5.029, p=0.025.

Table 4.5 Crosstabulation of G8 score group and severe chemotherapy toxicity

	Severe chemotherapy toxicity		Total
	Yes	No	
G8 score			
O-14	64	35	99
14.5-17	30	34	64
Total	94	69	163

Secondary aims:

1. Does the VES-13 score predict severe chemotherapy toxicity?

Our hypothesis was that a high VES-13 score (≥3), previously associated with increased risk of functional decline or death, would identify and predict a population of patients at increased risk of severe chemotherapy toxicity. Cross tabulation of VES-13 group scores (<3 and ≥3) and the presence of severe chemotherapy toxicity showed that a greater proportion of patients with VES-13 score of ≥3 experienced severe toxicity, 76.3% (29/38) compared to 54.1% (66/122) with a score of <3. The chi-square statistic showed this to be statistically significant: χ^2 = 5.929, p= 0.015

Table 4.6 Crosstabulation of VES-13 score group and severe chemotherapy toxicity

	Severe chemotherapy toxicity		Total
	Yes	No	
VES-13 score			
<3	66	56	122
≥3	29	9	38
Total	95	65	160

2. Does performance status predict severe chemotherapy toxicity?

Cross tabulation between PS scores and severe chemotherapy toxicity (table 5.7) did not show any statistical significant difference between the two PS groups (PS 0/1 v ≥ 2) and likelihood of developing severe toxicity ($\chi^2 = 0.996$, p=0.318).

TABLE 4.7 Crosstabulation of Performance Status (PS) group and severe chemotherapy toxicity

	Severe chemotherapy toxicity		Total
	Yes	No	
PS group			
PS 0 or 1	77	56	133
PS ≥2	33	17	50
Total	110	73	183

3. Comparison of the sensitivity and specificity of G8, VES-13 and PS scores in predicting the risk of severe chemotherapy toxicity:

The sensitivity and specificity of G8, VES-13 and PS scores in predicting the risk of severe chemotherapy toxicity were calculated:

Table 4.8 Sensitivity and specificity of G8, VES-13 and PS in predicting severe chemotherapy toxicity in the study population:

	G8 score (≤14 vs >14)	VES-13 score (<3 vs ≥3)	PS score (0,1 vs ≥2)
Sensitivity	68.0 %	30.5%	30.0%
Specificity	49.3%	86.2%	76.7%

Receiver operator characteristic curves (ROC) were plotted to explore if there were identifiable cut-off values for any of the three scores in predicting chemotherapy toxicity. The area under the curve (AUC) for G8 score was 0.405 (95% confidence interval 0.316- 0.495). The AUC for VES-13 score was 0.605 (95% confidence interval 0.517 – 0.694) and the AUC for PS score was 0.599 (95% confidence interval 0.515-0.683). No suitable cut-off values were identified. (ROC curves are in APPENDIX S).

4. Do comorbidity scores predict severe chemotherapy toxicity?

Crosstabulation of comorbidity scores versus severe chemotherapy toxicity was performed (Tables 5.9 to 5.12). There were missing comorbidity scores for eight patients and two patients had missing outcomes for overall pre-defined chemotherapy toxicity (see tables 5.2 and 5.4). Therefore, results could be analysed for 175/185 patients. Comorbidity scores were divided into two groups at different cut-off values. No significant correlation between comorbidity scores

and the presence of severe chemotherapy toxicity was detected (p values are displayed below each table).

Charlson comorbidity scores:

Table 4.9 Crosstabulation of Charlson comorbidity score (0 vs ≥1) and severe chemotherapy toxicity

	Severe chemotherapy toxicity		Total
	Yes	No	
Charlson score			
0	60	41	101
≥1	44	30	74
Total	104	71	175

χ^2 = 0.000, p=0.994

Table 4.10 Crosstabulation of Charlson comorbidity score (0-1 vs ≥2) and severe chemotherapy toxicity

	Severe chemotherapy toxicity		Total
	Yes	No	
Charlson score			
0 or 1	86	57	143
≥2	18	14	32
Total	104	71	175

χ^2 = 0.164, p=0.685

ACE-27 comorbidity scores:

Table 4.11 Crosstabulation of ACE-27 comorbidity score (0 vs ≥1) and severe chemotherapy toxicity

	Severe chemotherapy toxicity		Total
	Yes	No	
ACE-27 score			
O	31	29	60
≥1	73	42	115
Total	104	71	175

χ^2 = 2.281, p=0.131

Table 4.12 Crosstabulation of ACE-27 comorbidity score (0-1 vs≥ 2) and severe chemotherapy toxicity

	Severe chemotherapy toxicity		Total
	Yes	No	
ACE-27 score			
O or 1	78	58	136
≥2	26	13	39
Total	104	71	175

χ^2 = 1.090, p=0.296

Unplanned sub-group analysis

It was decided to perform an unplanned sub-group analysis as it was thought that the study composite pre-defined "severe chemotherapy toxicity" as an end-point may not have been specific enough. Of the five domains included, it was hypothesized that unplanned hospital admission or early cessation of treatment may be good at discriminating whether a patient had experienced severe treatment-related toxicity.

1.Unplanned Hospital admission:

Crosstabulation of the G8, VES-13 and PS scores (within each of the cut-off groups) and unplanned hospital admission (yes/no) are displayed in tables 5.13, 5.14 and 5.15 respectively.

Table 4.13. Crosstabulation of G8 score groups and unplanned hospital admission

	Unplanned hospital admissions		Total
	Yes	No	
G8 score			
O-14	26	74	100
14.5-17	12	52	64
Total	38	126	164

Crosstabulation between G8 group scores and unplanned hospital admissions did not show any statistical significant difference between the two G8 groups and likelihood of hospital admission occurring : $\chi^2 = 1.152$, p=0.283.

Table 4.14. Crosstabulation of VES-13 score groups and unplanned hospital admission

	Unplanned hospital admissions		
	Yes	No	Total
VES-13 score			
<3	23	100	123
≥3	14	24	38
Total	37	124	161

Crosstabulation of VES-13 group scores (<3 and ≥3) and unplanned hospital admissions showed that a greater proportion of patients with VES13 score of ≥3 were admitted to hospital -36.8% compared to 18.7% with a score of <3. The chi-square statistic showed this to be statistically significant: χ^2 = 5.399, p=0.02

Table 4.15. Crosstabulation of Performance Status (PS) group and unplanned hospital admission

	Unplanned hospital admissions		
	Yes	No	Total
PS group			
PS 0 or 1	24	110	134
PS ≥2	19	31	50
Total	43	141	184

Cross tabulation between PS scores and unplanned hospital admission showed a statistically significant difference between the two PS groups (PS 0/1 v ≥ 2) and likelihood of hospital admission. 38.0% of those with a PS >=2 were admitted compared to 17.9% of those with a PS of 0 or 1 : χ^2 = 8.206, p=0.004.

2. Early treatment cessation:

Crosstabulation of the three score groups (G8 VES-13 and PS) versus early cessation of treatment is shown in tables 4.16, 4.17 and 4.18 respectively:

Table 4.16. Crosstabulation of G8 score groups and early cessation of treatment

	Chemotherapy stopped early?		Total
	Yes	No	
G8 score			
O-14	34	66	100
14.5-17	17	47	64
Total	51	113	164

χ^2 = 1.007, p=0.316

Table 4.17. Crosstabulation of VES-13 score groups and early cessation of treatment

	Chemotherapy stopped early?		Total
	Yes	No	
VES-13 score			
<3	33	90	123
≥3	19	19	38
Total	52	109	161

A greater proportion of patients with a VES-13 score of ≥3 stopped chemotherapy treatment early (50.0%) compared to those with a score <3 (26.8%), χ^2 = 7.128, p=0.008.

Table 4.18. Crosstabulation of PS score groups and early cessation of treatment

	Chemotherapy stopped early?		Total
	Yes	No	
PS group			
PS 0 or 1	40	94	134
PS ≥2	21	29	64
Total	61	123	184

χ^2 = 2.425, p=0.119

There were no statistically significant results within the G8 and PS groups and early cessation of treatment (p=0.316 and p=0.119 respectively).

Within the study population there were eight deaths within thirty days of treatment. The numbers are small and do not meet requirements for the Chi-squared test. Six out of the eight patients who died within thirty days had a PS ≥2.

4.5. Discussion

Chemotherapy toxicity in older cancer patients is of concern both to patients and health professionals. In this study 59.5% (110/185 respondents) experienced severe chemotherapy toxicity. Severe chemotherapy toxicity in this study was defined as one or more of either: grade III/IV toxicity (CTCAE version 3.0); dose reduction; unplanned hospitalization; treatment discontinuation or death within thirty days of treatment. A third of patients (33.0%) had their chemotherapy treatment stopped early, a third of patients (33.5%) had a dose modification, just over a quarter (26.5%) had documented grade III/IV toxicity and just under a quarter (23.2%) of patients were admitted to hospital during the period of chemotherapy treatment. Eight patients (4.3%) died within thirty days of chemotherapy administration.

A considerable proportion of patients that receive chemotherapy within our cancer network are older. Of all patients that returned study questionnaires, 40.2% were aged sixty-five or over and this may even under-represent the proportion of older patients that we treat with systemic therapies. The group of older study participants, aged sixty-five and over, comprised an equal number of men and women (49.7% and 50.3% respectively) and 102/185 (55.1%) were aged seventy and over. The common tumour types were represented with lower gastrointestinal, lung and breast cancers being the top three common cancer diagnoses in our study population and this is comparable with statistical data of cancer diagnoses registered in older adults (8).

Almost half (47.6%) of all patients were receiving palliative chemotherapy. In the palliative setting, the primary aim of treatment is to improve symptom control and optimize a patient's quality of life. Additional survival benefit of palliative chemotherapy is usually measured in months but varies according to tumour type and treatment options available. So, for the patient (and treating physician) it is important that any treatments used do not cause additional distressing side-effects, hospital admissions or early death due to treatment-related complications.

The ability of patients to self-complete assessment questionnaires would be useful in the clinical setting. In this study, patients were sent the questionnaires in the post and of the returned forms the majority were completed fully. All patients were able to complete the question relating to performance status. However, for the VES-13 score, 23/185 (12.4%) of patients and for the G8 score 20/185 (10.8%) of patients did not answer questions adequately for a score to be calculated. If self-completed assessment tools were found to be informative this would be useful in an often time-pressured clinical setting, however some provision would need to be made to assist those patients that needed extra help.

The majority of participants (73%) self-rated their PS as zero or one. This is reassuring as most oncologists would commence chemotherapy treatment only in patients of a good or reasonable PS in both curative and palliative settings. However in some situations, such as when patients have highly chemo-sensitive cancers, patients of poor PS may derive significant benefit from chemotherapy. Seven patients self-rated their PS as three which means that they required help with activities of daily living and were confined to a chair or bed for more than half of waking hours. One hundred and sixty two (87.6%) of patients answered the questions that comprised the VES-13 score. Of all the study patients, thirty-eight (38/185 or 20.5%) had a VES-13 score of three of greater which has been associated with and increased risk of functional decline or death at two years (38). One hundred and sixty five (89.2%) of patients answered the questions that comprised the G8 score and of all the study patients, one hundred (100/185 or 54.1%) had a G8 score of fourteen or less which has been shown to be predictive of failing a CGA (42).

In the field of geriatric oncology, the now agreed definition of older patients are those aged seventy and over. In this study population of patients aged sixty-five and over, 55.1% were seventy years of age or older. The distribution of the PS, VES-13 and G8 scores between patients aged 65-69 years old and seventy years old and over was explored. There was no statistically significant difference in the distribution of PS scores (0,1 v $\geq$ 2) or VES-13 scores (<3 v $\geq$3) between the two age groups (p=0.602 and p=0.244 respectively). One hundred patients (54.1%)

had a G8 score below the cut-off value of fourteen or less. A greater proportion of patients aged seventy and over had G8 scores below the cut-off value compared to those aged 65-69 years old (69.9% versus 48.6% respectively) and this difference was statistically significant (p=0.006). Both VES-13 and G8 scores have age as a component of the score. In the VES-13 survey, patients score one if aged 75-84 years old and score three if aged ≥85 years old. In the G8 survey, patients score zero if greater than 85 years old, score one if aged 80-85 and two if less than 80 years old. However, given the distribution of ages within the study population and the scores allocated for age within the G8 score, the scoring system is highly unlikely to account for the difference in G8 score distribution between patients in the two age groups.

The primary aim of this study was to ascertain if the G8 score predicted defined severe chemotherapy toxicity in older cancer patients. A G8 score of fourteen or less has been proposed as being predictive of a patient failing a comprehensive geriatric assessment (42). In this sample, a greater proportion of older patients with G8 scores below the cut-off value of fourteen experienced severe toxicity compared to those with G8 scores above the cut-off value (64.6% versus 46.9%). This observed difference between the two groups was found to be statistically significant (χ^2 = 5.029, p=0.025).

Secondary aims included exploring if VES-13 and PS scores also predicted severe chemotherapy toxicity. A VES-13 score of three or greater is predictive of death and functional decline in older patients (38). Patients with VES-13 scores above the cut-off value (≥3) were more likely to have severe chemotherapy toxicity – 76.3% of patients with a score of ≥ 3 experienced severe toxicity compared to 54.1% of patients with a score <3 and this difference was found to be statically significant (χ^2 = 5.929, p= 0.015). Performance status was not found to be a predictor of severe chemotherapy toxicity in this study population.

The sensitivity and specificity of the three scores (G8: ≤ 14 v >14, VES-13: <3 v ≥3 and PS: 0,1 v ≥2) in predicting severe chemotherapy toxicity varied. The G8 score was more sensitive, 68.0%, than both VES-13 and PS whose sensitivities were 30.5% and 30.0% respectively. However the specificities of VES-13 and PS were greater than G8. VES-13 score had a specificity of 86.2% and PS had a specificity of 76.7% compared to G8's specificity of 49.3%. ROC curve analyses did not identify any alternative cut-off values for any of the three scores and the area under the curve was near to 0.5 for all three scores. This is not surprising given the calculated sensitivities and specificities for the G8, VES-13 and PS scores.

So, from exploring the results from our study population it appears that the ability of G8, VES-13 or PS scores to predict our defined severe chemotherapy toxicity could be promising. However, the scores, either when examined in their current cut-off groups or within the score scale, do not appear to be adequately sensitive or specific in identifying a group of patients at increased risk of severe chemotherapy toxicity. There are still a reasonable proportion of patients below the cut-off values for all three scores, who experience severe chemotherapy toxicity.

An unplanned sub-group analysis was undertaken as it was thought that the pre-defined definition of severe chemotherapy toxicity may be too generalised and not specific. Five domains were included in the study pre-defined severe chemotherapy toxicity: Grade III/IV toxicity; dose reduction; unplanned hospital admission; early treatment discontinuation and death with thirty days of treatment. Of these five domains it was thought that unplanned hospital admission or early cessation of treatment may be good at discriminating whether patients have experienced clinically significant treatment-related toxicity. Crosstabulation of the G8, VES-13 and PS scores (within each of the cut-off groups) and unplanned hospital admission (yes/no) showed no significant difference between G8 score cut-off groups and admission to hospital (p=0.283). 36.8% of those with a VES-13 score ≥3 had an unplanned hospital admission compared to 18.7% of those with a VES-13 score <3 (p=0.02). 38.0% of those with a PS >=2 were admitted compare to 17.9% of those with a PS of 0 or 1 (p=0.04). A greater proportion of patients with a

VES-13 score of ≥3 stopped chemotherapy treatment early (50.0%) compared to those with a score <3 (26.8%), p=0.008. There were no statistically significant results within the G8 and PS groups and early cessation of treatment.

Within the study population there were eight deaths within thirty days of treatment. The numbers are small and did not meet requirements for the Chi-squared test. It was noted that six out of the eight patients who died within thirty days had a PS ≥2.

Some patients were unable to fully complete the questionnaires. In the study population 59.5% of participants (110/185) had severe chemotherapy toxicity. Patients who did not return complete questionnaires were observed to have higher rates of severe chemotherapy toxicity. Of the twenty-three patients with missing VES-13 scores, 65.2% (15/23) had defined chemotherapy toxicity. Of the twenty patients with missing G8 scores, 80% (16/20) had defined chemotherapy toxicity. A patient's ability to complete a questionnaire in itself may be an indication of their general health and likelihood of experiencing treatment related toxicities.

The presence of other medical conditions is taken into account when oncologists weigh up the risks versus benefits of chemotherapy treatment. The Charlson comorbidity index and ACE-27 score were used to measure comorbidities in this study population and scores were presented for one hundred and seventy seven patients (177/185). Around three-quarters of patients scored zero or one on both scales. 81.4% of patients scored zero or one in the Charlson score, 77.4% scored zero or one in the ACE-27 score. This is probably to be expected as many older patients with severe or multiple comorbidities are likely to have been deemed unfit for treatment and so may not have been included in this group of patients about to commence systemic therapy. Therefore for practical reasons this may mean that a comorbidity score is not a useful predictor of chemotherapy toxicity

Study limitations

In this study, patients were required to complete and return the three questionnaires themselves with no assistance from a health professional. Interpretation of questions may have been difficult for some patients and there were a number of patients that were unable or chose not to, answer some of the questions. Study invites and questionnaires were posted to patients along with details of their chemotherapy treatment and first appointment. Non-responders may have included patients with literacy difficulties, impaired vision, physical or mental disabilities, or those who were too frail, unwell or over-whelmed by paperwork to take part at that time. These patient groups may be under-represented in our study population.

Seventeen patients' responses were not included in the analysis. They comprised patients who returned questionnaires with consent forms that were dated after the date they had commenced chemotherapy and so it could not be certain that the answers they had given were reflective of their health status pre-treatment. Other patients had been sent questionnaires in error when they did not meet the eligibility criteria as they were on targeted, non-cytotoxic chemotherapy (for example sunitinib).

The questions in the individual questionnaires required patients to indicate their answer by ticking a particular box. On a few returned questionnaires, in the performance status question, patients ticked more than one box. In this scenario, the highest score was taken as indication of their performance status.
In the G8 score, one of the questions asks about whether the patient suffers from mild or severe depression or dementia. This direct question was not included in the questionnaires sent to patients as it was felt it may cause some distress if asked in the form of a written question and when there was no health professional available at the time of completion to address any concerns or distress that the question may have caused. Details regarding patients' mental status were obtained from medical records in order to complete that particular question and so calculate the total G8 score. Mental health issues may not always be raised by patients or

detected by health professionals. Patients in this study with mental health problems (especially mild depression or mild dementia) may not have been detected through relying on medical records alone. In the G8 score, "no psychological problems" scores two points, "mild depression or dementia" scores one point, "severe depression or dementia" scores zero. Some patients may have been rated as having no psychological problems when there were minor issues. These patients may have a higher total G8 score, by one point. This may mean that some patients in this study population have a higher G8 score that does not fully reflect their general health and over-estimate their fitness. This may have implications for data interpretation and introduce bias, as there may be a slightly higher proportion of patients who should in reality fall below the G8 cut-off value of 14 or less. In future research this issue could be addressed if questions were asked by a health researcher or if patients completed the questionnaire in a health-care setting where there were personnel available to answer any queries, assist in questionnaire completion and deal directly with any issues that this question (or indeed others) may raise.

Grade III/IV toxicity information was obtained from medical records on the electronic chemotherapy database and from patients' paper notes. Details of side effects recorded were noted and graded according to CTCAE version 3.0 criteria by the study researcher. Not all treatment-related toxicity may have been recorded in these records and the incidence of severe side effects from treatment may be under-estimated in this category. In future work, this could be addressed with the prospective recording of side effects prior to each treatment cycle on a specific proforma to be completed by both the patient and responsible health professional. However, a grade III or IV toxicity is likely to initiate a subsequent dose modification, early treatment cessation or hospital admission. So, although the percentage of patients recorded as having a grade III/IV toxicity may be under represented it is not felt that this would affect the overall number of patients with the composite study-defined severe toxicity that has been calculated.

Conclusions

In this study, 59.5% of older patients aged sixty-five and over experienced adverse side-effects (study pre-defined severe chemotherapy toxicity) when undergoing systemic chemotherapy treatment. The majority of patients receiving chemotherapy were able to self-complete the assessment questionnaires. Of the three assessment tools studied, oncologists currently only use performance status to assess patients' fitness for treatment. In this study, performance status was not a good predictor of the likelihood of patients developing severe chemotherapy toxicity. A significant proportion of patients with scores in the poorer prognostic cut-off groups of both G8 (≤ 14) and VES-13 (≥3) scores were likely to develop severe chemotherapy toxicity. However, there were many patients in the "fitter" groups of the G8 and VES-13 scores who also experienced adverse treatment-related events. The sensitivity and specificity of the G8 and VES-13 scores were found to be unsuitable to enable either tool to be useful (in isolation) as a predictive screening tool for severe chemotherapy toxicity. In this study population co-morbidity scores, measured using Charlson and ACE-27 comorbidity scales, were not found to be predictive of severe chemotherapy toxicity,

Further work could explore whether certain components of the G8 and VES-13 scores or additional measurements such as functional assessment scores may be useful in assessing and predicting older patients' risk of chemotherapy-related adverse events and toxicities.

Chapter Five

5. Malnutrition in metastatic colorectal cancer patients - a comparison of three screening tools

5.1. Introduction

Malnutrition is one of a number of co-existing conditions which may affect patients with cancer, but which may go undetected within the oncology outpatient clinic (166) . In a time-pressured environment, health professionals may prioritise focusing on issues relating to the cancer such as treatment related side effects, and symptom control such as pain. Poor oral intake and weight loss may be noticed and recorded but not formally addressed. Malnutrition may have been present before a cancer diagnosis, or developed as a result of the primary cancer diagnosis (especially in head and neck and gastrointestinal cancers). Malnutrition affects patients' ability to tolerate potentially toxic treatments, their general sense of well-being, overall quality of life and prognosis (166, 167). Altered taste, reduced calorie intake and weight loss may also develop as treatments such as chemotherapy and radiotherapy are initiated. Furthermore, these symptoms (and others) often evolve as the cancer progresses. In the palliative setting, nutritional intake problems and related questions are often raised by patients and their families.

In older people, nutritional problems and malnutrition can be a common issue both within community and hospital settings (168). Involuntary weight loss in older people may occur due to depression, cancer, cardiac illness, conditions affecting functional abilities and in households on low incomes (169). Geriatricians recognized that nutritional status impacted on many aspects of older people's general health and that there was not a simple assessment process to identify patients at risk of malnutrition (86). A comprehensive geriatric assessment was of benefit to elderly patients and the Mini-Nutritional Assessment tool was originally devised as a nutritional screening tool to be used in conjunction with other CGA assessment tools (86, 170).

Malnutrition is an important issue in cancer patients and in the elderly and therefore older patients with cancer are at particular risk. Formal assessment of patients nutritional status can assist health professionals in clearly identifying malnourished patients (which may or may not be obvious) and just as importantly, those who are at risk of malnutrition. Preventative and supportive measures can be initiated early on in patients' cancer management. These strategies can improve patients physical ability to tolerate treatments and in addition can enable them have an element of control over their cancer care. Importantly, regular monitoring by the dietetic team can identify any changes that may occur so that they can respond accordingly with appropriate advice and alternative management strategies.

Assessment tools have been devised to screen for malnutrition and assess nutritional status in the general hospital or outpatient population. However, these are not routinely applied in oncology clinics or in older patients with cancer. Three assessment tools: The Mini-nutritional assessment tool (MNA); Malnutrition Universal Screening Tool (MUST) and the Patient-Generated Subjective Global Assessment (PG-SGA) have been described in chapter one. These tools have been validated in various patient populations but there is not one agreed assessment tool that is used, particularly in the oncology setting. The MNA is the most widely used and presently the closest to a "gold standard" nutritional assessment tool in the geriatric population (86). The MUST score is in routine use in our cancer centre. It is easier and quicker to conduct than the MNA and therefore we wanted to compare the MUST score with a gold standard score such as the MNA. The PG-SGA has been validated in many cancer populations, has a high sensitivity and specificity and as a result could be considered to be the gold standard in cancer patients (82, 166). However, the PG-SGA is time consuming and may not be practical to use in routine clinical practice. In increasingly busy clinics, it would be useful if there was a validated nutritional assessment tool that patients were able to complete themselves or with minimal assistance of a health-care professional. The Abridged PG-SGA is a questionnaire that patients can answer themselves and this format of the PG-SGA will be studied in this study.

5.2. Aims

Primary:

To ascertain the proportion of patients with metastatic colorectal cancer at risk of malnutrition, according to the Mini-Nutritional Assessment (MNA).

Secondary:

(i) To compare rates of malnutrition in older (≥70 years old) and younger (aged 18-69 years old) patients with metastatic colorectal cancer.

(ii) To compare the sensitivity and specificity of the Malnutrition Universal Screening Test (MUST) with the Mini-Nutritional Assessment (MNA) in patients with metastatic colorectal cancer.

(iii) To calculate the proportion of patients in whom referral to the dietician was required for previously unrecognized malnutrition.

(iv) To explore whether any components of the Abridged Patient Generated Subjective Global Assessment (APG-SGA) predict which patients are at risk of malnutrition according to the MNA.

5.3. Methods

Study Design

Cross-sectional survey.

Study population

Patients aged eighteen and over with a diagnosis of metastatic colorectal cancer were recruited from oncology outpatient clinics and inpatient wards at the Royal Sussex County Hospital and Eastbourne District General Hospital. Eligible patients were identified according to the following criteria:

Inclusion criteria

Patients aged eighteen years and over.
Diagnosed with cancer of the colon or rectum.
Stage IV disease.
Written informed consent.

Exclusion criteria

Patients with stage I-III colon or rectal cancer.
Those diagnosed within last 8 weeks.
Patients unable to give informed consent.
Patients with a life expectancy of less than 3 months.

Recruitment

Eligible patients were identified in outpatient clinics, chemotherapy day units and on the wards at the Sussex Cancer Centre, Royal Sussex County Hospital, and Eastbourne District General Hospital. Eligible patients were provided with an information sheet. Those interested were asked to sign a consent form by the researcher. The patient's GP was informed of their involvement in the study (APPENDIX T). The researcher performed three nutritional assessments (the MNA, MUST and APG-SGA). These are questionnaire-based, and also involve anthropometric measurements. The patient completed the APG-SGA first and the researcher was available at the time to offer any guidance if required.

Scoring criteria:

(i) MNA

The MNA was scored according to standard criteria, i.e. the MNA screening assessment tool was performed and if patients scored <12 they were "at risk" and the full MNA assessment was completed. In some patients, the assessors completed the full MNA assessment, even if the screening score was >12. On completion of the full MNA assessment, patients are classified as malnourished if they score <17, at risk of malnutrition if they score 17-23.5 and not at risk of malnutrition if they score ≥24 (86) (APPENDIX H).

(ii) MUST

The MUST score was scored according to standard criteria. The patient's body mass index (BMI) was calculated, unplanned weight loss assessed and the presence of acute disease causing no nutritional intake for five days recorded. These three criteria were scored and combined to produce the overall MUST score allocating patients into low (score=0), medium (score=1) or high risk (score ≥2) groups (APPENDIX I)

(iii) APG-SGA

The APG-SGA consists of four questions (APPENDIX J) and was scored as follows:

Q1: 1 point if weight decreased over last two weeks, otherwise 0.
Q2: 1 point if eating "less than usual" otherwise 0 (the second part of the question not scored as most respondants left it blank).
Q3: A point for each of the symptoms that they ticked, maximum score of 4 (range 0-4).
Q4: Performance status score (the range of possible scores was 0-4).

The maximum score possible was 10. A higher score, indicated more nutritional concerns or needs.

All patients on completion of the interviews were given a Patient Information Leaflet: "Eating Well: A guide to the importance of nutrition in cancer". Additional

demographic, tumour and treatment history details for individual patients were obtained from medical records. Where a patient was found to be at risk of malnutrition or have established malnutrition and was not receiving dietician input, a referral was sent to a local dietician. The patient was informed of this in a letter. A copy of the referral was sent to the patient's GP and oncology consultant.

Ethical approval for the study was obtained from the local ethics committee, REC reference number 09/H1107/83, and recruitment took place over an eighteenth month period from November 2009 to May 2011.

Data analysis was conducted using SPSS Version 18.0

5.4. Results

5.4.1. Patient demographics

Patient demographics and characteristics are shown in Table 5.1

Table 5.1 Patient demographics

	Number of patients (Total n=78)	Percent %
Sex		
Female	34	43.6
Male	44	56.4
Age		
<70 years old	49	62.8
≥70 Years old	29	37.2
Diagnosis		
Stage IV colon cancer	54	69.2
Stage IV rectal cancer	24	30.7
Current management*		
Palliative chemotherapy	40	51.3
Targeted therapy	5	6.4
Palliative radiotherapy	1	1.3
Supportive care	37	47.4
Outpatient	77	98.7
Inpatient	1	1.3
Performance status		
0	22	28.2
1	34	43.6
2	17	21.8
3	5	6.4
Body Mass Index**		
Underweight	1	1.3
Normal	28	35.9
Overweight	32	41.0
Obese	17	21.8

* Some patients were receiving a combination of treatments and this is why the total percentage exceeds 100%.
**Body mass index score groups: Underweight: BMI <18.5, Normal 18.5 to 24.99, Overweight ≥25 , Obese ≥30

The body mass index (BMI) scores for patients were calculated as part of the MNA assessment. The median BMI was 26.7 (Range 18.3-45.6, SD 4.6). The number of patients who were classed as underweight, normal, overweight or obese according to their BMI is shown above in Table 5.1.

5.4.2. Nutritional assessment scores:

MNA and MUST scores are shown in Table 5.2.

Table 5.2 Summary of MNA and MUST nutritional assessment scores

Nutritional assessment tool	Number (%) Total n=78
MNA score:	
At possible risk of malnutrition	31 (39.7%)
Not at risk of malnutrition	47 (60.3%)
At risk of malnutrition group	Total n=31
Malnourished	4 (12.9%)
At risk of malnutrition	17 (54.8%
Not at risk of malnutrition	10 (32.3%)
MUST score:	
0	57 (73.1%)
1	10 (12.8%)
2	10 (12.8%)
3	1 (1.3%)

The proportion of patients with metastatic colorectal cancer at risk of malnutrition according to the MNA:

According to the MNA screening tool, thirty one out of seventy eight (39.7%) of patients with metastatic colorectal cancer were identified as being "at possible risk of malnutrition", 95% CI 29.6% - 50.8% (171).

On completion of the full MNA assessment, twenty one out of thirty one patients (67.7%) were identified as being malnourished or at risk of malnutrition. Therefore of the total study population, 21/78 (26.9%) were malnourished or at risk of malnutrition.

Comparison of the rates of malnutrition in older patients (≥70 years olds) with younger patients (<70 years old) with metastatic colorectal cancer:

Table 5.3 shows the crosstabulation of older and younger patients who were at risk and not at risk of malnutrition, according to the MNA screening score:

Table 5.3 Crosstabulation of patients aged under and over seventy years of age and nutritional risk according to the MNA screening tool

	MNAscreen At risk	MNAscreen Not at risk	Total
<70 years old	17	32	49
≥70 years old	14	15	29
Total	31	47	78

On comparing the groups, there was no statistically significant difference in the rates of malnutrition risk between the two age groups, $\chi^2 = 1.403$, p=0.236.

On completion of the full MNA assessment, twenty two patients were found to be at risk of malnutrition/ malnourished. Crosstabulation according to age group was repeated and there was no statistically significant difference in the incidence of malnutrition/risk of malnutrition compared to those not at risk, in patients under and over seventy years of age $\chi^2 = 0.182$, p=0.669.

Table 5.4 Comparison of older and younger of the 22 patients who were at risk or malnourished on completion of the full MNA assessment.

	MNAassessment At risk	MNAassessment Not at risk	Total
<70 years old	13	36	49
≥70 years old	9	20	29
Total	22	56	78

Comparison of the sensitivity and specificity of the MUST score with the MNA tool in patients with metastatic colorectal cancer:

Using the MUST tool, fifty seven patients (73.1%) scored zero and were in the low risk group. Ten patients scored one (12.8%) and were in the medium risk group and eleven patients (14.1%) had a MUST score of two or greater and were in the high risk group (see table 6.2).

The MUST and MNA screening scores were divided into two groups ("at risk" versus "not at risk/low risk") and crosstabulated as shown in table 5.5:

Table 5.5 Crosstabulation of MUST and MNA screening nutritional scores (low risk/not at risk and medium-highrisk/at risk)

	MNA At risk	MNA Not at risk	Total
MUST score Medium/high risk (score ≥1)	16	5	21
MUST score Low risk (score =0)	15	42	57
Total	31	47	78

If the MNA score is taken as the gold standard, when comparing the MUST scores with the MNA screening scores, the MUST score correctly identified sixteen patients out of thirty one patients as "at risk of malnutrition" and forty two out of forty seven were correctly identified as not being at risk of malnutrition. Therefore, on comparing the MUST with the MNA screening tool, the sensitivity of the MUST score is 51.6% (95% CI 34.8% -68.0%) and the specificity is 89.4% (95% CI 77.4%-95.4%) (171). The Kappa measure of agreement is 0.434. This is in the 0.40-0.60 range which can be interpreted as moderate correlation between the MUST and MNA scores.

On completion of the full MNA assessment, twenty two patients were found to be at risk of malnutrition or malnourished. These results were also crosstabulated with the MUST scores:

Table 5.6 Crosstabulation of MUST and MNA assessment nutritional scores (low risk/not at risk and medium-high risk/at risk)

	MNAassessment At risk	MNAassessment Not at risk	Total
MUST score Medium/high risk (score ≥1)	12	9	21
MUST score Low risk	10	47	57
Total	22	56	78

Comparing the MUST scores with the MNA assessment scores, the MUST score had a sensitivity of 54.5% (95% CI 34.7%-73.1%) and a specificity of 83.9% (95% CI 72.2%-91.3%) (171).

Proportion of patients where referral to a dietician was necessary in previously undetected malnutrition:

Thirty one patients were identified as being at risk of possible malnutrition after the initial MNA screening assessment. In these patients, following full MNA assessment, twenty one patients were identified as being at risk of malnutrition or malnourished. In some patients, even if they had had a satisfactory MNA screening score, the full MNA was completed. One patient who was not identified as at risk on the MNA screening assessment was found to be at risk on completion of the full MNA assessment, so a total of twenty two patients were recorded as being "at risk of malnutrition or malnourished"

The number of previous dietician referrals, cases of previous nutritional advice and oral supplements is displayed in Table 5.7. They are displayed as results within the total study population (n=78), within those found to be at potential risk after MNA screening (n=31) and in the patients who were found to be malnourished or at risk following full MNA assessment (n=22).

Table 5.7. Summary details of previous dietetic input in study population

Nutritional input	Total study population N=78 (%)	MNA screening "possible malnutrition risk N=31 (%)	MNA assessment "malnourished/at risk malnutrition" N=22 (%)
Previous dietician referral			
Yes	17 (21.8)	10 (32.3)	9 (40.9)
No	61 (78.2)	21 (67.7)	13 (59.1)
Previous nutritional advice			
Yes	29 (37.2)	15 (48.4)	11 (50.0)
No	49 (62.8)	16 (51.6)	11 (50.0)
Received oral supplements			
Yes	27 (34.6)	13 (41.9)	10 (45.5)
No	51 (65.4)	18 (58.1)	12 (54.5)

Of the twenty two patients that were malnourished or at risk of malnutrition, thirteen (59.1%) had never been seen by a dietician. Eleven patients (50%) had not received previous nutritional advice and twelve (54.5%) had never received oral nutritional supplementation.

Exploration of whether the APG-SGA is able to predict whether patients are at risk of malnutrition as identified by the MNA and a comparison of the sensitivity and specificity of the APG-SGA with the MNA:

The four questions comprising the APG-SGA questionnaire resulted in total scores ranging from zero to nine. The range of scores, compared to the MNA screening assessment "at risk" and "not at risk" groups are displayed in table 5.8.

Table 5.8 APG-SGA scores compared to MNA screening scores

	MNA screening		
	At risk	Not at risk	Total
APG-SGA score			
0	2	13	15
1	3	16	19
2	2	8	10
3	4	1	5
4	6	3	9
5	2	3	5
6	5	2	7
7	2	0	2
8	4	1	5
9	1	0	1
Total	31	47	78

A higher APG-SGA score indicates increased nutritional needs due to symptoms such as weight loss, symptoms related to the cancer diagnosis and overall poor performance status.

A ROC curve was created to show the APG-SGA score versus the MNA screening score (at risk/not at risk of malnutrition):

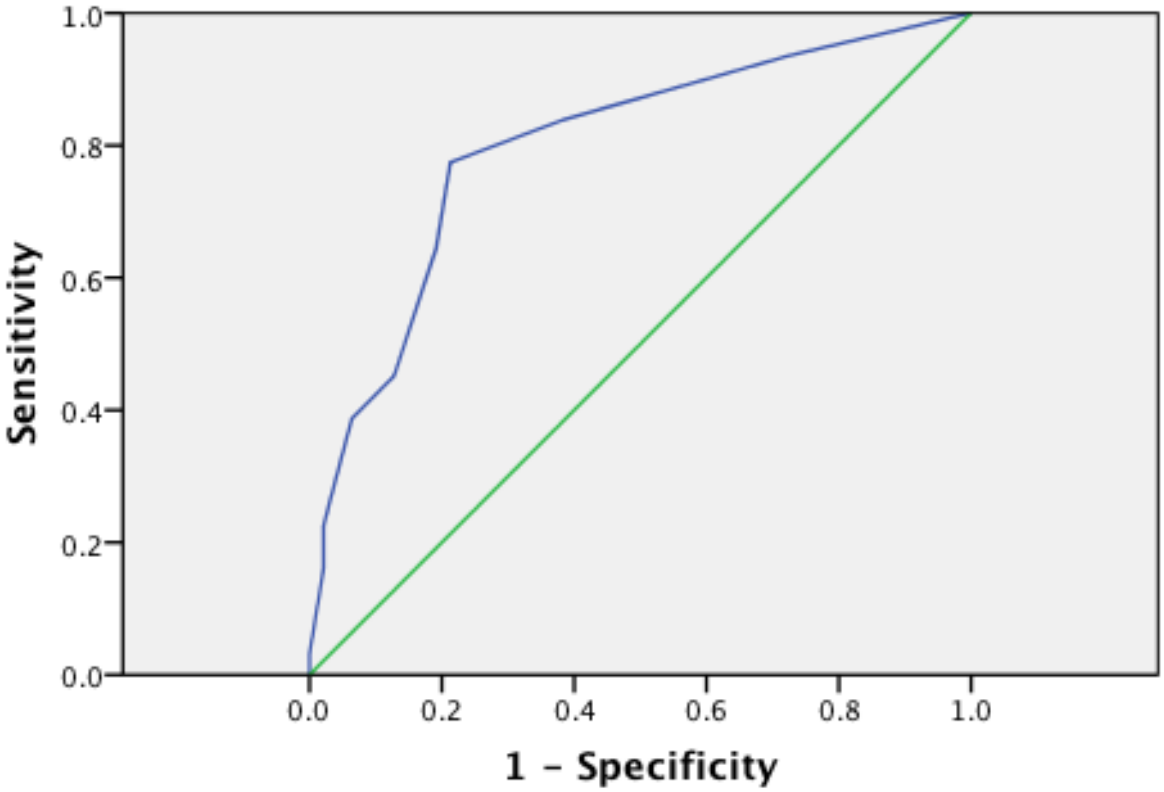


Figure 5.1: A ROC curve to show APG-SGA score versus MNA screening score

The ROC curve is to the left of the line of no discrimination. The area under the curve is 0.799 (95% CI 0.695 to 0.903).

Potential cut off values for the APG-SGA score were explored through crosstabulation of different APG-SGA cut-off groups versus MNA screening scores (at risk or not at risk of malnutrition) and the sensitivity and specificity of the APG-SGA test according to various cut-off scores is shown in table 5.9:

Table 5.9 Sensitivity and specificity of APG-SGA cut off scores when compared to MNA screening scores.

APG-SGA cut off score	**Sensitivity**	95% CI	**Specificity**	95%CI
≥1	**93.5%**	70.3%-98.2%	**27.7%**	16.9%-41.8%
≥2	**83.9%**	67.4%-92.9%	**61.7%**	47.4%-74.2%
≥3	**77.4%**	60.2%-88.6%	**78.7%**	65.1%-88.0%
≥4	**64.5%**	47.0%-78.9%	**80.8%**	67.5%-89.6%

For example, if a patient scored a APG-SGA score of two or greater the sensitivity of the APG-SGA score compared to the MNA screening tool, in identifying a patient who may be at risk of malnutrition, is 83.9% and the specificity is 61.7%.

5.5. Discussion

The risk of malnutrition should be considered in all patients with cancer. Whilst patients are undergoing oncological treatments such as chemotherapy and radiotherapy, toxicities may affect patients' appetite and ability to consume adequate calories. In the metastatic setting, disease progression can impact on the body's metabolism and weight loss may be accelerated.

There are a number of nutritional assessment tools which are in use and this study aimed to compare two tools commonly used in hospital, outpatient and community settings (MNA and MUST) and a third tool that was in a shortened format (APG-SGA). The APG-SGA tool, unlike the other two tools, would be able to be completed by patients with no or minimal health professional assistance.

In this study seventy eight patients with a diagnosis of metastatic colorectal cancer were recruited from outpatient clinics. Inpatients on the oncology ward were regularly screened. Very few eligible inpatients were identified and during the recruitment period one inpatient was approached and consented to take part. Therefore, the study population comprised patients who were able to travel for a clinic appointment or palliative therapies. The mean age of study participants was 64.4 years (median 66.0, SD 10.623, range 27-82 years) and 37.2 % (29/78) were aged seventy or over. The mean age reflects the fact that colorectal cancer is common in patients aged sixty and over. However a smaller proportion of patients were aged seventy and over (37.2%) than might be expected and this may be due to a number of reasons. Older patients with metastatic colorectal cancer may not be fit enough for palliative treatment such as chemotherapy or may choose to not undergo further treatments, and so not be regular attendees in a outpatient clinic (remaining under the care of their general practitioner and community palliative care team). In this study population, forty patients (51.3%) were receiving palliative chemotherapy, five targeted therapies, and one patient was receiving a course of palliative radiotherapy. Thirty seven patients (47.4%) were receiving supportive care.

Overweight and obese people are at increased risk of colorectal cancer. As part of the nutritional assessment process within this study, body mass index (BMI) was measured. Thirty two patients (41.0%) were overweight and seventeen (21.8%) were obese. Twenty eight patients (35.9%) had a normal BMI and one patient was underweight.

Overweight and obese patients can be malnourished or at risk of malnutrition. Of the twenty two patients that were at risk of malnutrition after completion of the full MNA assessment, 5/22 were overweight and 4/22 were obese. 13/22 had a normal BMI. Interestingly, the one patient who was underweight according to their BMI had a total MNA assessment score of 24 (above the cut-off value of 23.5). In this study patient population, BMI alone would not be an adequate assessment of their nutritional status or malnutrition risk.

Malnutrition in older patients

Studies have shown that malnutrition and nutritional problems are more prevalent in elderly populations and that screening for malnutrition in older persons is important (86). We hypothesized that in older patients with metastatic colorectal cancer, the incidence of malnutrition or those at risk of malnutrition would be higher compared to younger patients. The rates of malnutrition in older (seventy years old and over) versus younger patients, according to assessment using the MNA, was compared and is shown in tables 5.3 and 5.4. There was no statistically significant difference in the rates of malnutrition risk between the two age groups (p=0.236) in this study population. This may be due to a number of factors including sample size and that frailer older cancer patients may not attend outpatient clinics. A larger study population and recruitment of patients (with metastatic colorectal cancer) within other healthcare settings (e.g. palliative care and primary care) would provide a more representative sample of patients.

MNA scores

The primary aim was to ascertain the proportion of patients with metastatic CRC at risk of malnutrition according to the MNA. According to the MNA screening tool, thirty one out of seventy eight (39.7%) of patients (95% CI: 29.6% - 50.8%) were

identified as being possibly at risk of malnutrition and required further assessment. The confidence interval is quite wide and this may reflect the small sample size. However the upper value of the confidence interval indicates that a significant proportion of the sample population could be at risk of malnutrition. Of the thirty one patients who were identified as being "at risk" by the MNA screening tool (score <12), twenty one patients (67.7%) were identified on completion of the full MNA assessment to be either "at risk of malnutrition" or "malnourished". Ten patients (32.3%) were not found to have any nutritional issues on further MNA assessment and this is quite a high false positive rate for the MNA assessment tool in this study population. In some patients, assessors completed the full MNA assessment, irrespective of the screening score. This explains the discrepancy in the total numbers in tables 5.2 and 5.7(92). Overall, a total of twenty two patients (28.2%) were at risk of malnutrition according to the MNA assessment and in need of dietetic referral and input.

MUST scores

The MUST score was designed to be used to assess patients of all ages in inpatient, outpatient and community settings. It is simple and quick to use and can be used by all healthcare professionals. In this study population of seventy eight patients with metastatic colorectal cancer, the MUST score identified ten patients at medium risk and eleven patients at high risk of malnutrition. Therefore, according to the MUST scores, 26.9% (21/78) of patients were at risk of malnutrition.

Comparison of MNA and MUST scores

The MUST scores were compared to the MNA scores (both screening scores and assessment scores). If the MNA score is taken as the gold standard, on comparison of the MUST and MNA screening score, the MUST score correctly identified sixteen out of thirty-one patients as at risk of malnutrition and forty-two out of forty-seven were correctly identified as not being at risk. The sensitivity of the MUST score was low (51.6%) but the specificity was high (89.4%). The Kappa measure of agreement between MUST and MNA screening scores was 0.434. This is within the lower end of the range of moderate correlation. The MUST scores were also cross tabulated with the MNA assessment scores and the sensitivity (54.4%) and

specificity (83.9%) were similar to those calculated on cross tabulation with the MNA screening scores.

For any screening tool, high sensitivity and specificity is important. High sensitivity ensures that test correctly identifies affected (in this case, at risk of malnutrition) individuals and a test with high specificity correctly identifies individuals who are unaffected. On comparing the MUST score with the MNA score, the sensitivity of the MUST tool was found to be low but the specificity high in this sample population. A nutritional screening tool should have a high sensitivity in order to correctly identify affected patients who require further nutritional assessment. If the test had a lower specificity (i.e. more patients were incorrectly identified as "at risk" when they were well) in this situation it would mean that patients would undergo further questions and assessment. This would be time-consuming for the patient and assessor but it would not be harmful or involve any invasive procedures and may be preferable to ensure that an adequately sensitive tool correctly identifies affected individuals.

The MUST score is calculated using three criteria: a body mass index of less than nineteen; unintentional weight loss of more than five to ten percent and the presence or absence of acute illness causing the patient to have had no nutritional intake for five days. There are management guidelines that can be followed for patients identified as at risk (APPENDIX I). The MUST score has been studied and validated in the acute hospital setting and compared favorably with other nutritional assessment tools in a study by Stratton et al (82, 92). However, the use of the MUST score in cancer patient populations has not been extensively studied. In this study, the majority of patients were outpatients and would be unlikely to have had no nutritional intake for five days and therefore have less chance of scoring on that component of the MUST score. When symptomatic from treatment-related toxicities or disease-related symptoms, cancer patients are often advised to eat "little and often" in order to maximize calorific intake. The MUST score would not detect this, where as the MNA assessment tool asks questions about number of full meals eaten in a day and particular food group consumption (meat, dairy, vegetables etc). However, both scores include questions on body

mass index and weight loss. This research suggests that the utility of the MUST score in the cancer outpatient setting may be limited as it may miss patients at risk of malnutrition. This does not rule out a potential role in the in-patient setting, but this was not examined in this study.

Dietician assessment

Within the total study population, seventeen patients (21.8%) had previously seen a dietician, twenty nine (37.2%) had received nutritional advice and twenty seven patients (34.6%) had received oral supplements (Table 6.7). If the MNA assessment is taken as the "gold standard" nutritional assessment tool used in this study, of the twenty two patients found to be at risk of malnutrition or malnourished, thirteen patients (59.1%) had not previously seen a dietician, eleven patients (50%) had never received nutritional advice and twelve patients (54.5%) had not received oral supplements. In Table 6.7, as the patient groups become smaller (n=78, n=31 and n=22) and patients with nutritional concerns are identified, the proportion of patients who have had some degree of dietary input can be seen to increase. This could imply that a proportion of appropriate patients are being offered help. However, the proportion of study patients who had not been previously referred to a dietician but were found to be at risk of malnutrition or malnourished, was high at 59.1%.

Explore whether the APG-SGA is able to predict whether patients are at risk of malnutrition as identified by the MNA and compare the sensitivity and specificity of the APG-SGA with the MNA

The PG-SGA is described in chapter 1. It has been validated in cancer patients and consists of two sections. The first section the patient completes but the second sections requires clinician assessment, including physical examination, which may limit its usefulness in busy clinical settings. The Abridged Patient Generated Subjective Global Assessment (APG-SGA) is a shortened version of the PG-SGA and can be completed by patients without requiring health professional input. If this tool was found to be adequately sensitive and specific in identifying patients at risk of malnutrition, the fact that patients could complete the questionnaire prior to

clinic appointments would help in saving time and also it would direct and focus consultations.

This study was exploring the usefulness of the APG-SGA and the scoring system that was used was designed by the researcher (JS). The APG-SGA consists of four questions. The total possible score was ten. Patients scored one point if their weight had decreased over the last two weeks and one point if they were eating less than usual. A maximum of four points was possible in each of the questions asking about symptoms and performance status. The range of scores is shown in table 6.8 and based on the scoring system used patients with higher scores are more likely to have nutritional needs. The APG-SGA scores were plotted against the MNA screening scores and the ROC curve was to the left of the line of no discrimination, area under the curve 0.799 (95%CI 0.695 to 0.903) (figure 6.1).

This suggests that compared to the gold-standard MNA screening score the APG-SGA is a relatively good test. Potential cut-off values were explored and it can be seen that as the APG-SGA scores increase, the sensitivity of the test decreases but the specificity increases. A cut-off value of one has a high sensitivity (93.5%) but very low specificity (27.7%). A cut-off value of two or three may be more useful. A cut-off value of two or greater is preferred due to the higher sensitivity, 83.9% versus 77.4% if a cut-off score of three used. It would seem that this tool might be useful in correctly identifying patients who may be at risk of malnutrition. The range of scores, using this scoring system, was one to ten. As patients do not need to score a very high score to be potentially at risk of malnutrition, it may be that certain questions within the APG-SGA are more informative than others and this could be explored in future work. Also due to the nature of the questions within the questionnaire, the APG-SGA provides an indication of “where” to intervene to improve patients nutritional status, eg by addressing nausea or mucositis. This would not be detected in either the MNA or MUST scores. The APG-SGA can be self-completed and does not require a health professional to administer unlike the MNA and MUST scores.

Limitations

The study sample size was small (n=78) and a larger study population would have enabled more robust comparison of the nutritional assessment tools being studied. Colorectal cancer is more prevalent in older patients but in this study population, 62.8% of patients were under seventy years of age. Patients were approached by the researcher in the outpatient clinic and given time to consider taking part before their appointment. Unwell patients, patients who were anxious about their visit and patients within unknown literacy problems may have been less willing to consent to take part and be under-represented in this sample. Unfortunately, the total number of patients who declined to take part was not formally recorded (although the fact that they were invited to take part was noted in their medical records). If it had been possible for the researchers, by increasing the sites of study recruitment e.g. primary care and palliative care settings, a larger number of patients could possibly have been approached and may have participated. Of the three assessment tools being studied, the MNA was used as the gold standard for a number of the statistical comparisons. The MNA has been validated in many patient populations, particularly older patients, but there is limited research validating the tool for use with cancer patients (82). The PG-SGA has been validated in cancer patient populations (95). Read et al reported a sensitivity of 97%, specificity of 54% using the PG-SGA in one hundred and fifty-seven newly diagnosed cancer patients and that the MNA "lacked specificity" (166). The MNA may over-estimate the risk of malnutrition in cancer patients due to the nature of questions comprising the score. For example, cancer patients may take more than three medications a day and eat many small meals instead of three large meals and so may score highly on MNA assessment when they are in fact maintaining satisfactory nutritional health (82).

Conclusions

Within our study population of patients with metastatic colorectal cancer, twenty two patients (28.2%) were found to be at risk of malnutrition or malnourished and in need of further nutritional assessment and support, if the MNA is used as the gold standard nutritional assessment tool. Given that this study sample included a higher proportion of younger (less than seventy years old) and probably fitter

group of patients (who were receiving treatments and well enough to attend clinic) compared to the average colorectal cancer patient population, this is likely to be an under-estimation of the scale of nutritional problems in metastatic colorectal cancer patients. It therefore indicates the importance of undertaking nutritional screening in all patients, as there are probably many more colorectal cancer patients with undetected nutritional problems in the community.

The MNA has been validated in elderly patients (86) but certain components of the score may need to be revised in order for it to be useful in the oncology outpatient clinic. The screening tool is quick to use, but the assessment tool requires further time and anthropometric measurements need to be taken which may limit its use in certain healthcare settings.

The MUST score is quick and easy to use. Compared to the MNA, we found the MUST score to have low sensitivity but high specificity. A number of patients who were at risk of malnutrition may have gone undetected. The MUST score has been validated in inpatient settings, where patients are more likely to be acutely unwell, but it may not be useful in assessing cancer patients who are at home or in community settings.

The APG-SGA tool was investigated and it may be a useful self-completion screening tool in identifying patients in need of further nutritional input. Further work needs to be done in exploring how to score patients, but in this study suitable cut-off values were identified. It could be a promising tool and it would be time-efficient in busy oncology outpatient clinics as the majority of patients would be able to complete the questionnaire themselves.

Nutrition is likely to be an issue in many cancer patients at some point during their care and so the assessment of nutritional status should be undertaken routinely. Many nutritional assessment tools are in use, but further research is required to establish the most appropriate tool to use in patients with cancer. The impact of any nutritional interventions should also be studied. An assessment tool, such as the APG-SGA, that could be completed by patients would be an advantage in a time-pressured clinical environment.

Chapter Six

6. Social isolation in cancer patients

6.1. Introduction

A patient's social situation can potentially have a considerable impact on many aspects of their journey as a cancer patient. The support of family and friends, psychologically and practically, can be instrumental in helping patients complete a course of treatment, attend hospital appointments and cope emotionally.

A social network is the structure through which support, in many forms, may be provided. It measures and records social ties such as the presence of a partner, number of friends and family members that a person has contact with and how often and participation in social activities within the community. A number of tools have been devised to formally measure and grade social networks. The Berkman-Syme social network index (SNI) was devised following a large community study undertaken in the 1960s and 1970s. The research showed that people with few social ties (with people and within their community) had a higher rate of death compared to those with numerous contacts socially (122).

Since then, numerous studies have looked at the importance of social networks and social isolation in many aspects of people's health and overall mortality. Some studies have focused on cancer patients and cancer-specific mortality. A large meta-analysis concluded that cancer patients have a higher mortality risk if their social network was small, they were unmarried and if they perceived themselves to have less support (172). In a large study of women with breast cancer, social isolation was shown to be an independent predictor of mortality (120). However, other factors in addition to the size of an individual's social network are important. It is recognized that emotional and psychological support is provided within social networks and the perceived availability of all forms of support impacts on patients quality of life (117).

Social isolation is more common in older age groups and around half of people aged seventy-five and over live alone in the UK (173). The Health Survey for England in 2005 looked at the health of older people. A section of the survey studied social capital and health (social support and networks) in people aged sixty-five and over across the United Kingdom (174). Social networks were measured through asking questions about perceived social support and contact with friends and family. In the survey, some lack of social support was reported by both sexes of all ages (29% men, 23% women) and a severe lack of social support was reported by 18% men and 11% of women (174). Participants were asked about contacts with friends and a greater percentage of older men (36%) reported low levels of contact with friends than women (31%). The percentage of respondents reporting low levels of contact increased with increasing age in both sexes (whilst medium levels decreased and high levels were similar across all age groups)(174). More men than women reported low levels of contact with family but this did not vary across age groups and 54% of were not a member of any organized social group (174).

Within the Sussex Cancer Network, many older people undergo cancer therapies. As older people are more likely to live alone, have fewer social contacts with family and friends and may be at increased risk of developing treatment-related side effects they are a particularly vulnerable group. In this observational survey we aimed to measure the degree of social isolation in outpatients attending Sussex Cancer Centre using a self-complete assessment tool (Berkman-Syme SNI) and to compare the rates of social isolation between older and younger patients.

6.2. Aims

1) To measure the degree of social isolation in all cancer patients attending our outpatient department using the Berkman-Syme Social Network Index.

2) To compare social isolation between older (≥ 70 years old) and younger (18-69 years old) patients.

6.3. Methods

A questionnaire was designed based on the questions used to construct the Berkman-Syme Social Network Index (SNI) [5] (APPENDIX L). The Berkman-Syme SNI is calculated from 4 questions about social status: marital status; number of close friends and relatives and frequency of contact; church membership and participation in social group activities. The index is calculated through combining the answers and intimate contacts are weighted more than church and group attendance [5]. The composite SNI score ranges from 1 (few social contacts, socially isolated) to 4 (numerous social contacts and socially integrated).

Over a ten week period, patients attending the outpatient department at the Sussex Cancer Centre, Brighton, were invited to complete the survey on registering their attendance at outpatients' reception. Patients completed the survey themselves and returned them to the receptionist. Information on their medical diagnosis was obtained from their clinic attendance record.

Chi-Squared test was used to analyse the differences between those aged 70 and over or under 70 years old. Data analysis was undertaken using Excel and SPSS programmes.

6.4. Results

6.4.1. Patient population

Three hundred and fifty-four completed questionnaires were returned. Three questionnaires were included in the analysis due to illegibility or because they were not fully completed. As a result 351 responses were analysed in total. Based on the number of patients attending outpatient clinics within the time period of the survey distribution, the overall survey response rate was 36.3%.

Two hundred and fifty (71.2%) of patients were under 70 years of age, of whom 136 (54.4%) were male and 114 (45.6%) female. One hundred and one (28.8%) were 70 years old and over, of whom 65 (64.4%) were male and 36 (35.6%) were female.

The five most common diagnoses were: urological cancer (22.2%), lymphoma (16.2%), gastrointestinal cancers (14.5%), head and neck cancers (12.3%) and breast cancer (9.7%). The majority (71%) of patients were not receiving active treatment (chemotherapy or radiotherapy) at the time of the survey. Of those completing the survey 174 (49.6%) were in the curative setting and 165 (47%) in the palliative setting (status unknown in 12). There were no significant differences between the two age groups (above and below 70 years) in terms of whether patients were receiving treatment or treatment intent at the time of the survey.

6.4.2. Social situation and contacts

Table 6.1 shows a breakdown of the responses, by age group, to the component questions that are used to calculate the SNI score.

Sixty-eight (67.3%) respondents in the 70 and over age group were married, compared to 144 (57.6%) of those aged 70 and under. The older age group were more likely to be widowed and less likely to be divorced/separated or single than the under 70s (χ^2 =39.170, df=3, p<0.001).

There was a significant association between age group and number of close friends.
Older patients were more likely than younger to have “no, 1 or 2 friends”: 23.7% vs 12.8% (χ^2=9.500, df=3, p=0.023).

There was no significant association between age group and number of close relatives (p=0.643) or number of contacts (p=0.560).

Older patients were more likely to belong to a church or religious group (χ^2 =6.512, p=0.011).The proportion of older and younger patients reporting that they did not belong to any social group was similar (54.5% v 56%) and overall there was no significant difference in social group membership between the two age groups (χ^2 =0.439, p=0.803).

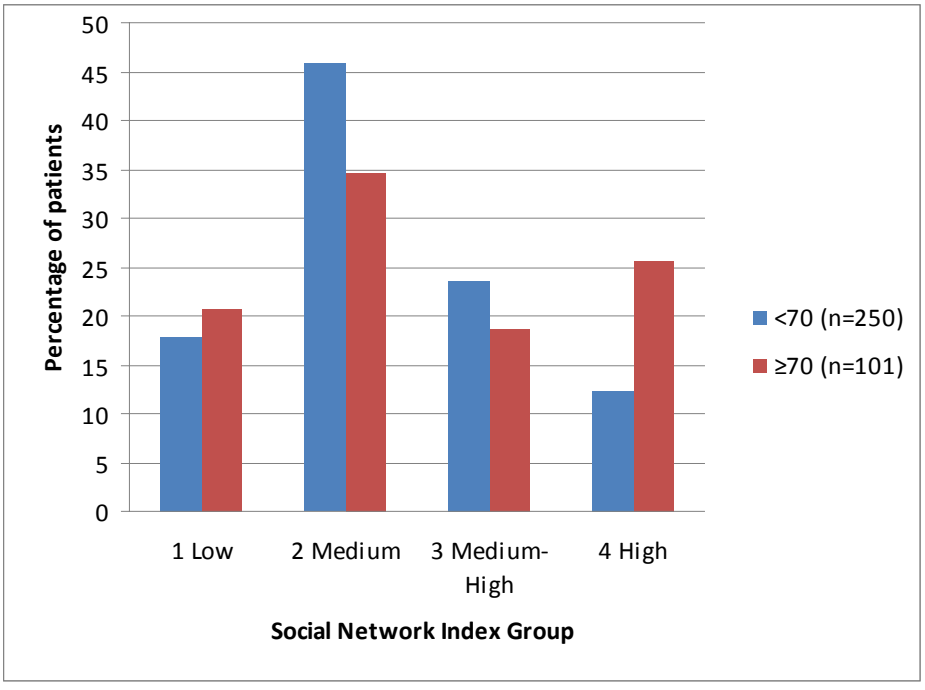
Table 6.1. Responses to component questions of Berkman-Syme Social Network Index (SNI), and SNI total score (n= 351)

	Under 70 years old (n=250) (%)	≥70 years old (n=101) (%)	TOTAL (%)
Marital Status			
Divorced	34 (13.6)	5 (5.0)	39 (11.1)
Married	144 (57.6)	68 (67.3)	212 (60.4)
Single	43 (17.2)	5 (5.0)	48 (13.7)
Separated	15 (6.0)	0 (0.0)	15 (4.3)
Widowed	14 (5.6)	23 (22.7)	37 (10.5)
Number of close friends	**Under 70 years old (n=250) (%)**	**≥70 years old (n=101) (%)**	**TOTAL (%)**
None	0 (0.0)	8 (7.9)	8 (2.3)
1 or 2	32 (12.8)	16 (15.8)	48 (13.7)
3 to 5	108 (43.2)	38 (37.6)	146 (41.6)
6 to 9	53 (21.2)	12 (11.9)	65 (18.5)
10+	57 (22.8)	25 (24.8)	84 (23.9)
Number of close relatives	**Under 70 years old (n=250) (%)**	**≥70 years old (n=101) (%)**	**TOTAL (%)**
None	7 (2.8)	1 (1.0)	8 (2.3)
1 or 2	45 (18.0)	21 (20.8)	66 (18.8)
3 to 5	104 (41.6)	39 (38.6)	143 (40.7)
6 to 9	55 (22.0)	19 (18.8)	74 (21.1)
10+	39 (15.6)	21 (20.8)	60 (17.1)
How many friends/relatives seen once a month	**Under 70 years old (n=250) (%)**	**≥70 years old (n=101) (%)**	**TOTAL (%)**
None	7 (2.8)	5 (5.0)	12 (3.4)
1 or 2	47 (18.8)	23 (22.8)	70 (19.9)
3 to 5	115 (46.0)	41 (40.6)	156 (44.4)
6 to 9	46 (18.4)	16 (15.8)	62 (17.7)
10+	35 (14.0)	16 (15.8)	51 (14.5)
Church/ Religious Group Membership	**Under 70 years old (n=250) (%)**	**≥70 years old (n=101) (%)**	**TOTAL (%)**
Yes	30 (12.0)	23 (22.8)	53 (15.1)
No	220 (88.0)	78 (77.2)	298 (84.9)
Social Group membership	**Under 70 years old (n=250) (%)**	**≥70 years old (n=101) (%)**	**TOTAL (%)**
None	140 (56.0)	55 (54.5)	195 (55.6)
1 group	71 (28.4)	32 (31.7)	103 (29.3)
>1 group	39 (15.6)	14 (13.9)	53 (15.1)
Social Network Index (SNI Score)	**Under 70 years old (n=250) (%)**	**≥70 years old (n=101) (%)**	**TOTAL (%)**
1 Low	45 (18.0)	21 (20.8)	66 (18.8)
2 Medium	115 (46.0)	35 (34.7)	150 (42.7)
3 Medium- High	59 (23.6)	19 (18.8)	78 (22.2)
4 High	31 (12.4)	26 (25.7)	57 (16.3)

The SNI scores, calculated from the individual component questions, for the study population are shown in Table 6.1 and Figure 6.1. An SNI score of 1 represents individuals who are socially isolated, a score of 3 or 4 represents those who are more socially integrated.

Eighteen percent of the younger age group and 20.8% of the older age group were socially isolated (SNI score=1). Older patients were more likely to have strong social ties (SNI score =4) compared to younger patients (25.7% v 12.4%, χ^2=11.094, p=0.011).

Figure 6.1. Social Network Index (SNI) for study population according to patient age (n=351). (SNI score 1= socially isolated,; SNI score 4=strong social ties).



6.5. Discussion

This survey shows that a significant proportion of patients of all ages (18.8%), attending our oncology outpatient department are socially isolated. This may not always be detected by health professionals. Interestingly, a greater proportion of our older cancer patients had a high level of social integration compared to younger patients and this difference was found to be statistically significant. This goes against the assumption that as we age, our social network and available social support may diminish. Although it should be recognised that the different age groups derived social support by different means. Older patients were more likely to be married or attend a church or religious group. The latter could provide additional types of social support such as emotional and instrumental or practical help. Younger patients on the other hand were more likely to have more than two friends. 55.6% of all respondents were not a member of any organized or informal social group and there was not significant difference between older and younger patients (54.4% <70 years old versus 56.0% older patients). This level of non-participation in social groups was also reported in a national survey of older people in the UK (174).

The importance of social networks has been described in a number of different cancer populations. A study of women with breast cancer has shown that socially isolated women had a higher incidence of all-cause mortality (HR=1.66, 95% CI 1.04-2.65) and a two-fold increased risk of death from breast cancer (HR=2.14, 95% CI 1.11-4.12) [3]. In a group of colorectal cancer patients, emotional and instrumental support affected health related quality of life [2].

This observational study has a number of limitations. The response rate of the survey was low (36.3%). Those patients' who had poor eyesight, poor literacy skills, in whom English was not their preferred language and those who were frail or unwell may not have taken part. In addition the survey only included ambulatory patients able to attend clinic for treatment or follow up appointments. The very frail will not have been fully represented in this sample.

The structure of today's modern social network is changing. This can be reflected in the differing ways in which people (of all ages) may keep in contact, for example, by texting, email and social networking websites. The Berkman-Syme SNI score was designed in the 1970s .The questions that make up the overall score do not necessarily cover more modern methods of accessing support, which patients may perceive as important. Therefore certain groups of patients may be "underscored" and fall into a lower SNI score category.

In summary, social isolation was relatively common in all age groups in this ambulatory population of patients attending our cancer centre however due to the limitations outlined previously, one should interpret the results with caution.
The presence of social isolation could have significant implications for how patients experience treatment, subsequent outcomes and patients willingness to accept treatment. Healthcare professionals should therefore ask patients of all ages about their social situation and availability of social support, using tools sensitive to current methods of maintaining social contact. It is important that socially isolated patients are identified and increased support offered.

Summary

7. Summary

The epidemiology of colorectal cancer in patients aged sixty-five and over, in Great Britain, has been described. Colorectal cancer is the third commonest cancer and this analysis has shown that the number of older people diagnosed with colorectal cancer has increased by 61.6% during the time period 1971 to 2006. This amounts to around an extra 10,000 cases per year. The increase in incidence is a reflection of an increasingly ageing population and changes in aetiological factors over time. The introduction of the national bowel screening programme in 2006 and planned commencement of one-only flexible sigmoidoscopy in patients aged fifty-five, is likely to increase patients' awareness of bowel cancer, its symptoms and in addition to detecting patients with pre-malignant polyps, may also encourage symptomatic patients to seek medical advice earlier. The planned age extension of colorectal cancer screening is also very likely to have an impact on the number of cases of colorectal cancer in older patients in the future. This analysis highlights the current and increasing burden of colorectal cancer in older patients in Great Britain.

The management of older patients with colorectal cancer is challenging and needs to take into account current health status. The assessment of older colorectal cancer patients using a comprehensive geriatric assessment (CGA), was undertaken in one hundred and twelve patients aged sixty-five and over. The aim was to ascertain if specific assessment tools could predict for functional decline or death at one year in all patients and if they could predict for severe chemotherapy toxicity in patients receiving adjuvant chemotherapy. Follow-up at one year found that 20.5% of patients (23/112) had functionally declined or died. The primary aim was to ascertain if the Vulnerable Elders Survey (VES-13) predicted for functional decline or death at one year. A greater proportion of patients with VES-13 scores of three or greater had functionally declined at one year compared to patients with scores under three, but the difference between the two groups was not statistically significant ($p=0.132$). Analysis did not confirm the primary hypothesis but the sample size was smaller than planned and so the study was

under-powered. No other assessment tools were found to be predictive of functional decline at one year but recruitment of patients continues, so further analysis with a larger sample size will be possible in the near future.

Thirty patients (26.7% of all patients) received adjuvant chemotherapy and twenty seven (90% of patients on chemotherapy) developed severe chemotherapy toxicity. Severe toxicity was defined as any of: grade III/IV toxicity; dose reduction; unplanned hospitalization; treatment discontinuation or death within thirty days of treatment. Three patients (10%) required hospital admission. There was a trend for functional scores to be worse at the end of treatment, but the sample size was too small to establish if a particular assessment tool was useful in predicting for severe chemotherapy toxicity and for any formal statistical comparisons to be made.

Logistic regression analysis found that higher performance status scores were associated with a higher risk of functional decline or death at one year and this was statistically significant, p=0.027. For every one point increase in the performance status score, the risk of functional decline increased by 2.34 (95% CI 1.10-4.96). In this study, performance status scoring was performed jointly by the assessor and patient and this may have resulted in more accurate scores than if only the assessor had assigned patients a score. This may be important to consider in older patients as performance status scores may over-estimate their fitness and patient participation in assessment may counter balance this.

The value of assessment tools such as a CGA, VES-13 and G8 in predicting treatment-related toxicity and future functional decline is currently being researched internationally. Hurria et al, identified certain risk factors that could help predict and stratify patients' risk of chemotherapy toxicity (175). Their predictive model included patient and tumour characteristics, chemotherapy regimen to be used, blood parameters, functional scores and social activity (175). The G8 score has been investigated as part of the ONCODAGE project and has been reported to be useful as a screening tool to predict patients likely to fail at least one domain of a CGA (43). The usefulness of the G8 score in predicting the likelihood of patients in developing treatment-related toxicities whilst undergoing systemic chemotherapy had not been published at time of our study design. We aimed to

investigate this in our project, “Global health measures and chemotherapy”. Patients self-completed questionnaires measuring performance status, G8 and VES-13 scores prior to commencing chemotherapy. In this study, responses from one hundred and eight five patients aged sixty-five and over, who planned to undergo chemotherapy, were analysed and one hundred and ten (59.5%) developed severe chemotherapy toxicity. Of patients who scored below the G8 cut-off score of fourteen, 64.6% developed severe toxicity compared to 46.9% who had higher scores. The difference between these groups was significant, p=0.025. Of patients who scored above the VES-13 cut-off score of three, 76.3% developed severe toxicity compared to 54.1% who scored below the cut-off value. The difference between these groups was also found to be significant, p=0.015. No significant difference between the proportion of patients with performance status scores of zero or one versus those of performance status two or higher who developed severe chemotherapy toxicity was found, p=0.318.

Older patients about to commence chemotherapy may be at increased risk of treatment-related toxicities if they score low G8 scores (≤14) or high VES-13 (≥ 3) scores. A low G8 score is considered to be predictive of failing a CGA and a high VES-13 score indicates patients are at increased risk of functional decline or death at two years (38). In these groups of patients a full CGA should be considered to establish if patients have any deficits in assessment domains that could be supported by appropriate interventions and which may mitigate any potential treatment side-effects. In addition, the clinician should consider these factors when formulating management plans and considering treatment regimens. For example chemotherapy drug combinations, timing and dosing and weighing up the risks versus overall benefit of treatment.

The use of functional assessment tools that patients can self-complete would save time in a busy clinic and potentially provide clinicians with information that may inform management discussions with patients. In our study, the majority of patients were able to self-complete the questionnaires but relying on this as an assessment method has limitations. Patients with reading, writing or language difficulties may be under-represented in a study sample if appropriate support is not made available. Some patients may be over optimistic in answers they provide

to questions about their general health. They may have concerns that if they provide realistic answers it may affect treatment options. Conversely, some patients may feel more able to answer questions honestly in a written format. The use of self-completed questionnaires would be feasible and should be explored but it is important that patients with specific needs are identified and adequate support provided.

Older people are at risk of nutritional problems for a number of reasons including the presence of co-morbid illnesses, physiological changes and psychosocial issues. Many cancer patients have nutritional problems, which may be more common in certain tumour types. The disease process, particularly in older patients with metastatic cancers, and the side effects of chemotherapy and radiotherapy treatments also can affect patients' nutritional intake. Formal assessment on a regular basis would ensure dietician referral and intervention is initiated. A time-efficient and reliable screening tool would be helpful in the outpatient setting as this is the environment that the majority of cancer patients are seen and managed. In our study of patients with metastatic colorectal cancer three nutritional screening tools were assessed (MNA, MUST and APG-SGA score). In the study population of seventy-eight patients, twenty-two patients (28.2%) were found to be at risk of malnutrition or malnourished and in need of further nutritional assessment and input. Of these, thirteen patients (59.1%) had not previously seen a dietician and had previously undetected nutritional concerns. On comparing MUST scores with MNA scores, the MUST score had a low sensitivity (51.6%) but higher specificity (89.4%). In our study population there was no statistically significant difference in rates of malnutrition between older and younger patients but the sample size was small. The usefulness of the APG-SGA tool was explored and scores compared with the MNA assessment tool. As a screening nutritional tool, the APG-SGA looks promising. In our study it had high sensitivity and specificity. Further work on the scoring system, validity and reliability is required. As patients are able to complete the APG-SGA themselves, it would be advantageous to use in many healthcare settings.

Social networks and the support provided by friends and family both informally and formally are often vital in helping patients through a course of cancer treatment. Socially isolated cancer patients may be at higher risk of death and the support provided by an individual's social network has been shown to affect their overall quality of life. The observational survey that we carried out in our oncology outpatient department, using the Berkman-Syme Social Network Index, showed that a significant proportion (18.8%) of patients of all ages were socially isolated. We had hypothesized that rates of social isolation may be higher in older patients, however in our study population a greater proportion of older cancer patients had strong social ties compared to younger patients and this difference was found to be statistically different. Our survey had limitations and the difference observed may not be reflective of cancer patient population, however social isolation may be present in patients of all ages. It is important that health professionals ask patients of all ages about their social situation and appropriate support offered if required.

This MD highlights the increasing burden of colorectal cancer in older patients and how the incorporation of tools assessing fitness, malnutrition and social isolation may be practical and improve the care of these patients.

J Stokoe
May 2012

Glossary

AAPC	Average annual percent change
ACE-27	Adult Comorbidity Evaluation 27
ADL	Activities of Daily Living
APC	Annual percent change
APG-SGA	Abrigded Patient Generated Subjective Global Assessment
ATAC	Arimidex, Tamoxifen, Alone or in Combination Study
BMI	Body Mass Index
CALGB	Cancer and Leukaemia Group B
CCI	Charlson Comorbidity Index
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CIRS	Cumulative Illness Rating Scale
CIRS-G	Cumulative Illness Rating Scale- Geriatric
CRC	Colorectal Cancer
CRP	C Reactive Protein
CRUK	Cancer Research United Kingdom
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FOLFOX	FOLinic acid, Fluorouracil, OXaliplatin (chemotherapy regimen)
GDS	Geriatric Depression Score
G8	G8 or ONCODAGE score
HADS	Hospital Anxiety and Depression Scale
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
ICED	Index of Coexistent Disease
JS	Dr Joanna Stokoe (researcher)
KPS	Karnofsky Performance Status
MDM	Multi-disciplinary meeting
MMSE	Mini-mental state examination
MNA	Mini Nutritional Assessment tool

MOS	Medical Outcomes Study
MOS-SSS	Medical Outcomes Study Social Support Survey
MOSAIC	Multi-centre International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant treatment of Colon Cancer
MUST	Malnutrition Universal Screening Tool
NCCN	National Comprehensive Cancer Network
NCIN	National Cancer Intelligence Network
NICE	National Institute for Clinical Excellence
ONS	Office for National Statistics
PGSGA	Patient Generated Subjective Global Assessment
PS	Performance status
ROC	Receiver operating characteristic
SIOG	International Society of Geriatric Oncology
SNI	Social Network Index
SPSS	Statistical Package for the Social Sciences
STATA	Statistical software package
VES-13	Vulnerable Elders Survey
TFT	Thyroid Function Test
TUG	Timed Up and Go
UICC	Union for International Cancer Control
UK	United Kingdom
WHO	World Health Organisation

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APPENDIX

INDEX OF APPENDICES

APPENDIX A

ECOG/WHO Performance Status scale

Performance status scale (0-4) used in studies that comprise this thesis. This format was used for doctor (chapter 3) and patient self-completion (chapter 4).

WHICH OF THE FOLLOWING BEST DESCRIBES HOW YOU ARE CURRENTLY?

I am fully active and more or less as I was before my illness	☐
I cannot carry out heavy physical work, but can do everything else	☐
I am up and about more than half the day, I can look after myself but am not well enough to work.	☐
I am in bed or sitting in a chair for more than half the day and I need some help in looking after myself	☐
I am in bed or in a chair all the time and need a lot of looking after.	☐

APPENDIX B

The Vulnerable Elders (VES-13) score

1. What is your age?.....

2. In general, compared to other people your age, would you say that your health is (please circle one):

Poor Fair Good Very good Excellent

3. How much difficulty, on average, do you have with the following physical activities?

(please tick one box in each row)

	No difficulty	**A little difficulty**	**Some difficulty**	**A lot of difficulty***	**Unable to do***
Stooping, crouching or kneeling					
Lifting or carrying objects as heavy as 10 pounds (5kg)					
Reaching or extending arms above shoulder level					
Writing or handling and grasping small objects					
Walking a quarter of a mile					
Heavy housework such as scrubbing floors or washing windows					

4. Because of your health or physical condition, do you have any difficulty (please circle):

a) Shopping for personal items (like toiletries or medicines)?

NO

YES ⟶ Do you get help with your shopping? YES* NO

DON'T DO ⟶ Is that because of your health? YES* NO

VES-13 Continued:

Because of your health or physical condition, do you have any difficulty (please circle):

b) Managing money (like keeping track of expenses or paying bills)?

NO

YES → Do you get help with managing money? YES* NO

DON'T DO → Is that because of your health? YES* NO

c) Walking across the room (use of a walking stick or frame is OK)?

NO

YES → Do you get help with walking? YES* NO

DON'T DO → Is that because of your health? YES* NO

d) Doing light housework (like washing dishes, tidying up or light cleaning)?

NO

YES → Do you get help with light housework? YES* NO

DON'T DO → Is that because of your health? YES* NO

e) Bathing or showering?

NO

YES → Do you get help with bathing or showering? YES* NO

DON'T DO → Is that because of your health? YES* NO

VES-13 Scoring:

Q1: 1 point for age 75-84, 3 points for ≥ 85
Q2: 1 point for FAIR or POOR
Q3: 1 point for each reponse* of "a lot of difficulty" or "unable to do" – maximum of 2 points
Q4: 4 points for one or more* "YES" responses

APPENDIX C

G8 score

	Items	Possible answers	Score
1	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	**0**: severe reduction in food intake **1**: moderate reduction in food intake **2**: normal food intake	……...
2	Weight loss during the last 3 months?	**0**: weight loss >3kg **1**: does not know **2**: weight loss between 1 and 3 kg **3**: no weight loss	……...
3	Mobility	**0**: bed or chair bound **1**: able to get out of bed/chair but does not go out **2**: goes out	……...
4	Neuropsychological problems	**0**: severe dementia or depression **1**: mild dementia or depression **2**: no psychological problems	……...
5	Body Mass Index (weight in kg/height in m^2)	**0**: BMI less than 19 **1**: BMI 19 to less than 21 **2**: BMI 21 to less than 23 **3**: BMI 23 or greater	……...
6	Takes more than 3 medications per day	**0**: yes **1**: no	……...
7	In comparison with other people of the same age, how does the patient consider his/her health status?	**0,0**: not as good **0,5**: does not know **1,0**: as good **2,0**: better	……...
8	Age	**0**: >85 **1**: 80-85 **2**: <80	……...
	Total score (0-17)		……...

APPENDIX D
Activity of Daily Living (ADL) score

BATHING	
□ Receives no assistance (gets in and out of bath or shower by self if bath is usual means of bathing)	I
□ Receives assistance in bathing only one part of the body (such as back or leg)	I
□ Receives assistance in bathing more than one part of the body (or not bathed)	D
DRESSING	
□ Gets clothes and gets completely dressed without assistance	I
□ Gets clothes and gets completely dressed without assistance except for assistance in tying shoe laces	I
□ Receives assistance in getting clothes or in getting dressed, or stays partly or completely undressed	D
TOILETTE	
□ Goes to "toilet room", cleans self, and arranges clothes without assistance (may use object for support such as cane, walk frame, or wheelchair and may manage night bedpan or commode, emptying same in morning)	I
□ Receives assistance in going to "toilet room" or in cleaning self or in arranging clothes after elimination or in use of night bedpan or commode	D
□ Doesn't go to room termed "toilet" for the elimination process	D
TRANSFER	
□ Moves in and out of bed as well as in and out of chair without assistance (may be using object for support such as cane or walk frame)	I
□ Moves in and out of bed or chair with assistance	D
□ Doesn't get out of bed	D
CONTINENCE	
□ Controls urination and bowel movement completely by self	I
□ Has occasional "accidents"	D
□ Needs supervision for urine or bowel control; catheter is used, or is incontinent	D

ADL score continued

FEEDING	
□ Feeds self without assistance	I
□ Feeds self except for getting assistance in cutting meat or buttering bread	I
□ Receives assistance in feeding or is fed partly or completely by using tubes or intravenous fluid	D
I = independent / D = dependent	

Number of times independent (0-6)	……
Number of times dependent (0-6)	……

APPENDIX E

Instrumental Activity of Daily Living (IADL) score

	Score
ABILITY TO USE TELEPHONE	
□ Operates telephone on own initiative, looks up and dials numbers, etc.	1
□ Dials a few well known-numbers	1
□ Answers telephone but does not dial	1
□ Does not use telephone at all	0
SHOPPING	
□ Takes care of all shopping needs independently	1
□ Shops independently for small purchases	0
□ Needs to be accompanied on any shopping trip	0
□ Completely unable to shop	0
FOOD PREPARATION	
□ Plans, prepares and serves adequate meals independently	1
□ Prepares adequate meals if supplied with ingredients	0
□ Heats, serves, and prepares meals but does not maintain adequate diet	0
□ Needs to have meals prepared and served	0
HOUSEKEEPING	
□ Maintains house alone or with occasional assistance (e.g. “heavy work domestic help”)	1
□ Performs light daily tasks such as dish-washing, bed-making	1
□ Performs light daily tasks but cannot maintain acceptable level of cleanliness	1
□ Needs help with all home maintenance tasks	1
□ Does not participate in any housekeeping tasks	0

IADL score continued

	Score
LAUNDRY	
□ Does personal laundry completely	**1**
□ Launders small items-rinses stocking, etc.	**1**
□ All laundry must be done by others	**0**
MODE OF TRANSPORTATION	
□ Travels independently on public transportation or drives own car	**1**
□ Arranges own travel via taxi, but does not otherwise use public transportation	**1**
□ Travels on public transportation when accompanied by other	**1**
□ Travel limited to taxi or automobile with assistance of another	**0**
□ Does not travel at all	**0**
RESPONSABILITY FOR OWN MEDICATION	
□ Is responsible for taking medication in correct dosages at correct time	**1**
□ Takes responsibility if medication is prepared in advance in separate dosage	**0**
□ Is not capable of dispensing own medication	**0**
ABILITY TO HANDLE FINANCES	
□ Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to the bank), collects and keeps track of income	**1**
□ Manages day to day purchases, but needs help with banking, major purchases, etc.	**1**
□ Incapable of handling money	**0**
Total score (0-8)	……

APPENDIX F

Charlson comorbidity index

Comorbidities	Present	Points
Myocardial infarction		**1**
Congestive cardiac failure		**1**
Peripheral vascular disease		**1**
Cerebrovascular disease (except hemiplegia)		**1**
Dementia		**1**
Chronic obstructive pulmonary disease		**1**
Connective tissue disease		**1**
Ulcers		**1**
Mild liver disease		**1**
Diabetes Mellitus (without end-organ damage)		**1**
Diabetes Mellitus (with end-organ damage)		**2**
Hemiplegia		**2**
Moderate / Severe chronic renal failure		**2**
Second malignancy (non metastatic)		**2**
Leukaemia		**2**
Lymphoma		**2**
Moderate / Severe liver disease		**3**
Second malignancy (metastatic)		**6**
AIDS		**6**
Total points (0-37)		……..

APPENDIX G

ACE-27 comorbidity score

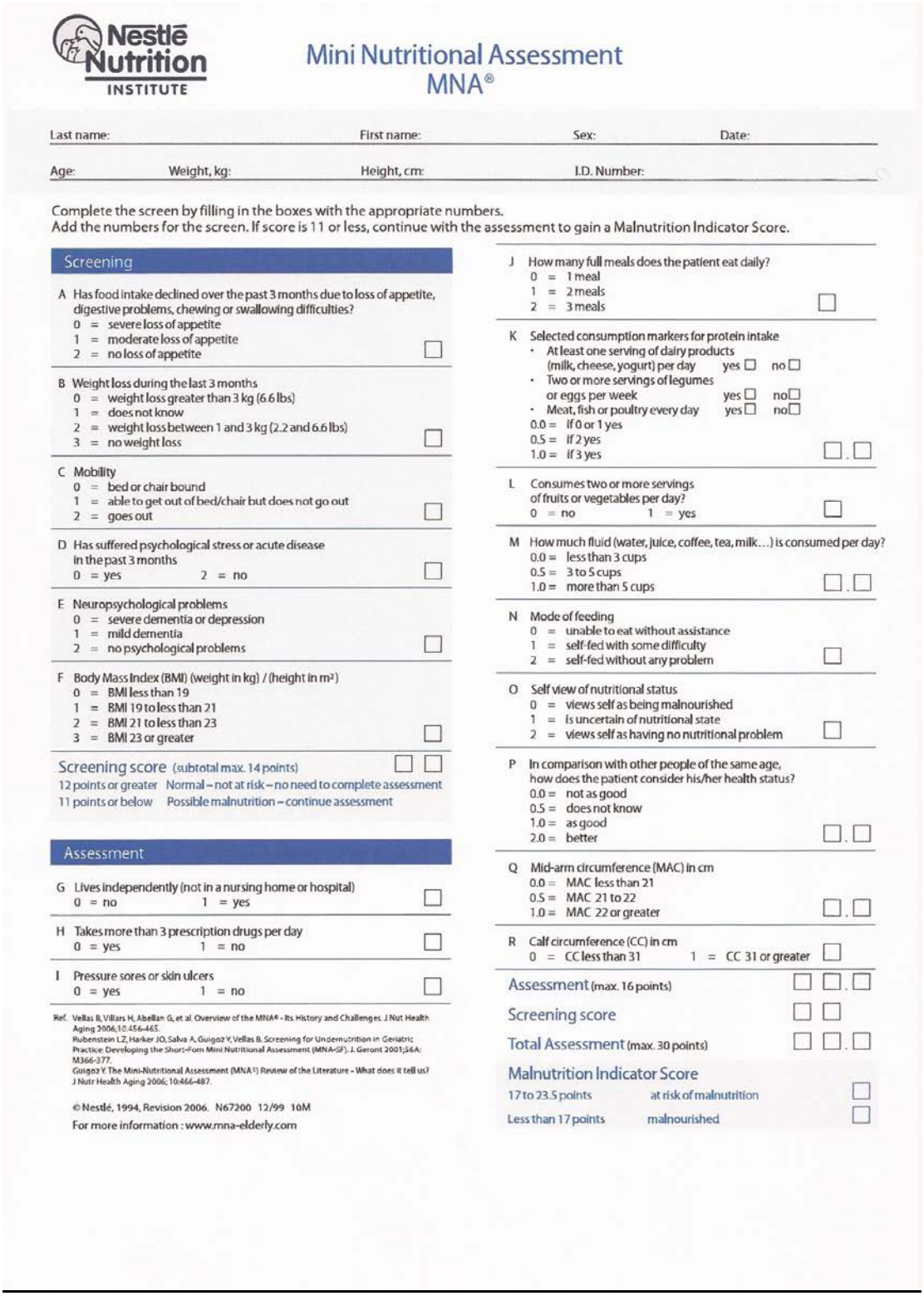
Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Cardiovascular System			
Myocardial Infarct	☐ MI ≤ 6 months	☐ MI > 6 months ago	☐ MI by ECG only, age undetermined
Angina / Coronary Artery Disease	☐ Unstable angina	☐ Chronic exertional angina ☐ Recent (≤ 6 months) Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA) ☐ Recent (≤ 6 months) coronary stent	☐ ECG or stress test evidence or catheterization evidence of coronary disease without symptoms ☐ Angina pectoris not requiring hospitalization ☐ CABG or PTCA (>6 mos.) ☐ Coronary stent (>6 mos.)
Congestive Heart Failure (CHF)	☐ Hospitalized for CHF within past 6 months ☐ Ejection fraction < 20%	☐ Hospitalized for CHF >6 months prior ☐ CHF with dyspnea which limits activities	☐ CHF with dyspnea which has responded to treatment ☐ Exertional dyspnea ☐ Paroxysmal Nocturnal Dyspnea (PND)
Arrhythmias	☐ Ventricular arrhythmia ≤ 6 months	☐ Ventricular arrhythmia > 6 months ☐ Chronic atrial fibrillation or flutter ☐ Pacemaker	☐ Sick Sinus Syndrome ☐ Supraventricular tachycardia
Hypertension	☐ DBP≥130 mm Hg ☐ Severe malignant papilledema or other eye changes ☐ Encephalopathy	☐ DBP 115-129 mm Hg ☐ DBP 90-114 mm Hg while taking antihypertensive medications ☐ Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	☐ DBP 90-114 mm Hg while not taking antihypertensive medications ☐ DBP <90 mm Hg while taking antihypertensive medications ☐ Hypertension, not otherwise specified
Venous Disease	☐ Recent PE (≤ 6 mos.) ☐ Use of venous filter for PE's	☐ DVT controlled with Coumadin or heparin ☐ Old PE > 6 months	☐ Old DVT no longer treated with Coumadin or Heparin
Peripheral Arterial Disease	☐ Bypass or amputation for gangrene or arterial insufficiency < 6 months ago ☐ Untreated thoracic or abdominal aneurysm (≥6 cm)	☐ Bypass or amputation for gangrene or arterial insufficiency > 6 months ago ☐ Chronic insufficiency	☐ Intermittent claudication ☐ Untreated thoracic or abdominal aneurysm (< 6 cm) ☐ s/p abdominal or thoracic aortic aneurysm repair
Respiratory System			
	☐ Marked pulmonary insufficiency ☐ Restrictive Lung Disease or COPD with dyspnea at rest despite treatment ☐ Chronic supplemental O_2 ☐ CO_2 retention (pCO_2 > 50 torr) ☐ Baseline pO_2 < 50 torr ☐ FEV1 (< 50%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which limits activities ☐ FEV1 (51%-65%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which has responded to treatment ☐ FEV1 (66%-80%)
Gastrointestinal System			
Hepatic	☐ Portal hypertension and/or esophageal bleeding ≤ 6 mos. (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)	☐ Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	☐ Chronic hepatitis or cirrhosis without portal hypertension ☐ Acute hepatitis without cirrhosis ☐ Chronic liver disease manifested on biopsy or persistently elevated bilirubin (>3 mg/dl)
Stomach / Intestine	☐ Recent ulcers(≤ 6 months ago) requiring blood transfusion	☐ Ulcers requiring surgery or transfusion > 6 months ago	☐ Diagnosis of ulcers treated with meds ☐ Chronic malabsorption syndrome ☐ Inflammatory bowel disease (IBD) on meds or h/o with complications and/or surgery
Pancreas	☐ Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	☐ Uncomplicated acute pancreatitis ☐ Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or GI bleeding)	☐ Chronic pancreatitis w/o complications

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Renal System			
End-stage renal disease	☐ Creatinine > 3 mg% with multi-organ failure, shock, or sepsis ☐ Acute dialysis	☐ Chronic Renal Insufficiency with creatinine >3 mg% ☐ Chronic dialysis	☐ Chronic Renal Insufficiency with creatinine 2-3 mg%.
Endocrine System	**(Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)**		
Diabetes Mellitus	☐ Hospitalization ≤ 6 months for DKA ☐ Diabetes causing end-organ failure ☐ retinopathy ☐ neuropathy ☐ nephropathy* ☐ coronary disease* ☐ peripheral arterial disease*	☐ IDDM without complications ☐ Poorly controlled AODM with oral agents	☐ AODM controlled by oral agents only
Neurological System			
Stroke	☐ Acute stroke with significant neurologic deficit	☐ Old stroke with neurologic residual	☐ Stroke with no residual ☐ Past or recent TIA
Dementia	☐ Severe dementia requiring full support for activities of daily living	☐ Moderate dementia (not completely self-sufficient, needs supervising)	☐ Mild dementia (can take care of self)
Paralysis	☐ Paraplegia or hemiplegia requiring full support for activities of daily living	☐ Paraplegia or hemiplegia requiring wheelchair, able to do some self care	☐ Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but able to do some self care	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	☐ Recent suicidal attempt ☐ Active schizophrenia	☐ Depression or bipolar disorder uncontrolled ☐ Schizophrenia controlled w/ meds	☐ Depression or bipolar disorder controlled w/ medication
Rheumatologic	**(Incl. Rheumatoid Arthritis, Systemic Lupus, Mixed Connective Tissue Disorder, Polymyositis, Rheumatic Polymyositis)**		
	☐ Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)	☐ Connective Tissue Disorder on steroids or immunosuppressant medications	☐ Connective Tissue Disorder on NSAIDS or no treatment
Immunological System	**(AIDS should not be considered a comorbidity for Kaposi's Sarcoma or Non-Hodgkin's Lymphoma)**		
AIDS	☐ Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	☐ HIV+ with h/o defining illness. $CD4^+ < 200/\mu L$	☐ Asymptomatic HIV+ patient. ☐ HIV^+ w/o h/o AIDS defining illness. $CD4^+ > 200/\mu L$
Malignancy	**(Excluding Cutaneous Basal Cell Ca., Cutaneous SCCA, Carcinoma in-situ, and Intraepithelial Neoplasm)**		
Solid Tumor including melanoma	☐ Uncontrolled cancer ☐ Newly diagnosed but not yet treated ☐ Metastatic solid tumor	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago
Leukemia and Myeloma	☐ Relapse ☐ Disease out of control	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o leukemia or myeloma with last Rx > 1 yr prior
Lymphoma	☐ Relapse	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o lymphoma w/ last Rx >1 yr prior
Substance Abuse	**(Must be accompanied by social, behavioral, or medical complications)**		
Alcohol	☐ Delirium tremens	☐ Active alcohol abuse with social, behavioral, or medical complications	☐ H/o alcohol abuse but not presently drinking
Illicit Drugs	☐ Acute Withdrawal Syndrome	☐ Active substance abuse with social, behavioral, or medical complications	☐ H/o substance abuse but not presently using
Body Weight			
Obesity		☐ Morbid (i.e., BMI ≥ 38)	

OVERALL COMORBIDITY SCORE (Circle one.) **0** None **1** Mild **2** Moderate **3** Severe **9** Unknown

APPENDIX H

Mini Nutritional Assessment (MNA) Tool



Nestlé Nutrition INSTITUTE

Mini Nutritional Assessment MNA®

Last name: First name: Sex: Date:

Age: Weight, kg: Height, cm: I.D. Number:

Complete the screen by filling in the boxes with the appropriate numbers.
Add the numbers for the screen. If score is 11 or less, continue with the assessment to gain a Malnutrition Indicator Score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe loss of appetite
1 = moderate loss of appetite
2 = no loss of appetite

B Weight loss during the last 3 months
0 = weight loss greater than 3 kg (6.6 lbs)
1 = does not know
2 = weight loss between 1 and 3 kg (2.2 and 6.6 lbs)
3 = no weight loss

C Mobility
0 = bed or chair bound
1 = able to get out of bed/chair but does not go out
2 = goes out

D Has suffered psychological stress or acute disease in the past 3 months
0 = yes 2 = no

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems

F Body Mass Index (BMI) (weight in kg) / (height in m²)
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater

Screening score (subtotal max. 14 points)
12 points or greater Normal – not at risk – no need to complete assessment
11 points or below Possible malnutrition – continue assessment

Assessment

G Lives independently (not in a nursing home or hospital)
0 = no 1 = yes

H Takes more than 3 prescription drugs per day
0 = yes 1 = no

I Pressure sores or skin ulcers
0 = yes 1 = no

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals

K Selected consumption markers for protein intake
- At least one serving of dairy products (milk, cheese, yogurt) per day yes ☐ no ☐
- Two or more servings of legumes or eggs per week yes ☐ no ☐
- Meat, fish or poultry every day yes ☐ no ☐

0.0 = if 0 or 1 yes
0.5 = if 2 yes
1.0 = if 3 yes

L Consumes two or more servings of fruits or vegetables per day?
0 = no 1 = yes

M How much fluid (water, juice, coffee, tea, milk…) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups

N Mode of feeding
0 = unable to eat without assistance
1 = self-fed with some difficulty
2 = self-fed without any problem

O Self view of nutritional status
0 = views self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem

P In comparison with other people of the same age, how does the patient consider his/her health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 = MAC 21 to 22
1.0 = MAC 22 or greater

R Calf circumference (CC) in cm
0 = CC less than 31 1 = CC 31 or greater

Assessment (max. 16 points)
Screening score
Total Assessment (max. 30 points)

Malnutrition Indicator Score
17 to 23.5 points at risk of malnutrition
Less than 17 points malnourished

Ref. Vellas B, Villars H, Abellan G, et al. Overview of the MNA® - Its History and Challenges. J Nut Health Aging 2006;10:456-465.
Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for Undernutrition in Geriatric Practice: Developing the Short-Form Mini Nutritional Assessment (MNA-SF). J. Geront 2001;56A: M366-377.
Guigoz Y. The Mini-Nutritional Assessment (MNA®) Review of the Literature - What does it tell us? J Nutr Health Aging 2006; 10:466-487.

For more information : www.mna-elderly.com

APPENDIX I

BAPEN
Advancing Clinical Nutrition

'Malnutrition Universal Screening Tool' ('MUST')

MAG
Malnutrition Advisory Group
A Standing Committee of BAPEN

BAPEN is registered charity number 1023927 www.bapen.org.uk

'MUST'

'MUST' is a five-step screening tool to identify **adults,** who are malnourished, at risk of malnutrition (undernutrition), or obese. It also includes management guidelines which can be used to develop a care plan.

It is for use in hospitals, community and other care settings and can be used by all care workers.

This guide contains:

- A flow chart showing the 5 steps to use for screening and management
- BMI chart
- Weight loss tables
- Alternative measurements when BMI cannot be obtained by measuring weight and height.

The 5 'MUST' Steps

Step 1

Measure height and weight to get a BMI score using chart provided. *If unable to obtain height and weight, use the alternative procedures shown in this guide.*

Step 2

Note percentage unplanned weight loss and score using tables provided.

Step 3

Establish acute disease effect and score.

Step 4

Add scores from steps 1, 2 and 3 together to obtain overall risk of malnutrition.

Step 5

Use management guidelines and/or local policy to develop care plan.

Please refer to *The 'MUST' Explanatory Booklet* for more information when weight and height cannot be measured, and when screening patient groups in which extra care in interpretation is needed (e.g. those with fluid disturbances, plaster casts, amputations, critical illness and pregnant or lactating women). The booklet can also be used for training. See *The 'MUST' Report* for supporting evidence. Please note that 'MUST' has not been designed to detect deficiencies or excessive intakes of vitamins and minerals and is of **use only in adults.**

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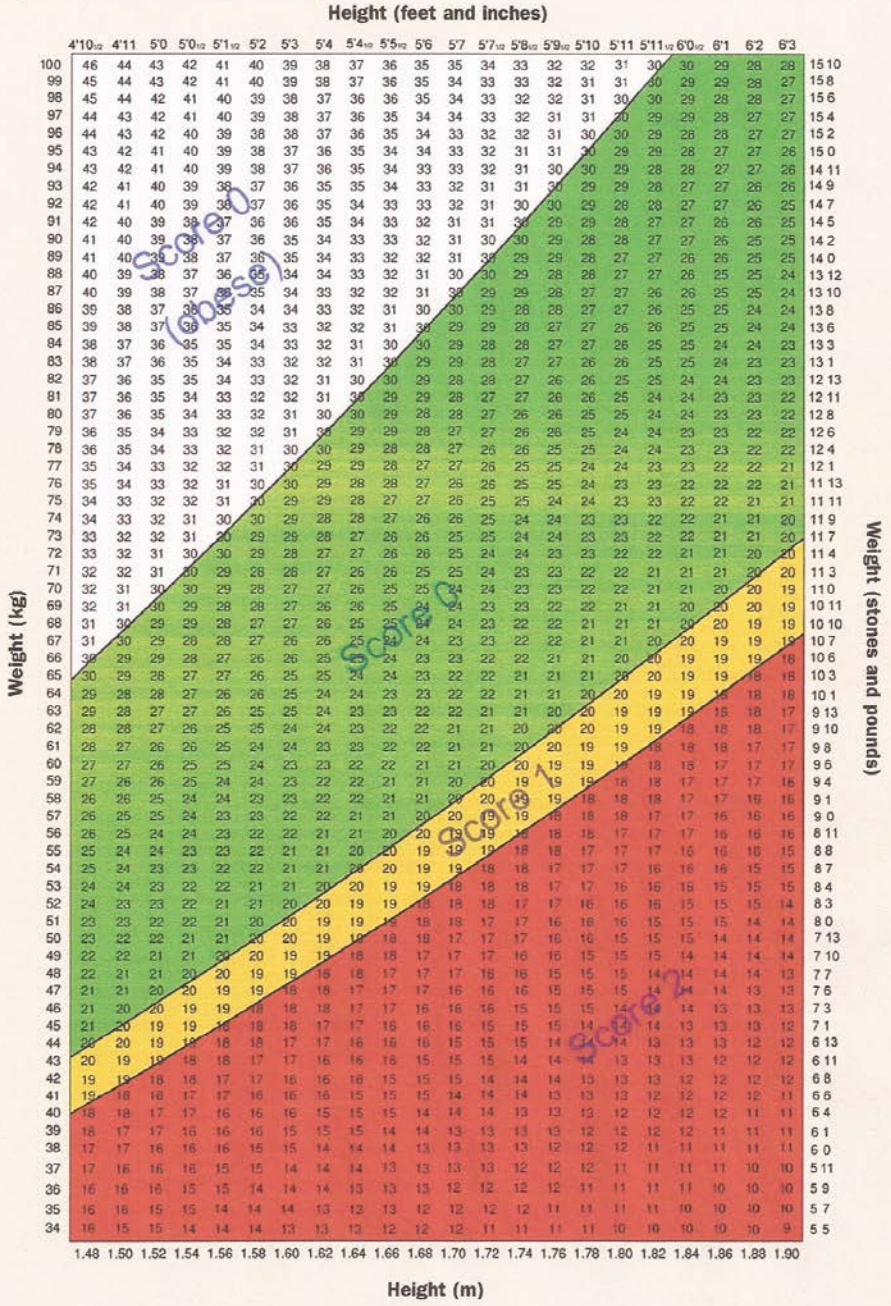
Step 1 – BMI score (& BMI)



Note : The black lines denote the exact cut off points (30,20 and 18.5 kg/m²), figures on the chart have been rounded to the nearest whole number.

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Step 1 + Step 2 + Step 3

Step 1 — BMI score

BMI kg/m²	Score
>20(>30 Obese)	= 0
18.5-20	= 1
<18.5	= 2

Step 2 — Weight loss score

Unplanned weight loss in past 3-6 months

%	Score
<5	= 0
5-10	= 1
>10	= 2

Step 3 — Acute disease effect score

If patient is acutely ill and there has been or is likely to be no nutritional intake for >5 days
Score 2

If unable to obtain height and weight, see reverse for alternative measurements and use of subjective criteria

Step 4

Overall risk of malnutrition

Add Scores together to calculate overall risk of malnutrition
Score 0 Low Risk Score 1 Medium Risk Score 2 or more High Risk

Step 5

Management guidelines

0 Low Risk

Routine clinical care

- Repeat screening
  Hospital – weekly
  Care Homes – monthly
  Community – annually
  for special groups
  e.g. those >75 yrs

1 Medium Risk

Observe

- Document dietary intake for 3 days if subject in hospital or care home
- If improved or adequate intake – little clinical concern; if no improvement – clinical concern - follow local policy
- Repeat screening
  Hospital – weekly
  Care Home – at least monthly
  Community – at least every 2-3 months

2 or more High Risk

Treat*

- Refer to dietitian, Nutritional Support Team or implement local policy
- Improve and increase overall nutritional intake
- Monitor and review care plan
  Hospital – weekly
  Care Home – monthly
  Community – monthly

* Unless detrimental or no benefit is expected from nutritional support e.g. imminent death.

All risk categories:

- Treat underlying condition and provide help and advice on food choices, eating and drinking when necessary.
- Record malnutrition risk category.
- Record need for special diets and follow local policy.

Obesity:

- Record presence of obesity. For those with underlying conditions, these are generally controlled before the treatment of obesity.

Re-assess subjects identified at risk as they move through care settings

See *The 'MUST' Explanatory Booklet* for further details and *The 'MUST' Report* for supporting evidence.

'Malnutrition Universal Screening Tool' ('MUST')

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Step 2 – Weight loss score

Weight before weight loss (kg)

	SCORE 0 Wt Loss < 5%	SCORE 1 Wt Loss 5-10%	SCORE 2 Wt Loss > 10%
34 kg	<1.70	1.70 – 3.40	>3.40
36 kg	<1.80	1.80 – 3.60	>3.60
38 kg	<1.90	1.90 – 3.80	>3.80
40 kg	<2.00	2.00 – 4.00	>4.00
42 kg	<2.10	2.10 – 4.20	>4.20
44 kg	<2.20	2.20 – 4.40	>4.40
46 kg	<2.30	2.30 – 4.60	>4.60
48 kg	<2.40	2.40 – 4.80	>4.80
50 kg	<2.50	2.50 – 5.00	>5.00
52 kg	<2.60	2.60 – 5.20	>5.20
54 kg	<2.70	2.70 – 5.40	>5.40
56 kg	<2.80	2.80 – 5.60	>5.60
58 kg	<2.90	2.90 – 5.80	>5.80
60 kg	<3.00	3.00 – 6.00	>6.00
62 kg	<3.10	3.10 – 6.20	>6.20
64 kg	<3.20	3.20 – 6.40	>6.40
66 kg	<3.30	3.30 – 6.60	>6.60
68 kg	<3.40	3.40 – 6.80	>6.80
70 kg	<3.50	3.50 – 7.00	>7.00
72 kg	<3.60	3.60 – 7.20	>7.20
74 kg	<3.70	3.70 – 7.40	>7.40
76 kg	<3.80	3.80 – 7.60	>7.60
78 kg	<3.90	3.90 – 7.80	>7.80
80 kg	<4.00	4.00 – 8.00	>8.00
82 kg	<4.10	4.10 – 8.20	>8.20
84 kg	<4.20	4.20 – 8.40	>8.40
86 kg	<4.30	4.30 – 8.60	>8.60
88 kg	<4.40	4.40 – 8.80	>8.80
90 kg	<4.50	4.50 – 9.00	>9.00
92 kg	<4.60	4.60 – 9.20	>9.20
94 kg	<4.70	4.70 – 9.40	>9.40
96 kg	<4.80	4.80 – 9.60	>9.60
98 kg	<4.90	4.90 – 9.80	>9.80
100 kg	<5.00	5.00 – 10.00	>10.00
102 kg	<5.10	5.10 – 10.20	>10.20
104 kg	<5.20	5.20 – 10.40	>10.40
106 kg	<5.30	5.30 – 10.60	>10.60
108 kg	<5.40	5.40 – 10.80	>10.80
110 kg	<5.50	5.50 – 11.00	>11.00
112 kg	<5.60	5.60 – 11.20	>11.20
114 kg	<5.70	5.70 – 11.40	>11.40
116 kg	<5.80	5.80 – 11.60	>11.60
118 kg	<5.90	5.90 – 11.80	>11.80
120 kg	<6.00	6.00 – 12.00	>12.00
122 kg	<6.10	6.10 – 12.20	>12.20
124 kg	<6.20	6.20 – 12.40	>12.40
126 kg	<6.30	6.30 – 12.60	>12.60

Weight before weight loss (st lb)

	SCORE 0 Wt Loss<5%	SCORE 1 Wt Loss 5-10%	SCORE 2 Wt Loss>10%
5st 4lb	<4lb	4lb – 7lb	>7lb
5st 7lb	<4lb	4lb – 8lb	>8lb
5st 11lb	<4lb	4lb – 8lb	>8lb
6st	<4lb	4lb – 8lb	>8lb
6st 4lb	<4lb	4lb – 9lb	>9lb
6st 7lb	<5lb	5lb – 9lb	>9lb
6st 11lb	<5lb	5lb – 10lb	>10lb
7st	<5lb	5lb – 10lb	>10lb
7st 4lb	<5lb	5lb – 10lb	>10lb
7st 7lb	<5lb	5lb – 11lb	>11lb
7st 11lb	<5lb	5lb – 11lb	>11lb
8st	<6lb	6lb – 11lb	>11lb
8st 4lb	<6lb	6lb – 12lb	>12lb
8st 7lb	<6lb	6lb – 12lb	>12lb
8st 11lb	<6lb	6lb – 12lb	>12lb
9st	<6lb	6lb – 13lb	>13lb
9st 4lb	<7lb	7lb – 13lb	>13lb
9st 7lb	<7lb	7lb – 13lb	>13lb
9st 11lb	<7lb	7lb – 1st 0lb	>1st 0lb
10st	<7lb	7lb – 1st 0lb	>1st 0lb
10st 4lb	<7lb	7lb – 1st 0lb	>1st 0lb
10st 7lb	<7lb	7lb – 1st 1lb	>1st 1lb
10st 11lb	<8lb	8lb – 1st 1lb	>1st 1lb
11st	<8lb	8lb – 1st 1lb	>1st 1lb
11st 4lb	<8lb	8lb – 1st 2lb	>1st 2lb
11st 7lb	<8lb	8lb – 1st 2lb	>1st 2lb
11st 11lb	<8lb	8lb – 1st 3lb	>1st 3lb
12st	<8lb	8lb – 1st 3lb	>1st 3lb
12st 4lb	<9lb	9lb – 1st 3lb	>1st 3lb
12st 7lb	<9lb	9lb – 1st 4lb	>1st 4lb
12st 11lb	<9lb	9lb – 1st 4lb	>1st 4lb
13st	<9lb	9lb – 1st 4lb	>1st 4lb
13st 4lb	<9lb	9lb – 1st 5lb	>1st 5lb
13st 7lb	<9lb	9lb – 1st 5lb	>1st 5lb
13st 11lb	<10lb	10lb – 1st 5lb	>1st 5lb
14st	<10lb	10lb – 1st 6lb	>1st 6lb
14st 4lb	<10lb	10lb – 1st 6lb	>1st 6lb
14st 7lb	<10lb	10lb – 1st 6lb	>1st 6lb
14st 11lb	<10lb	10lb – 1st 7lb	>1st 7lb
15st	<11lb	11lb – 1st 7lb	>1st 7lb
15st 4lb	<11lb	11lb – 1st 7lb	>1st 7lb
15st 7lb	<11lb	11lb – 1st 8lb	>1st 8lb
15st 11lb	<11lb	11lb – 1st 8lb	>1st 8lb
16st	<11lb	11lb – 1st 8lb	>1st 8lb
16st 4lb	<11lb	11lb – 1st 9lb	>1st 9lb
16st 7lb	<12lb	12lb – 1st 9lb	>1st 9lb

'Malnutrition Universal Screening Tool' ('MUST')

BAPEN
Advancing Clinical Nutrition

MAG
Malnutrition Advisory Group
A Standing Committee of BAPEN

BAPEN is registered charity number 1023927 www.bapen.org.uk

Alternative measurements and considerations

Step 1: BMI (body mass index)

If height cannot be measured

- Use recently documented or self-reported height (if reliable and realistic).
- If the subject does not know or is unable to report their height, use one of the alternative measurements to estimate height (ulna, knee height or demispan).

If height & weight cannot be obtained

- Use mid upper arm circumference (MUAC) measurement to estimate BMI category.

Step 2: Recent unplanned weight loss

If recent weight loss cannot be calculated, use self-reported weight loss (if reliable and realistic).

Subjective criteria

If height, weight or BMI cannot be obtained, the following criteria which relate to them can assist your professional judgement of the subject's nutritional risk.

1. BMI

- Clinical impression – thin, acceptable weight, overweight. Obvious wasting (very thin) and obesity (very overweight) can also be noted.

2. Unplanned weight loss

- Clothes and/or jewellery have become loose fitting (weight loss).
- History of decreased food intake, reduced appetite or swallowing problems over 3-6 months and underlying disease or psycho-social/physical disabilities likely to cause weight loss.

3. Acute disease effect

- No nutritional intake or likelihood of no intake for more than 5 days.

Further details on taking alternative measurements, special circumstances and subjective criteria can be found in *The 'MUST' Explanatory Booklet*. A copy can be downloaded at www.bapen.org.uk or purchased from the BAPEN office. The full evidence-base for 'MUST' is contained in *The 'MUST' Report* and is also available for purchase from the BAPEN office.

BAPEN Office, Secure Hold Business Centre, Studley Road, Redditch, Worcs, B98 7LG. Tel: 01527 457 850. Fax: 01527 458 718.
bapen@sovereignconference.co.uk BAPEN is registered charity number 1023927. www.bapen.org.uk

 ISBN 1 899467 85 8 Price £2.00

Royal College of Nursing

THE BRITISH DIETETIC ASSOCIATION

Published November 2003 by MAG the Malnutrition Advisory Group, a Standing Committee of BAPEN. *Review date December 2004 and annually thereafter.*
'MUST' is supported by the British Dietetic Association, the Royal College of Nursing and the Registered Nursing Home Association.

'Malnutrition Universal Screening Tool' ('MUST')

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A Standing Committee of BAPEN

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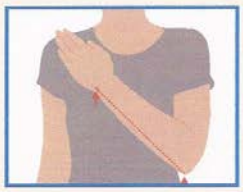
Alternative measurements: instructions and tables

If height cannot be obtained, use length of forearm (ulna) to calculate height using tables below.
(See The 'MUST' Explanatory Booklet for details of other alternative measurements (knee height and demispan) that can also be used to estimate height).

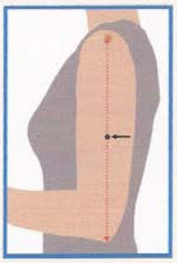
Estimating height from ulna length



Measure between the point of the elbow (olecranon process) and the midpoint of the prominent bone of the wrist (styloid process) (left side if possible).

HEIGHT (m)	Men (<65 years)	1.94	1.93	1.91	1.89	1.87	1.85	1.84	1.82	1.80	1.78	1.76	1.75	1.73	1.71
	Men (>65 years)	1.87	1.86	1.84	1.82	1.81	1.79	1.78	1.76	1.75	1.73	1.71	1.70	1.68	1.67
	Ulna length (cm)	32.0	31.5	31.0	30.5	30.0	29.5	29.0	28.5	28.0	27.5	27.0	26.5	26.0	25.5
HEIGHT (m)	Women (<65 years)	1.84	1.83	1.81	1.80	1.79	1.77	1.76	1.75	1.73	1.72	1.70	1.69	1.68	1.66
	Women (>65 years)	1.84	1.83	1.81	1.79	1.78	1.76	1.75	1.73	1.71	1.70	1.68	1.66	1.65	1.63
HEIGHT (m)	Men (<65 years)	1.69	1.67	1.66	1.64	1.62	1.60	1.58	1.57	1.55	1.53	1.51	1.49	1.48	1.46
	Men (>65 years)	1.65	1.63	1.62	1.60	1.59	1.57	1.56	1.54	1.52	1.51	1.49	1.48	1.46	1.45
	Ulna length (cm)	25.0	24.5	24.0	23.5	23.0	22.5	22.0	21.5	21.0	20.5	20.0	19.5	19.0	18.5
HEIGHT (m)	Women (<65 years)	1.65	1.63	1.62	1.61	1.59	1.58	1.56	1.55	1.54	1.52	1.51	1.50	1.48	1.47
	Women (>65 years)	1.61	1.60	1.58	1.56	1.55	1.53	1.52	1.50	1.48	1.47	1.45	1.44	1.42	1.40

Estimating BMI category from mid upper arm circumference (MUAC)



The subject's left arm should be bent at the elbow at a 90 degree angle, with the upper arm held parallel to the side of the body. Measure the distance between the bony protrusion on the shoulder (acromion) and the point of the elbow (olecranon process). Mark the mid-point.

Ask the subject to let arm hang loose and measure around the upper arm at the mid-point, making sure that the tape measure is snug but not tight.

If MUAC is < 23.5 cm, BMI is likely to be <20 kg/m².
If MUAC is > 32.0 cm, BMI is likely to be >30 kg/m².

1. Weight

I currently weigh about …… (Please insert your approximate weight)

I am about ……. Tall (please insert your approximate height)

One month ago I weighed about ……..

Six months ago I weighed about ……..

During the past two weeks my weight has (please tick one)

☐ Decreased ☐ Not Changed ☐ Increased

2. Food Intake

As compared with my normal intake, I would rate my food intake during the past month as (please tick one box only):

Unchanged More than usual Less than usual

☐ I am now taking (please tick one box only):

☐ Normal food, but less than normal amount

☐ Little solid food

☐ Only Liquids

☐ Only nutritionals

☐ Very little of anything

☐ Only tube feeding or nutrition by vein

3. Symptoms

I have had the following problems that have kept me from eating enough during the past two weeks (please tick all that apply or leave box empty if this does not apply to you):

□ No problems eating
□ No appetite, didn't feel like eating
□ Feeling full quickly
□ Food tasting funny/having no taste
□ Vomiting
□ Nausea
□ Pain: where?.....
□ Other*…….

□ Dry mouth
□ Mouth sores
□ Constipation
□ Diarrhoea
□ Problems swallowing
□ Smells bother me

* Examples: fatigue, depression, financial concerns

4. Activities and function

Over the past month, I would generally rate my activity as (please tick one box):

□ Normal with no limitations
□ Not my normal, but able to be up and about with fairly normal activities.
□ Not feeling up to most things, but in bed or chair for less than half of the day.
□ Able to do little activity and spend most of the day in bed or chair.
□ Pretty much bedridden, rarely out of bed.

APPENDIX K - MMSE

Orientation:

	Maximum score	Score
What is the year?	1	
What is the season?	1	
What is the month?	1	
What is the day?	1	
What is the date?	1	
Where are we: country?	1	
Where are we: county?	1	
Where are we: town?	1	
Where are we: hospital?	1	
Where are we: floor?	1	

Registration:

Ask the patient if you may test his memory. Name 3 objects: house, bread, cat (1 second to say each). Then ask the patient all 3 after you named them. Give 1 point for each correct answer. Then repeat them until he learns all 3. (house / bread / cat)	3 Count trials and record:	…….. ……..

Attention and calculation:

Ask the patient to begin with 100 and count backwards by 7. Stop after 5 subtraction. Score the total number of correct answers. (93 86 79 72 65) … … … … … If the patient cannot or will not perform this task, ask him to spell the word "W O R L D" backwards. The score is the number of the letters in correct order. D L R O W	*5* *5* Highest score:	…….. ……..

Memory:

Ask for the three objects repeated above. Give 1 point for each one. (house, bread, cat)	3	

Language:

	Maximum score	Score
Name a watch. Name a pencil.	1 1	
Repeat the following "No ifs, ands or buts".	1	
Follow a three stage command: *"take a paper in your right hand (1), fold it in half (2), and put it on the floor".*	3	
Read and obey the following: CLOSE YOUR EYES.	1	
Write a sentence.	1	
Copy the following drawing.	1	

Total score (0-30)	……

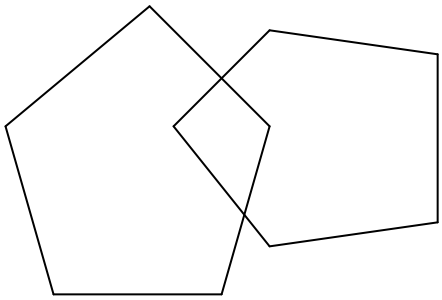
Notes:

……
……
……
……
……

Close your eyes

WRITE A SENTENCE

COPY THE FOLLOWING DRAWING



APPENDIX L

Berkman-Syme Social Network Index:

BERKMAN'S SOCIAL NETWORK INDEX

A) Original Items of 1965 HPL Questionnaire

(1) Marital Status:

1) Have you ever been married?

( ) yes ( ) no

2) Are you now married, separated, divorced, widowed?

( ) married ( ) separated ( ) divorced ( ) widowed

(2) Friends and Relatives:

1) How many close friends do you have?
(People that you feel at ease with, can talk to about private matters, and can call on for help.)

( ) none ( ) 1 or 2 ( ) 3 to 5 ( ) 6 to 9 ( ) 10 or more

2) How many relatives do you have that you feel close to?

( ) none ( ) 1 or 2 ( ) 3 to 5 ( ) 6 to 9 ( ) 10 or more

3) How many of these friends or relatives do you see at least once a month?

( ) none ( ) 1 or 2 ( ) 3 to 5 ( ) 6 to 9 ( ) 10 or more

(3) & (4) Church and Group Membership:

1) Do you belong to any of these kinds of groups?

	yes	no
a. A social or recreational group?	( )	( )
b. A labor union, commercial group, professional organization?	( )	( )
c. Church group?	( )	( )
d. A group concerned with children (PTA, Boy Scout)	( )	( )
e. A group concerned with community betterment, charity, or service?	( )	( )
f. Any other group? Describe	( )	( ) _____

APPENDIX M:

Study documents for "Assessment and management of older patients with colorectal cancer" (chapter 3)

CIRU Brighton and Sussex Clinical Investigation and Research Unit

Brighton and Sussex University Hospitals NHS Trust

	Clinical Investigation & Research Unit (CIRU) Level 5, The Royal Sussex County Hospital Eastern Road, Brighton, BN2 5BE Tel: 01273 696955 ext 3522/3528 Fax:01273 664855 www.bsuh.nhs.uk/research/

Dear

We would like to invite you participate in a study looking at older patients (aged 65 and over) who have been diagnosed with colorectal cancer. Colorectal cancer is very common and the majority of people diagnosed are aged 65 and over.

The study is questionnaire based and is to be carried out throughout the Sussex Cancer Network. It is looking into whether measures of general health and fitness can predict for future health in all patients and in those patients that are having chemotherapy, whether we can better predict those patients that may have side effects.

If you think you may be interested, we have enclosed a patient information sheet and consent form for you to read through. If you would like to ask any questions, contact details are listed at the end. We would be grateful if you could let us know your decision within the next 4-6 weeks. If we have not heard from you after 6 weeks, we will send you a reminder letter. Thereafter, we will not contact you any further.

Whether you take part or not, this study will have no effect on your treatment or future care.

Thank you very much for taking the time to read this letter.

Yours sincerely

Dr Joanna Stokoe MBChB MRCP FRCR

Sussex Cancer Fund Clinical Research Fellow

Brighton and Sussex Clinical Investigation and Research Unit

Brighton and Sussex University Hospitals NHS Trust

	Clinical Investigation & Research Unit (CIRU) Level 5, The Royal Sussex County Hospital Eastern Road, Brighton, BN2 5BE Tel: 01273 696955 ext 3522/3528 Fax:01273 664855 www.bsuh.nhs.uk/research/

Assessment and management of older patients with colorectal cancer

We would like to invite you to take part in a research study. Before you decide whether you would be happy to take part it is important that you understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and ask us if there is anything that is not clear or if you would like more information.

1. What is the purpose of this study?

The purpose of this study is to see if simple questionnaires asking patients about day to day activities, general fitness and appetite can predict for future fitness levels and side effects of any treatments you may be considered for. The study is looking at all patients aged 65 and over who have undergone surgery for colorectal cancer. After such surgery some patients have further treatment, such as chemotherapy, others do not.

2. Do I have to take part?

No, it is up to you to decide whether or not to take part in the study. The study is looking at all patients with colorectal cancer and it does not matter at this stage if you are not sure whether you may receive further treatment or not. If you do decide to take part we would like you to sign the attached consent form to show you have agreed to take part. It will not affect your management and treatment in any way if you decide you do or do not wish to take part.

3. What will happen to me if I take part?

If you decide to take part we would like to meet with you to complete some questionnaires. In addition to asking you some questions, we will measure your height and weight and hand-grip strength. This can be done at your next hospital visit if it is soon, or we can arrange to meet at a time and place that is convenient for you. The first assessments will take 30 minutes to complete.

Depending on whether you require further treatment, you will be in one of two groups of patients. The follow up is slightly different between the two groups, so please read the following section carefully to understand the slight difference.

In patients who have had surgery and require no further treatment:

After the first 30 minute assessment, we will need to contact you 12 months on from that first meeting to complete a short 5 minute questionnaire. This can be done over the telephone. We would contact you again at 2 and 5 years to complete the same 5 minute assessment. Again, this can be done over the telephone.

In those patients requiring treatment with chemotherapy:

If you are having chemotherapy, we will need to complete a short 5 minute questionnaire at the end of the course of chemotherapy treatment. This can be done over the telephone. We will not be making or suggesting any changes to your treatment or follow up, at any time. We would also need to contact you 12 months on from your first meeting with us, to complete a short 5 minute questionnaire. This can be done over the telephone. We would contact you again at 2 and 5 years to complete the same 5 minute assessment. Again this can be done over the telephone.

Both groups:

We would also like to look at some markers in your blood which can be measured when you have a routine blood test requested by your doctor. In the first group of patients this may be when you attend for a follow up appointment at the hospital. In the second group of patients, this will coincide with a blood test needed prior to chemotherapy. This is to avoid the need for an extra blood test wherever possible.

In both patient groups, this will be around the time of the first assessment. If you will not be having a blood test for some time, we may ask that you have a separate blood test for the purpose of this study.

4. What are the possible disadvantages and risks of taking part?

There are no disadvantages to taking part in the study other than the time taken to answer the questions and possibly needing one blood test. We will aim to carry out the baseline assessments when you attend hospital for an appointment or they can be done at a place and time convenient for you.

5. What are the possible benefits of taking part?

Taking part in the study will be of no direct benefit to you. However the responses that we receive from all of the patients involved will help us to better assess patients' general health and fitness. In patients who are to receive chemotherapy, the responses may help to predict which patients are more likely to get side effects.

6. What will happen if I don't want to carry on with the study?

You are free to withdraw at any time, without giving a reason. This would not affect the care that you receive.

7. Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential and stored securely in a manner compliant with the Data Protection Act. Any information about you will have your name and address removed so that you cannot possibly be recognised from it. In the unlikely event that you lose the capacity to express your wishes regarding this study, we would plan to continue to use the information that we had already collected, but would collect no further information.

8. Who is organising and funding the research?

The study is being organised by doctors from Brighton and Sussex Medical School.

9. Who has approved the study?

This study has been approved by Surrey Research Ethics Committee.

10. Involvement of your general practitioner (GP)

If you decide to take part in the study, we will inform your GP, but only if you are happy for us to do so. We will also ask for you consent for us to access your GP medical records if we need to check your medical history.

11. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers or your consultant who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

12. Further information and contact details?

When the study has been completed a copy of the report of the study will be made available to you if you are interested.

If you would like further information about the study please contact:

Research Nurse Lorraine Goodwin on **01273 696955 extension 3521** or Dr Joanna Stokoe on **01273 696955 extension 3522/3528**.

If the answerphone is on, please leave your name and contact details and state that you would like to speak to Lorraine Goodwin or Joanna Stokoe.

Alternatively, ask your treating team or nurse to contact Lorraine Goodwin or Dr Joanna Stokoe on your behalf and we will return your call as soon as possible.

Many thanks for your time and consideration.

Dr Joanna Stokoe
Sussex Cancer Centre

WHAT TO DO NOW?

If you are not willing to be involved then thank you for your time.

If you are willing to be involved, then you can contact us at the above telephone number and/or post your reply and consent form in the stamped-addressed envelope. Alternatively, we may contact you to find out your decision.
If we have not heard from you after 6 weeks, we may send a reminder letter. Thereafter, we will not make any further contact with you.
If you are willing to take part, we will need to arrange a time convenient to you, to complete the questionnaires. We will try and coincide this with your next hospital visit.

Brighton and Sussex University Hospitals NHS Trust

Clinical Investigation & Research Unit (CIRU)
Level 5, The Royal Sussex County Hospital
Eastern Road, Brighton, BN2 5BE
Tel: 01273 696955 ext 3522/3528
Fax:01273 664855
www.bsuh.nhs.uk/research/

Assessment and management of older patients with colorectal cancer

CONSENT FORM

PLEASE INITIAL THE BOXES IF YOU AGREE WITH EACH SECTION:

1. I confirm that I have read and understand the information sheet (Version 2.0. September 2009) for the above. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at time, without giving any reason, and without my medical treatment or legal rights be affected. ☐

3. I understand that relevant sections of my medical notes and research data colle during the study may be looked at by individuals from the research team, sponsor, f regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4.I give my permission for my GP to be contacted and give my consent for the resea team to access my medical records held by my GP. ☐

5. I agree to take part in the above study. ☐

OPTIONAL

6. I would like a summary of the findings when the research has been completed: Yes/ No (please circle)

Name of patient	Date	Signature
Countersigned: researcher	Date	Signature

Brighton and Sussex University Hospitals NHS Trust

Clinical Investigation & Research Unit (CIRU)
Level 5, The Royal Sussex County Hospital
Eastern Road, Brighton, BN2 5BE
Tel: 01273 696955 ext 3522/3528
Fax:01273 664855
www.bsuh.nhs.uk/research/

Research Project: Assessment and management of older patients with colorectal cancer
Research Ethics Number: 09/H1109/75

Dear Dr

Re:

Your patient has kindly consented to involvement in this study. This means that they have completed some questionnaires and baseline assessments in order to ascertain if any simple health measures can predict for changes in their general health and fitness.

The patient will be contacted again in 12 months time and they will be asked a few questions to reassess their functional status (activities of daily living). This second assessment will take less than 5 minutes. If they are having chemotherapy, a short 5 minute assessment will also be carried out at their last treatment visit.

We will also aim to contact patients at 2 and 5 years following entry into the study to complete the same 5 minute assessment. All these follow up assessments can be carried out through a telephone call to the patient. We may contact the practice to confirm current place of residence and status before contacting the patient.

Your patient has also given us permission to contact you, their GP for any additional information we may need regarding their past medical history.

Your patient's care will not be influenced in any way. If you have any questions regarding this project or would like further details then please feel free to contact me at the above address.

Many thanks for your help

Kind regards

Dr Joanna Stokoe MBChB MRCP FRCR
Sussex Cancer Fund Clinical Research Fellow

APPENDIX N – Results for reference

3.4.3.6 Confounding factors:

1. Crosstabulation tables of the 7 input variables used in the logistic regression analysis versus operation type (open v laparoscopic) is displayed:

1. VES-13 scores (<3 or ≥3) and Operation type

		Operation type		
		Laparoscopic surgery	Open surgery	Total
VES-13 Cut Off Group	VES-13 < 3	42	32	74
	VES-13 ≥3	17	21	38
Total		59	53	112

(χ^2 =1.45, p=0.228)

2. G8 scores (>14 or ≤14) and Operation type

		Operation type		
		Laparoscopic surgery	Open surgery	Total
G8Group	G8 score >14	23	20	43
	G8 score ≤14	36	33	69
Total		59	53	112

(χ^2 =0.18, p=0.892)

3. Performance status and Operation type

	Operation type		
	Laparoscopic surgery	Open surgery	Total
Baseline PS 0 or 1	47	38	85
Baseline PS >=2	12	15	27
Total	59	53	112

(χ^2 =0.968, p=0.325)

APPENDIX N contd:

4. Malnutrition group according to MNA assessment and Operation type

	Operation type		
	Laparoscopic surgery	Open surgery	Total
Not at risk of malnutrition	35	28	63
At risk or malnourished	24	25	49
Total	59	53	112

(χ^2 =0.478, p=0.489)

5.Frail (according to hand-grip strength) and Operation type

		Operation type		
		Laparoscopic surgery	Open surgery	Total
Frail	No	40	37	77
	Yes	19	16	35
Total		59	53	112

(χ^2 =0.053, p=0.818)

6. Charlson comorbidity score group and Operation type

	Operation type		
	Laparoscopic surgery	Open surgery	Total
Charlson score 0	42	34	76
Charlson score >=1	17	19	36
Total	59	53	112

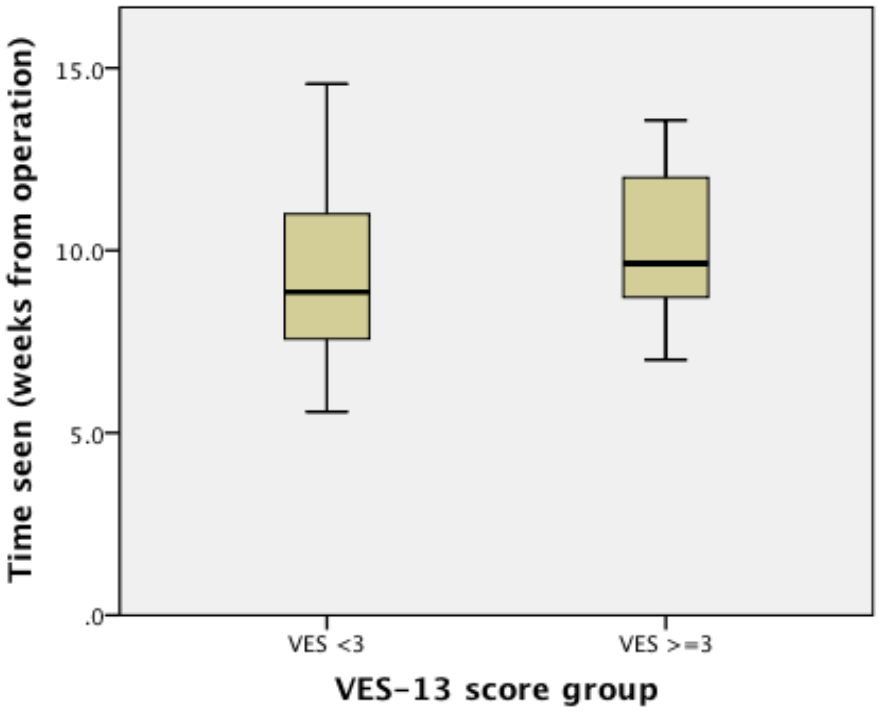
(χ^2 =0.634, p=0.426)

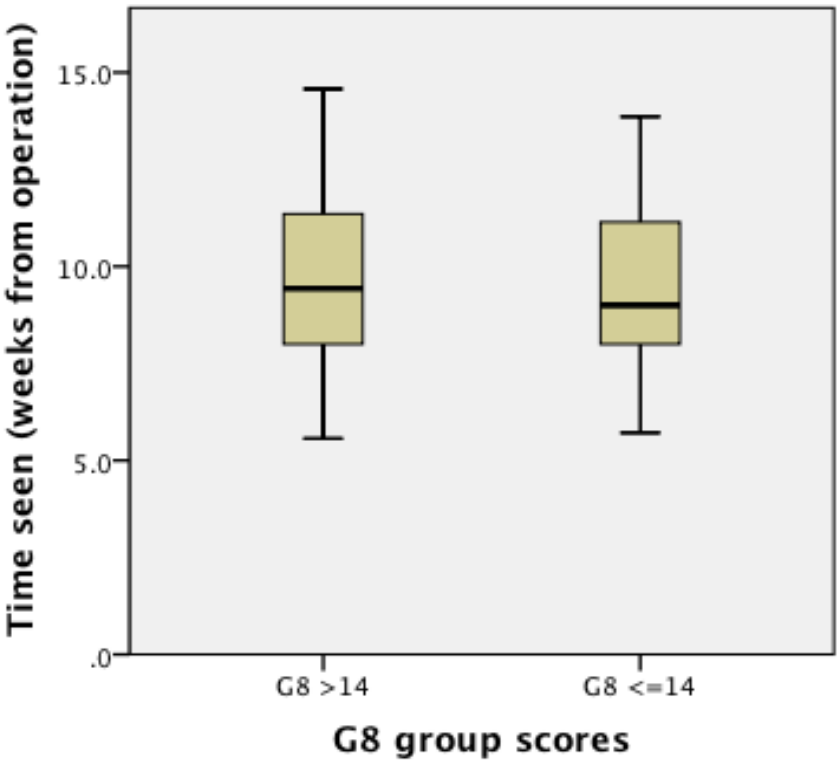
7. Age group and Operation type

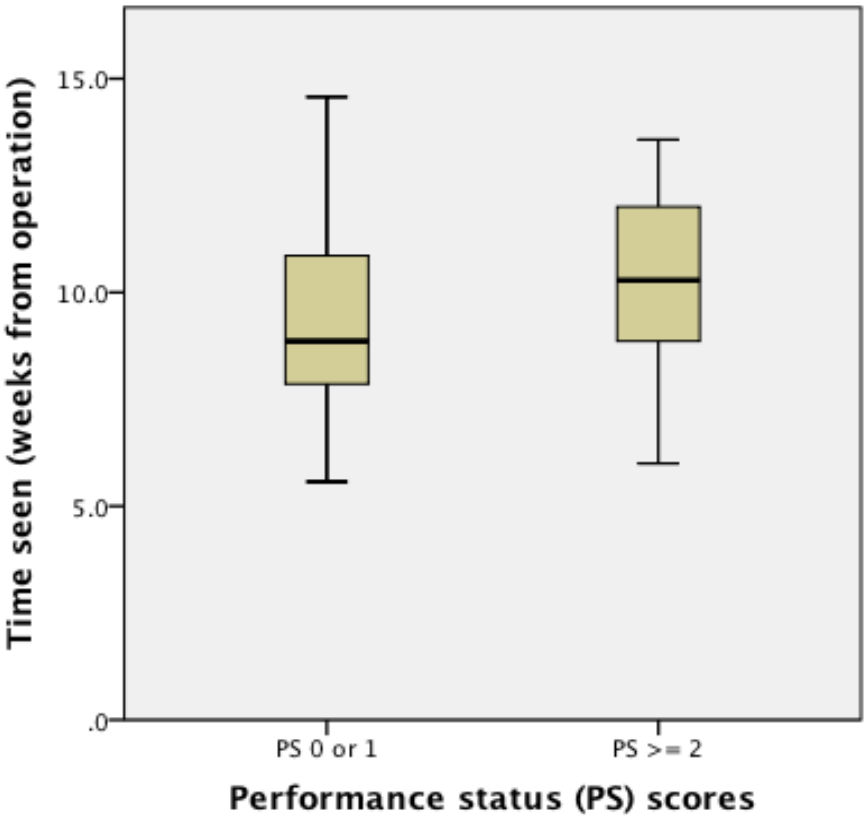
	Operation type		
	Laparoscopic surgery	Open surgery	Total
Under 70 years old	13	11	24
70 years old and over	46	42	88
Total	59	53	112

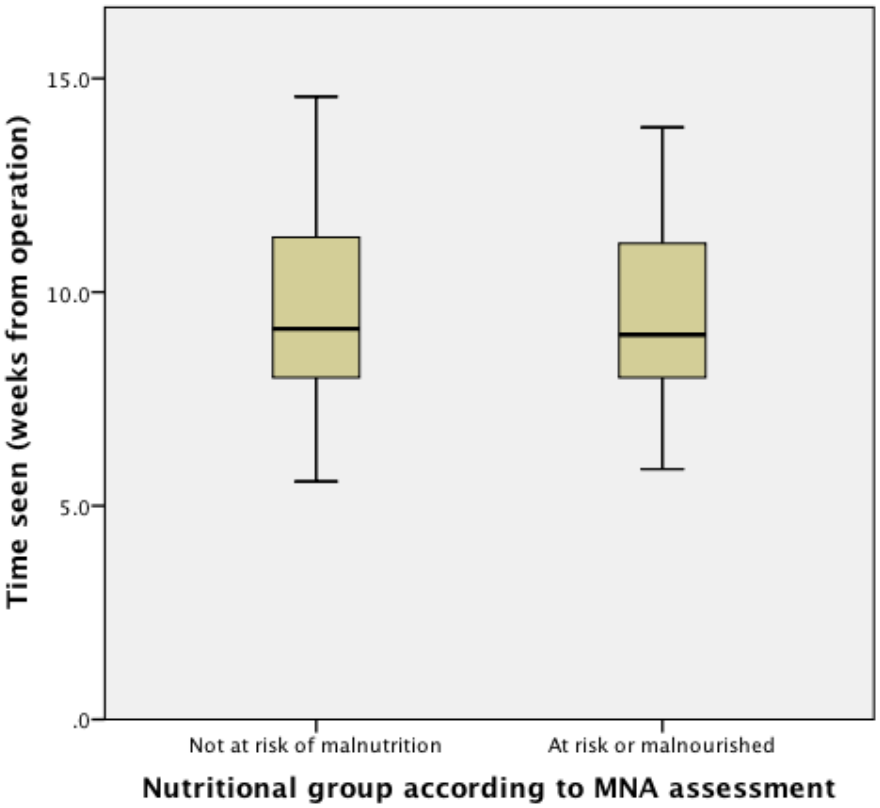
(χ^2 =0.027, p=0.869)

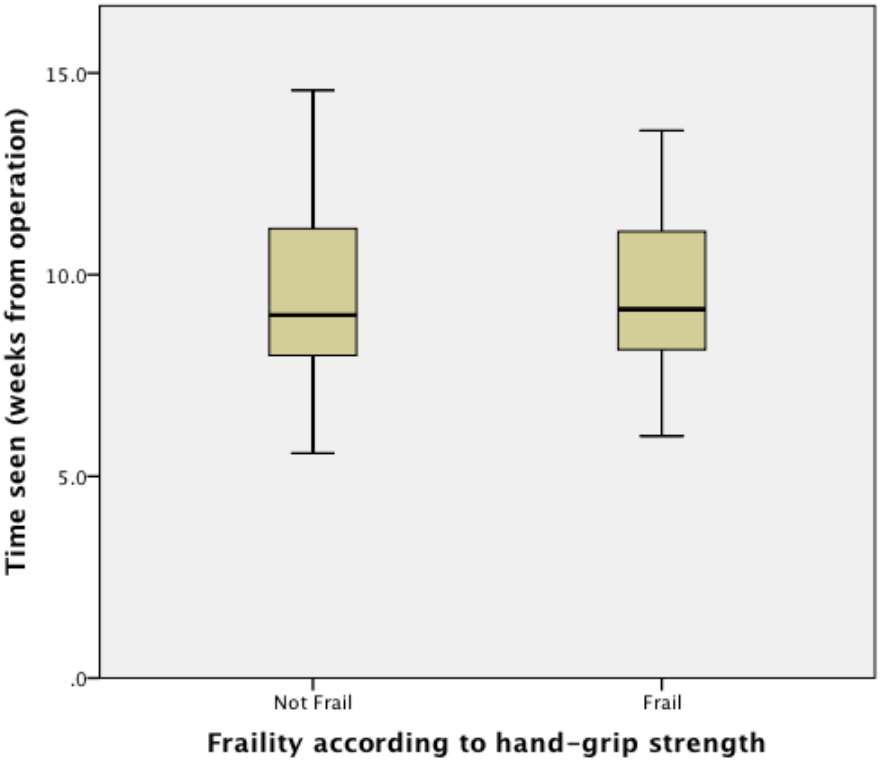
2. Graphical display (Box and Whisker plots) of scores (in cut-off groups) and time of baseline assessment (weeks from operation)

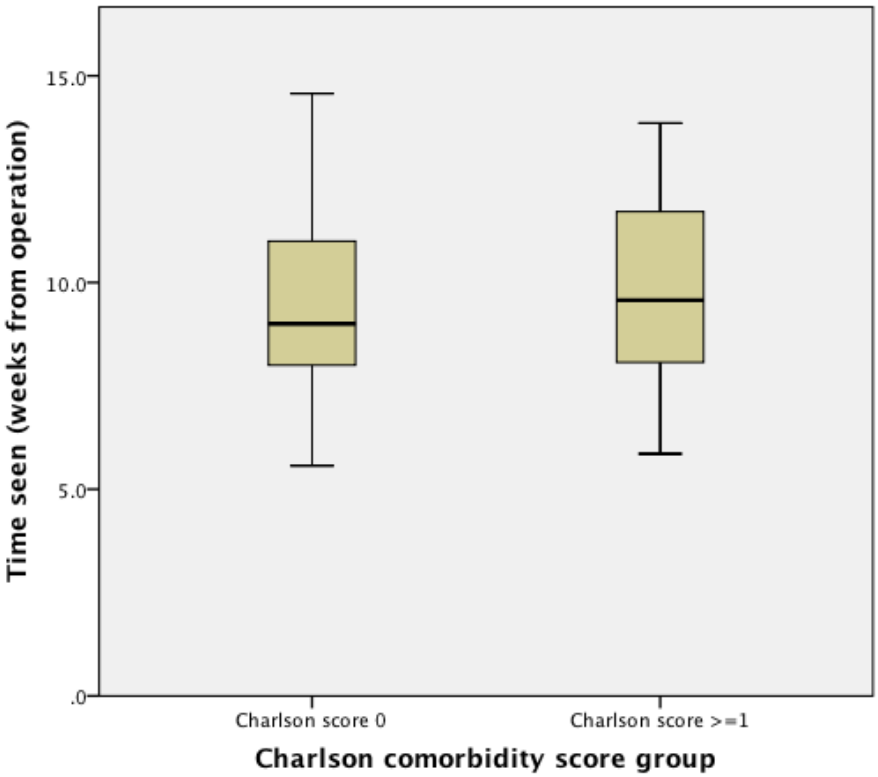



Time seen (weeks from operation)
15.0
10.0
5.0
.0
G8 >14
G8 <=14
G8 group scores


Time seen (weeks from operation)
15.0
10.0
5.0
.0
PS 0 or 1
PS >= 2
Performance status (PS) scores


15.0
10.0
5.0
.0
Time seen (weeks from operation)
Not at risk of malnutrition
At risk or malnourished
Nutritional group according to MNA assessment


15.0
10.0
5.0
.0
Time seen (weeks from operation)
Not Frail
Frail
Fraility according to hand-grip strength



END of APPENDIX N

APPENDIX O

Study Documents for "Global Health Measures and tolerance of cytotoxic chemotherapy" (chapter 4).

Brighton and Sussex University Hospitals NHS Trust

The Sussex Cancer Centre

Dr D Bloomfield
Dr A Chalmers
Dr A Hiersche
Dr R Langley
Dr K Lankester
Dr F McKinna
Dr S Mitra
Dr G Newman
Dr A Ring
Dr A Robinson
Dr R Simcock
Dr J Simpson
Dr A Webb
Dr S Westwell
Dr M Wilkins

Secretary:
e-mail:
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Fax Number: 01273 623312

The Royal Sussex County Hospital
Eastern Road
Brighton
BN2 5BE

Tel: 01273 696955

Ref/Hospital Number:	
NHS Number:	

***Research Project*: Global health measures and chemotherapy**

***Research Ethics Number*: 09/H1107/60**

We would like to invite you to take part in a research study which will involve you filling in some questionnaires, either today or anytime prior to your chemotherapy starting. This will take up about 10 minutes of our time. If you are interested then please read the information attached. If you are not interested then thank-you for your time.
Your treatment will not be influenced in any way.

Many thanks for your time and consideration,

Dr Alistair Ring
Senior Lecturer and Honorary Consultant in Oncology

Global health measures and chemotherapy

We would like to invite you to take part in a research study. Before you decide whether you would be happy to take part it is important that you understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and ask us if there is anything that is not clear or if you would like more information.

2. What is the purpose of this study?

The purpose of this study is to see if simple questionnaires asking patients about day to day activities, appetite and general fitness can help us to predict which patients develop side-effects from their chemotherapy and which do not.

2. Do I have to take part?

No, it is up to you to decide whether or not to take part in the study. If you do decide to take part we would like you to sign the attached consent form to show you have agreed to take part. It will not affect your treatment in any way if you decide you do or do not wish to take part.

3. What will happen to me if I take part?

If you decide to take part we would like you to fill in the questionnaires which we have enclosed with this information sheet. This should take up about 5 minutes of your time. You can either do this today, or any time before your chemotherapy starts. Once you have filled in these forms there is nothing else that you need to do. We will also record the details of your diagnosis, treatment and any side-effects from your medical notes.
We will not be making or suggesting any changes to your treatment at any time.

4. What are the possible disadvantages and risks of taking part?

There are no disadvantages to taking part in the study other than the time taken to answer the questions.

5. What the possible benefits of taking part?

Taking part in the study will be of no direct benefit to you. However the responses that we receive from all of the patients involved will help us to predict in the future if any particular patients are more likely to get side-effects from their chemotherapy.

6. What will happen if I don't want to carry on with the study?
You are free to withdraw at any time, without giving a reason. This would not affect the care that you receive.

7. Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential and stored securely. Any information about you will have your name and address removed so that you cannot possibly be recognised from it. In the unlikely event that you lose the capacity to express your wishes regarding this study, we would plan to continue to use the information that we had already collected, but would collect no further information.

8. Who is organising and funding the research?
The study is being organised by doctors from Brighton and Sussex Medical School.

9. Who has approved the study?
This study has been approved by Brighton East Research Ethics Committee.

10. Involvement of your general practitioner (GP)
If you decide to take part in the study, we will inform your GP, but only if you are happy for us to do so.

11. What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers or your consultant at the Sussex Cancer Centre who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

12. Further information and contact details?
When the study has been completed a copy of the report of the study will be made available to you if you are interested.
If you would like further information about the study, or would like help or advice about how to complete these questionnaires please ask the reception team or your nurse to contact: Dr Joanna Stokoe, by leaving a message at 01273 696955 extension 4600.

Many thanks for your time and consideration.

Dr Alistair Ring, Sussex Cancer Centre.

WHAT TO DO NOW?

If you are not willing to be involved then thank-you for your time.

If you are willing to be involved please do the following:

(i) Sign the consent form on the following page.
(ii) Complete the questionnaires attached (labeled 1, 2 and 3)
(iii) Return all of this paperwork in the envelope provided to the reception desk at any time prior to starting your chemotherapy.

Brighton and Sussex University Hospitals NHS Trust

Global health measures and chemotherapy.

CONSENT FORM

Please insert your Hospital Number:……

PLEASE **INITIAL** THE BOXES IF YOU AGREE WITH EACH SECTION:

1. I confirm that I have read and understand the information sheet (Version 2.0 May) for the above. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at time, without giving any reason, and without my medical treatment or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and research data collected during the study may be looked at by individuals from the research team, sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I give my permission for my GP to be contacted and give my consent for research team to access my medical records held by my GP. ☐

5. I agree to take part in the above study. ☐

OPTIONAL

6. I would like a summary of the findings when the research has been completed: Yes/ No (please delete)

_____ _____ _____

Name of patient Date Signature

_____

Countersigned: researcher Date Signature

APPENDIX P:

Global Health measures study: Patient self-completed questionnaires:

QUESTIONNAIRE 1

WHICH OF THE FOLLOWING BEST DESCRIBES HOW YOU ARE CURRENTLY?

PLEASE TICK ONE BOX ONLY:

I am fully active and more or less as I was before my illness ☐

I cannot carry out heavy physical work, but can do everything else ☐

I am up and about more than half the day, I can look after myself but am not well enough to work. ☐

I am in bed or sitting in a chair for more than half the day and I need some help in looking after myself ☐

I am in bed or in a chair all the time and need a lot of looking after. ☐

QUESTIONNAIRE 2

1. How old are you: ……..**years (please insert)**

2. In general, compared to other people your age, would you say that your health is (please circle one):

Poor Fair Good Very good Excellent

3. How much difficulty, on average, do you have with the following physical activities?

(please tick one box in each row)

	No difficulty	**A little difficulty**	**Some difficulty**	**A lot of difficulty**	**Unable to do**
Stooping, crouching or kneeling					
Lifting or carrying objects as heavy as 10 pounds (5kg)					
Reaching or extending arms above shoulder level					
Writing or handling and grasping small objects					
Walking a quarter of a mile					
Heavy housework such as scrubbing floors or washing windows					

4. Because of your health or physical condition, do you have any difficulty shopping for personal items (like toiletries or medicines)?

Please circle:

(i) NO

(ii) YES, if yes: do you get help with your shopping? **YES NO**

(iii) DON'T DO, if you do not do shopping is that because of your health? **YES NO**

5. Because of your health or physical condition, do you have any difficulty managing money (like keeping track of expenses or paying bills)?
(i) NO

(ii) YES, if yes: do you get help with managing money? **YES NO**

(iii) DON'T DO, if you don't manage money is that because of your health?**YES NO**

c) Because of your health or physical condition, do you have any difficulty walking across the room (use of a walking stick or frame is OK)?
(i) NO

(ii) YES, if yes: do you get help with walking? **YES NO**

(iii) DON'T DO, if you don't walk is that because of your health? **YES NO**

d) Because of your health or physical condition, do you have any difficulty doing light housework (like washing dishes, tidying up or light cleaning)?
(i) NO

(ii) YES, if yes: do you get help with light housework? **YES NO**

(iii) DON'T DO, if you don't do housework is that because of your health? **YES NO**

e) Because of your health or physical condition, do you have any difficulty bathing or showering?
(i) NO

(ii) YES, if yes: do you get help with bathing or showering? **YES NO**

(iii) DON'T DO, if you don't bath or shower is that because of your health? **YES NO**

QUESTIONNAIRE 3

1. Has your food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties? (Please tick one box).

Severe reduction in food intake ☐

Moderate reduction in food intake ☐

No reduction in food intake ☐

2. Have you suffered from weight loss during the last 3 months? (Please tick one box).

Yes, weight loss of more than 3 kilograms (6.6 pounds) ☐

I do not know ☐

Yes, weight loss between 1 and 3 kilograms (2 to 6 pounds) ☐

No weight loss ☐

3. How mobile are you? (Please tick one box).

I am bed or chair bound ☐

I am able to get out of bed/chair but I do not go out ☐

I go out ☐

4. Do you take more than 3 prescription medications per day? (Please tick one box).

Yes ☐

No ☐

5. In comparison with other people of the same age, how healthy do you think you are?

(Please tick one box).

Not as good ☐

I do not know ☐

As good ☐

Better ☐

6. How old are you?

(Please tick one box).

Less than 80 ☐

80-85 ☐

Over 85 ☐

APPENDIX Q:

	Number of patients (Total n=23)	Percent %
Sex		
Female	11	47.8
Male	12	52.2
Age (years)		
65-69	10	43.5
70-74	7	30.4
75-59	4	17.4
≥ 80	2	8.7
<70	10	43.5
≥70	13	56.5
Diagnosis		
Lower Gastrointestinal	4	17.4
Lung	6	26.1
Breast	4	17.4
Gynaecological	2	8.7
Urological	3	13.0
Upper Gastrointestinal	3	13.0
Lymphoma	1	4.3
Other	0	0.0
Stage		
I	0	0.0
II	2	8.7
III	9	39.1
IV	9	39.1
Other	3	13.0
Treatment intent		
Palliative	13	56.5
Adjuvant	5	21.7
Neoadjuvant	5	21.7
Primary/Radical	0	0.0

Table Q1: Demographic and cancer diagnosis details on patients (n=23) with missing VES-13 scores

Table notes
Diagnosis: Lower Gastrointestinal cancers include (number of patients in brackets) colon (2), rectal (2) and anal. (0) Lung cancer: non small cell (3) small cell (0) and mesothelioma (3). Gynaecological: Ovarian (1), Cervical (0), Endometrial (1), Fallopian tube (0). Urological: Bladder (1), Prostate (2). Lower Gastrointestinal: Oesophageal (0), Gastric (2), Pancreatic (1), Cholangiocarcioma (0). Other includes Brain, Head and Neck, Melanoma and Primary peritoneal.
Stage: "Other " includes staging for certain tumours types such as lung and brain.

Table Q2: Other score results for patients with missing VES-13 scores

Assessment score	Number of patients (Total n=23)	Percent %
Performance Status		
0	6	26.1
1	11	47.8
2	6	26.1
3	0	0.0
G8		
>14	2	8.7
≤14	10	43.5
Missing	11	47.8
Severe chemo toxicity		
Yes	15	65.2
No	8	34.8
Charlson score		
0	14	60.9
1	3	13.6
2	3	13.6
≥3	2	8.7
Missing	1	4.3
ACE-27 score		
0	6	26.1
1	9	39.1
2	6	26.1
≥3	1	4.3
Missing	1	4.3

Table Q3: Patients with missing G8 scores – demographic details

	Number of patients (Total n=20)	Percent %
Sex		
Female	10	50.0
Male	10	50.0
Age (years)		
65-69	11	55.0
70-74	6	30.0
75-59	2	10.0
≥ 80	1	5.0
Diagnosis		
Lower Gastrointestinal	4	20.0
Lung	5	25.0
Breast	3	15.0
Gynaecological	2	10.0
Urological	3	15.0
Upper Gastrointestinal	1	5.0
Lymphoma	1	5.0
Other	1	5.0
Stage		
I	0	0.0
II	2	10.0
III	8	40.0
IV	8	40.0
Other	2	10.0
Treatment intent		
Palliative	12	60.0
Adjuvant	3	15.0
Neoadjuvant	4	4.0
Primary/Radical	1	1.0

Table notes
Diagnosis: Lower Gastrointestinal cancers include (number of patients in brackets) colon (3), rectal (1) and anal. (0) Lung cancer: non small cell (3) small cell (0) and mesothelioma (2). Gynaecological: Ovarian (1), Cervical (0), Endometrial (1), Fallopian tube (0). Urological: Bladder (2), Prostate (1). Lower Gastrointestinal: Oesophageal (0), Gastric (0), Pancreatic (1), Cholangiocarcioma (0). Other includes Brain, Head and Neck, Melanoma and Primary peritoneal.
Stage: "Other " includes staging for certain tumours types such as lung and brain.

Table Q4: Other score results for patients with missing G8 scores

Assessment score	Number of patients (Total n=20)	Percent %
Performance Status		
0	5	25.0
1	10	50.0
2	5	25.0
3	0	0.0
VES-13		
<3	8	40.0
≥3	2	10.0
Missing	10	50.0
Severe chemo toxicity		
Yes	16	80.0
No	4	20.0
Charlson score		
0	11	55.0
1	5	25.0
2	3	15.0
≥3	0	0.0
Missing	1	5.0
ACE-27 score		
0	6	30.0
1	12	60.0
2	1	5.0
≥3	0	0.0
Missing	1	5.0

APPENDIX R: Global Health Measures Study and details of chemotherapy treatment: dose reductions, early cessation of treatment, treatment delays, Grade III/IV toxicities and hospital admissions

Chemotherapy details	Number (n=185)	Percent (%)
Primary reason for initial dose reduction		
Renal function	9	4.9
Age	5	2.7
Hepatic function	4	2.2
Poor PS	3	1.6
Previous chemotherapy	3	1.6
Other/not documented	6	3.2
Not applicable	155	83.8
Primary reason for stopping chemotherapy early		
Disease progression	13	7.0
No treatment response	6	3.2
Hospital admission	6	3.2
Other- not specified	6	3.2
Haemtological toxicity	5	2.7
GI toxicity	5	2.7
Patient request	4	2.2
Patient died	4	2.2
Unknown	4	2.2
Other	11	5.9
Not applicable	121	65.4
Primary reason for dose modifications		
Renal/Hepatic function	13	7.0
Haematological	11	5.9
GI	9	4.9
Skin toxicity	5	2.7
Neurotoxicity	4	2.2
Other	7	3.8
Other (not defined)	14	7.6
Not applicable	121	65.4
Missing	1	0.5
Reasons for treatment delays		
Haematological	18	9.7
Non-neutropenic infection	8	4.3
GI toxicity	4	2.2
Neutropenic sepsis	3	1.6
Missing	3	1.6
Other	4	2.2
Other (not defined)	9	4.9
Not applicable	136	73.5

Grade 3-4 toxicity		
Haematological	16	8.6
GI	11	5.9
Neutropenic sepsis	6	3.2
Neurotoxicity	4	2.2
Fatigue	4	2.2
Other	8	4.3
Other (not defined)	1	0.5
Not applicable	133	71.9
Missing	2	1.1
Reason for hospital admission		
Non-neutropenic infection	9	4.9
Neutropenic sepsis	5	2.7
Chest pain	4	2.2
PE/DVT	4	2.2
Symptom control of cancer	4	2.2
Symptom control of chemo	3	1.6
End of life care	3	1.6
Other	5	2.7
Other (not defined)	5	2.7
Not applicable	141	76.2
Missing	2	1.1

Other reasons for initial dose reduction (number of patients in brackets): Bone marrow suppression (1), cardiac history (1), Other not specified (2), Not documented (2). Second and third additional reasons cited for initial dose reduction: Age (3), Co-morbidities (1), Bone marrow suppression (1)

Other reasons for stopping chemo early: Renal toxicity (2), Cardiac toxicity (2), Neurotoxicity (3), Hepatic toxicity (1), Poor PS (2), Commenced definitive treatment (1). Second reasons cited for stopping early: GI toxicity (2), patient request (1), neurotoxicity(1), Haematological (1), Hospital admission (1), Commenced definitive treatment (1).

Other reasons for dose modifications: Neutropenic sepsis (2), cardiac toxicity (3), non-neutropenic infection (2). Second additional reasons cited for dose modifications: GI (1), renal/hepatic dysfunction (4), Neurotoxicity (2).

Other reasons for treatment delay: renal/hepatic dysfunction (3), skin toxicity(1). Second and third additional reasons cited for treatment delays: Non-neutropenic infection (1), Skin toxicity(2).

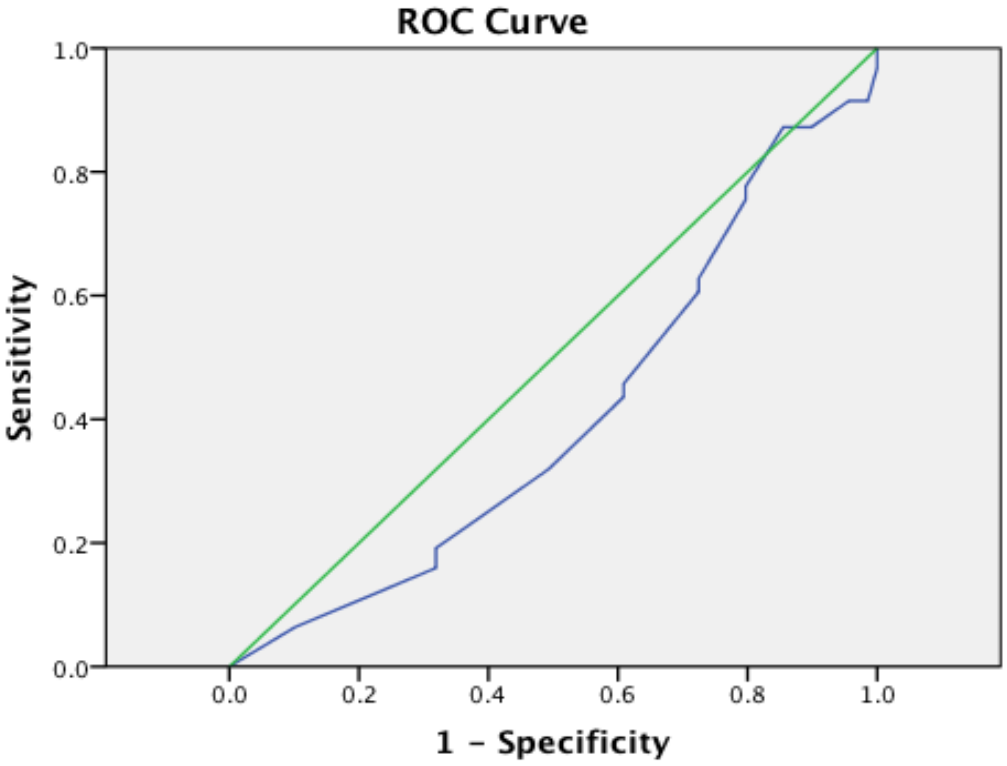
Other Grade 3-4 toxcities: Cardiac (3), Hepatic (1), Skin(2), Non-neutropenic infection (2). Second and third additional toxicities: Neurotoxicity (2), Haematological (2), Skin (1), Neutropenic sepsis(1), Hepatic (1), Fatigue (1), non-neutropenic infection (1).

Other reasons for hospital admission: GI (2), Pleural effusion (1), Myocardial infarction (1), Stroke (1). Second additional hospital admissions: non-neutropenic infection (1), GI (1), other symptom control of chemo (1), other (1).

APPENDIX S

G8 score

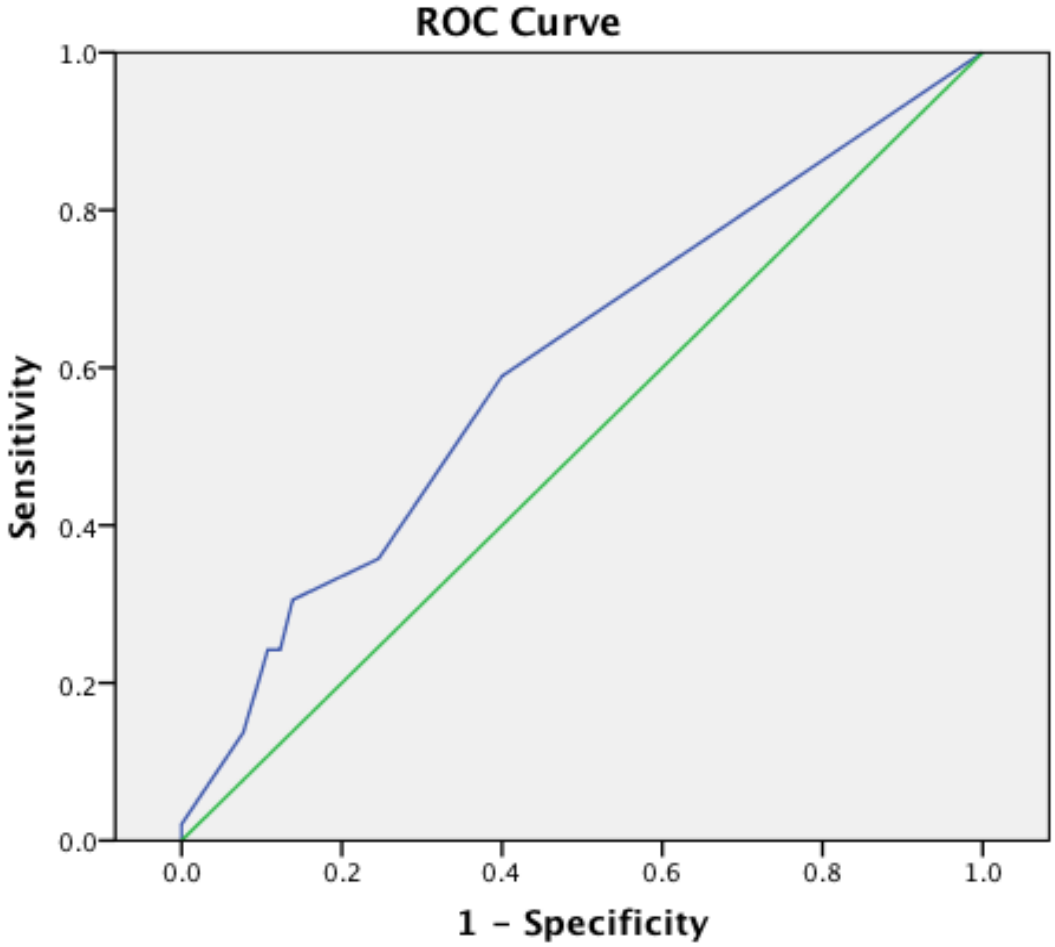
A ROC curve of G8 score versus defined severe chemotherapy toxicity



Area under the curve is 0.405 (95% CI 0.316- 0.495)

VES-13 score

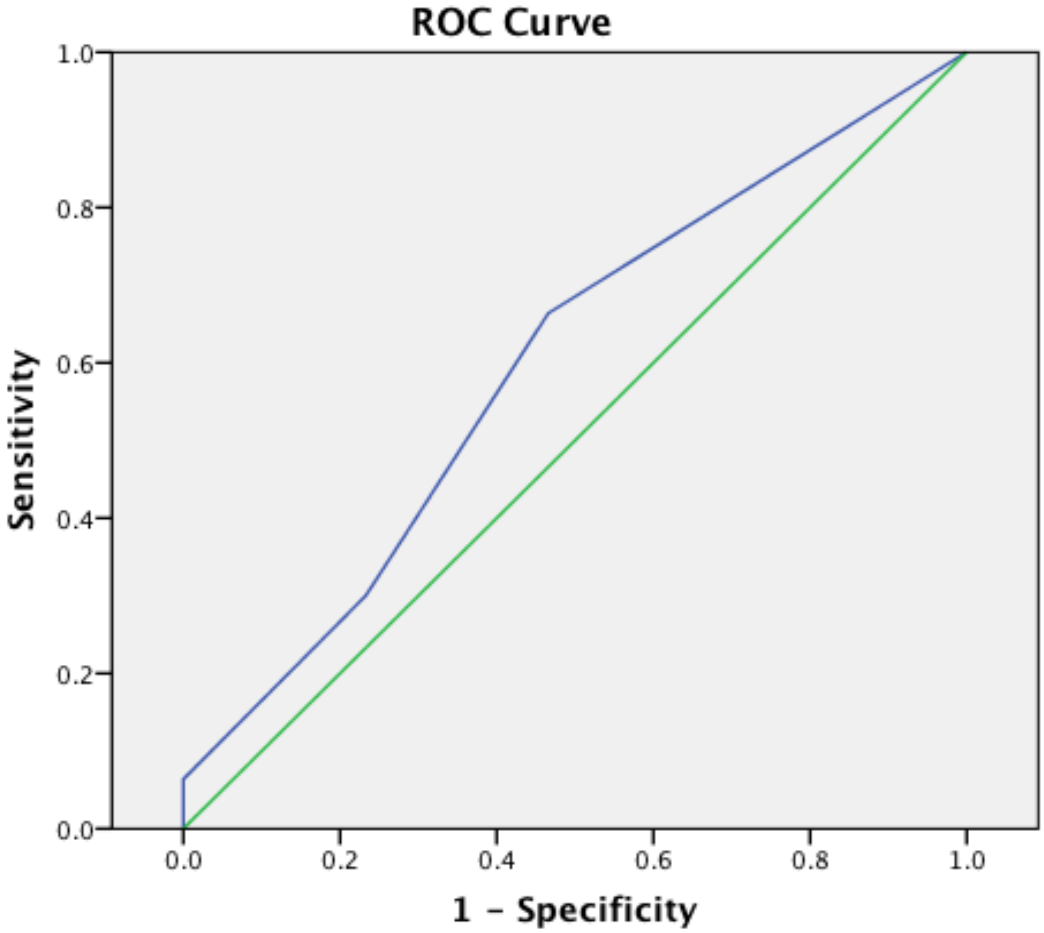
A ROC curve of VES-13 scores versus defined severe chemotherapy toxicity



Area under the curve is 0.605 (95% CI 0.517 – 0.694)

PS score

A ROC curve of Performance status (PS) scores versus defined severe chemotherapy toxicity



Area under the curve is 0.599 (95% CI 0.515 to 0.683)

APPENDIX T: Study documentation for the Malnutrition Study

Are you interested in taking part of a research study looking at nutritional status in patients with cancer?

If you are, please read this information leaflet to find out more.

Brighton and Sussex University Hospitals NHS Trust

The Royal Sussex County Hospital

Eastern Road

Brighton

BN2 5BE

Tel: 01273 696955

The Sussex Cancer Centre

Dr D Bloomfield
Dr A Chalmers
Dr A Hiersche
Dr R Langley
Dr K Lankester
Dr F McKinna
Dr S Mitra
Dr G Newman
Dr A Ring
Dr A Robinson
Dr R Simcock
Dr J Simpson
Dr A Webb
Dr S Westwell
Dr M Wilkins

PATIENT INFORMATION SHEET

Nutritional status in patients with colorectal cancer

We would like to invite you to take part in a study which is part of an educational project for two medical student researchers. Before you decide whether you would be happy to take part it is important that you understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

3. What is the purpose of this study?

Patients with cancer are at risk of having a poor food intake and losing weight. We would like to find out if this is a common problem in our patients and to work out which of the commonly used nutrition questionnaires is the best. Therefore we are interviewing men and women with cancer using three different questionnaires in order to compare them.

2. Do I have to take part?

No, it is up to you to decide whether or not to take part in the study. If you do decide to take part you will be asked to sign a consent form to show you have agreed to take part. It will not affect your treatment in any way if you decide you do or do not wish to take part.

3. What will happen to me if I take part?

If you decide to take part we will ask you some questions about your food intake, your appetite, and health. We will also weigh you, check your height and in some patients do additional measurements of your arms and legs. This should take up to a maximum of 10 minutes of your time. We will be able to do this when you are attending hospital for an

appointment. We will also record the details of your diagnosis and treatment from your medical notes. If you do have a low food intake, or weight loss, we will inform your GP and hospital consultant, but only if you are happy for us to do so.

4. What are the possible disadvantages and risks of taking part?

There are no disadvantages to taking part in the study other than the time taken to answer the questions.

5. What the possible benefits of taking part?

Taking part in the study is unlikely to be of direct benefit to you. However if we discover that you are at risk of malnutrition and are not receiving input from a dietician then we will ask a dietician to contact you. We will inform you that we are doing this.

6. What will happen if I don't want to carry on with the study?

You are free to withdraw at any time, without giving a reason. This would not affect the care that you receive.

7. Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential and stored securely. Any information about you will have your name and address removed so that you cannot possibly be recognized from it. In the unlikely event that you lose the capacity to express your wishes regarding this study, we would plan to continue to use the information that we had already collected, but would collect no further information.

8. Who is organising and funding the research?

The study is being organised by doctors at Brighton and Sussex Medical School.

9. Who has approved the study?

This study has been approved by Brighton East Research Ethics Committee.

10. Involvement of your general practitioner (GP)

If you decide to take part in the study, we will inform your GP, but only if you are happy for us to do so.

11. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers or your consultant at the Sussex Cancer Centre who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

12. Further information and contact details?

If you wish to receive information about the results of the whole study when it has been completed we would be happy to write and let you know, please indicate this in the area provided on the consent form.
If you would like any further information please ask the medical student researcher who has given you this form (Rebecca Smith) or contact Dr Alistair Ring, Sussex Cancer Centre, 01273 696955 extension 4600

Many thanks for your time and consideration.

Brighton and Sussex University Hospitals NHS Trust

The Sussex Cancer Centre

Dr D Bloomfield
Dr A Chalmers
Dr A Hiersche
Dr R Langley
Dr K Lankester
Dr F McKinna
Dr S Mitra
Dr G Newman
Dr A Ring
Dr A Robinson
Dr R Simcock
Dr J Simpson
Dr A Webb
Dr S Westwell
Dr M Wilkins

The Royal Sussex County Hospital
Eastern Road
Brighton
BN2 5BE
Tel: 01273 696955

Measuring nutritional status in patients with cancer

Thank you for reading the information about our research project. If you would like to take part, please read and sign this form.

Hospital Number Study number:

PLEASE **INITIAL** THE BOXES IF YOU AGREE WITH EACH SECTION:

1. I confirm that I have read and understand the information sheet (Version 4.0 18th September 2009) for the above study and have had the opportunity to answer 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 treatment or legal rights being affected. ☐

3. I understand that my medical records and research data collected during the study will be looked at by individuals from the research team and may also be looked at by the sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I give my permission for my GP to be contacted as part of my involvement in this study. ☐

5. I agree to take part in the above study. ☐

OPTIONAL
6. I would like a summary of the findings when the research has been completed: Yes/ No (please delete)

Name of patient	Date	Signature
Countersigned: researcher	Date	Signature

1 for patient, 1 for researcher, 1 to be kept with hospital notes (delete/amend as appropriate)

Brighton and Sussex University Hospitals NHS Trust

The Sussex Cancer Centre

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Dr A Chalmers
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Tel: 01273 696955

Secretary:
e-mail:
Tel number/Ext:
Fax Number: 01273 623312

Ref/Hospital Number:	
NHS Number:	

***Research Project*: Measuring nutritional status in patients with colorectal cancer**

Brighton East Research Ethics Committee: 09/H1107/83

Brighton and Sussex University Hospitals NHS Trust: 09/073/RIN

Dear Dr

Re:

Your patient has kindly agreed to be involved in this study in which we are comparing three different measures of nutritional status. Your patient's care will not be influenced in any way. However if we detect that your patient is malnourished or at risk of malnutrition we will refer them to a dietician and inform both you and their oncology consultant.

If you have any questions regarding this project then please feel free to contact me at the above address.
Many thanks for your help

Yours sincerely,

Dr Alistair Ring
Principal Investigator
Senior Lecturer and Honorary Consultant in Oncology

APPENDIX U

Poster publications

J.M. Stokoe, A. Ring "Observational survey of social isolation in older cancer patients"
Poster presentation: 10th International Society Geriatric Oncology (SIOG) meeting, October 15-17 2009, Berlin.

S.Cappleman, R Smith, **J.M Stokoe**, A. Ring "Malnutrition in metastatic colorectal cancer patients: a comparison of three screening tools"
Poster presentation: 11th SIOG Meeting, November 3-5th, 2011, Paris.

J.M. Stokoe, F Mckinna, A Webb, A Ring "Comprehensive geriatric assessment in older patients with localised colorectal cancer and its relationship to functional outcome"
Poster presentation: 11th SIOG Meeting, November 3-5th, 2011, Paris

J Stokoe, J Pearce, R Sinha, A Ring "G8 and VES-13 scores predict chemotherapy toxicity in older patients with cancer**"**
Poster presentation 12th SIOG Meeting, Manchester, October 2012

brighton and sussex medical school

OBSERVATIONAL SURVEY OF SOCIAL ISOLATION IN OLDER CANCER PATIENTS

Brighton and Sussex University Hospitals NHS Trust

*J. Stokoe MRCP FRCR and A. Ring MRCP MD
Sussex Cancer Centre, Royal Sussex County Hospital, Brighton, UK.
Brighton and Sussex Medical School, Brighton, UK

INTRODUCTION

Social isolation has been shown to be an independent predictor of mortality in the geriatric population and to correlate with mortality following a diagnosis of breast cancer (1,2,3). Degree of social support may be a particularly important factor in the management of older patients with cancer as it may help to mitigate against some of the physical and psychological impacts of diagnosis and treatment. The purpose of this study was to measure the degree of social isolation in outpatients attending our cancer centre, and to compare older and younger patients.

AIMS

- To measure degree of social isolation in all cancer patients.
- To compare older (≥ 70 years old) patients and younger patients and observe any differences between the two ages groups.

METHODS

A survey was designed based on the questions used to construct the Berkman-Syme Social Network Index (1). Questions included: marital status; number of close friends and relatives and frequency of contact; church membership and participation in group activities. Over a 5 week period patients attending outpatient appointments at the Sussex Cancer Centre, Brighton, UK, were invited to complete the survey. Patients completed the survey themselves and the responses were anonymous. The Chi-square test was used to analyse differences between those aged 70 or over, or less than 70.

RESULTS

Over a 5 week period, 250 completed questionnaires were returned. 689 patients had passed through the outpatient department during that period. Overall response rate was 36.3%. One respondent did not give their date of birth and 249 questionnaires were analysed.
The baseline demographics are shown in tables 1 and 2.

Table 1

	< 70 years old No. (%)	≥ 70 years old No. (%)	Total No. (%)
Male	99	48	147 (**59.0**)
Female	74	27	101 (**40.6**)
Unknown	0	1	1
Total number of patients	173 (**69.5**)	76 (**30.5**)	249 (**100**)

Of the respondents 76 (31%) were 70 years old or older, 71 (29%) were 60-69 years old and 102 (41%) were aged less than 60 years.

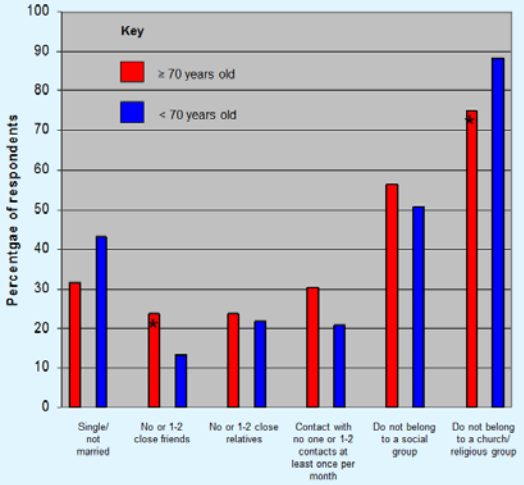
Table 2 Tumour site, treatment intent and current status of patient (on or off treatment according to age.

	< 70 years old No,	≥ 70 years old No.	Total No. (%)
Tumour site			
Urological cancers	38	19	57(**22.9**)
Lymphoma	32	8	40(**16.1**)
Head and Neck	15	13	28(**11.2**)
Upper/Lower GI	23	9	32(**12.9**)
Breast	19	2	21(**8.4**)
Gynae cancers	14	6	20(**8.0**)
Lung	11	4	15(**6.0**)
Other sites	19	9	28(**11.2**)
No information given	2	6	8(**3.2**)
Treatment intent			
Curative	95	31	126(**50.6**)
Palliative	76	39	115(**46.2**)
Unknown	2	6	8(**3.2**)
Current status			
On Treatment	32	7	39(**15.7**)
Off Treatment	139	63	202(**81.1**)
Unknown	2	6	8(**3.2**)

Social situation and contacts.

The proportion of patients who were unmarried, widowed or divorced was similar for older and younger patients (32% for those aged ≥70, vs 43% for those aged <70, p=0.09).
Older patients were more likely to report that they had no or only 1 or 2 close friends (24% vs 13%, p=0.04).
The proportion of patients who had no or only 1 or 2 close relatives was similar for older and younger patients (24% vs 22%, p=0.84).
Older patients were more likely to report that they saw no one, or only 1 or 2 of these contacts at least once per month, but this did not reach statistical significance (30% vs 21%, p=0.11).
Older patients were more likely to belong to a church or religious group (25% vs 12%, p=0.03).
The proportion of older and younger patients reporting that they did not belong to any social group was similar (57% vs 51%, P=0.4).

Figure 1. Chart showing percentage of respondents, < 70 and ≥ 70 years old, to questions about social contacts * Denotes statistically significant result



CONCLUSIONS

Many of our patients, of all ages, experience social isolation. Older patients are more likely to have few or no friends and there is a non-significant trend for them to have less contact with friends or relatives.

In all the patients that replied to the survey, it can be seen that a considerable number have few close friends or relatives. Lack of social contact and support may affect patients' ability to cope with a cancer diagnosis and any treatments they may undergo. It is an area that health professionals may not ask about, but may be highly relevant.

Acknowledgements

Thank you to the Sussex Cancer Fund for supporting this project.
Also, many thanks to the reception staff at Sussex Cancer Centre for their help in conducting the survey

REFERENCES
1) Berkman LF and Syme SL. American Journal of Epidemiology 1979;109:186-204.
2) Schoenbach VJ et al American Journal of Epidemiology 1986;123:577-591.
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MALNUTRITION IN PATIENTS WITH COLORECTAL CANCER:
A COMPARISON OF THREE SCREENING TOOLS (MNA, MUST, APG-SGA)

S Cappleman, R Smith, J Stokoe, A Ring

brighton and sussex medical school

CIRU Brighton and Sussex Clinical Investigation and Research Unit

Background

An estimated that 30-70% of patients with cancer are malnourished, with age an independent risk factor for becoming malnourished. (1) There is currently no universally recognised definition of malnutrition; NICE recommend the following parameters (2):

- BMI<18.5 kg/m^2
- Unintentional weight loss of >10% in the past 3-6 months
- BMI < 20 kg/m^2 + unintentional weight loss of >5% in the past 3-6 months.

It is important to detect malnutrition early as it has significant implications for tolerance of treatment, quality of life and survival.

A number of nutritional screening tools exist, which allow early identification of patients at risk and subsequent formal assessment and intervention. However few are in routine use, possibly because of the perception that malnutrition will be detected in the pattern of normal care and because of the need for a professional to conduct the screening test.

Aims

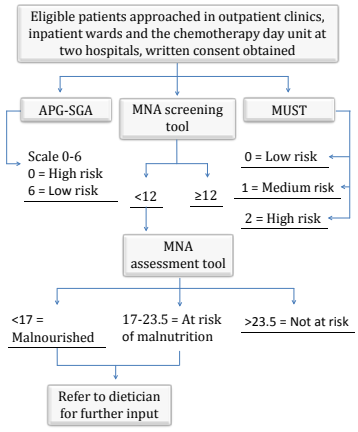
1. To assess with a 95% confidence interval the prevalence of malnutrition in patients with metastatic colorectal cancer using the Nestle Mini Nutritional Assessment (MNA) tool.

2. To ascertain whether malnutrition is more prevalent in the ≥ 70 year old age group.

3. To compare the sensitivity and specificity of the Malnutrition Universal Screening Tool (MUST) and Abridged Patient Generated Subjective Global Assessment (APG-SGA) with the MNA.

Methods

Inclusion criteria	Exclusion criteria
1. Patients aged ≥18 years	1. Stage I-III colon or rectal cancer.
2. Diagnosis of colon or rectal cancer	2. Those diagnosed within the last 8 weeks.
3. Stage IV disease	3. Patients unable to give written informed consent.
	4. Patients with a life expectancy of less than 3 months.



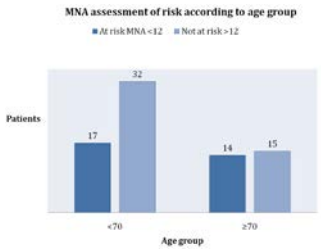
Additional details regarding height, weight, diagnosis, current treatment, performance status and previous dietary input were obtained from the patient and the medical records.

Results

Patient Characteristics	
Age	Age range: 27-82 Mean age: 64 Median age: 65
Inpatient/ Outpatient	Inpatient: 1 (1.3%) Outpatient: 77 (98.7%)
Gender	Males: 44 (56.4%) Females: 34 (43.6%)
Diagnosis	Colon cancer: 54 (71.1%) Rectal cancer: 24 (31.6%)
BMI	Range: 18-46 Mean: 27 Mode: 23
Treatment	Active supportive care: 37 (47.4%) Chemotherapy: 40 (51.3%) Radiotherapy: 1 (1.3%) Targeted therapy: 5 (6.4%)

MNA:
In the study population 31/78 (39.7%) were deemed to be at risk using the MNA screening tool (CI 28.8-51.5%).
21 of these patients (26.9% of total study population) were subsequently confirmed as being at risk of malnutrition on completion of the full MNA assessment.
This also shows that 10/31

Age:
17/31 (54.8%) of patients who were at risk of malnutrition using the MNA screening tool were <70 years old, 14/31 (45.2%) ≥ 70 years old.



Of those >70: 14 of 29 (48.3%) were at risk, where as of those <70: 17 of 49 (34.7%) were at risk.

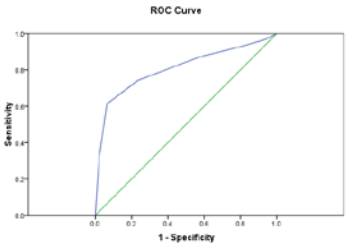
A chi-squared test of MNA screening at risk (score <12) correlated with age gave a p value of 0.236 , suggesting that there is no statistical significance at any confidence interval.

Of the 21 patients who warranted dietician referral after completion of the full MNA, 9/21 (42.9%) patients were ≥70 years old.

MUST:
-Taking the MNA as the gold standard screening tool the MUST correctly identified 16 of 31 as at risk, therefore had a sensitivity of 51.6%.
-42 of 47 were correctly identified as being not at risk, giving it a specificity of 89.4%.

APG-SGA:
No pre-established scoring system, correlation with MNA showed that when defining 'at risk' as scoring:
- ≤ 2 : sensitivity of 74%; specificity of 77%
- ≤3 : sensitivity of 87% ; specificity of 43%

Results continued...



A ROC curve of APG-SGA score vs. MNA screening score at risk <12. The curve is left of the line of dissociation, showing relatively good correlation, with area beneath the curve of 0.808.

Discussion

The MNA identified 39.7% of the study population as being at risk of malnutrition on screening. Around a quarter of the entire study population were 'at risk' after the full assessment, which is a significant proportion of patients. Taking the MNA as gold standard is a limitation, as it may not be accurately detecting malnutrition, however it has been extensively validated in the elderly population. (3)

There was a similar number of patient at risk in the <70 and >70 categories and a chi-squared test showed no correlation at any age. The ratio of 'at risk' to 'not at risk' was more significant when comparing categories, as this was almost equal in the over 70s category. These observations are limited however by the small sample size.

MUST is a fast assessment tool to perform, relying more heavily upon objective measurements; this however only identified half of the patients deemed as 'at risk' by the MNA. The low specificity may relate to the emphasis on acute illness in the questions, which is less relevant in a predominantly ambulatory outpatient population.

The APG-SGA correlated relatively well with the MNA and required less resources than the MNA, as it is completed by the patient. In order to improve sensitivity, specificity is compromised; this could be improved with larger studies or by comparing the tool with other validated nutritional assessment tools.

Conclusions

Malnutrition is common and under-detected, with 26.9% of patients with metastatic colorectal cancer requiring further nutritional assessment from a trained healthcare professional.

Rates of malnutrition were not significantly different between older and younger patient, however of those over 70 almost half were at risk, compared to only a third of patients under 70. however the sample size is small, which is a limitation that could be addressed in future studies.

MUST has a poor specificity in the out-patient setting, which may relate to the scope of the questions asked. The APG-SGA correlated well with the MNA and should be considered as a time-efficient screening tool in the outpatient setting.

References

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2. NICE Clinical Guidelines. Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. 2006 Feb.
3. B Vellas, H Villars, G Abellan, M Soto, Y Rolland, Y Guigoz, J Morley. Overview of the MNA – it's history and challenges. J Nutr Health Aging. 2006 Nov; 10(6): 456-465

11TH INTERNATIONAL SOCIETY GERIATRIC ONCOLOGY, PARIS, FRANCE, 3RD-5TH NOVEMBER 2011

COMPREHENSIVE GERIATRIC ASSESSMENT IN OLDER PATIENTS WITH LOCALISED COLORECTAL CANCER AND IT RELATIONSHIP TO FUNCTIONAL STATUS

JM Stokoe, F Mckinna, A Webb, A Ring

brighton and sussex medical school

CIRU Brighton and Sussex Clinical Investigation and Research Unit

Background

Colorectal cancer (CRC) is the third commonest cancer in the UK [1]. Assessing patients' fitness and the risks versus benefits of treatment following surgery is challenging in older patients. Presently, the use of assessment tools as part of a comprehensive geriatric assessment (CGA) is not routine in UK medical practice. A CGA can be time-consuming to perform and is not practical in a busy oncology outpatient clinic. Assessment tools such as the Vulnerable Elders Survey(VES-13) and screening tools such as G8/Oncodage may help identify a sub-group of patients who are vulnerable and would require further assessment. In a large study of over 65s living in the community, a VES-13 score of ≥3 was found to identify a group of vulnerable people who had 4.2 times the risk of death or functional decline over a two year period [2]. Studies are ongoing into the use of the G8/Oncodage as a screening tool. A score of ≤ 14 has been proposed as predictive of failing a CGA[3].

Interim results from this prospective cohort study are presented.

Aims

Primary aim:
-To ascertain if the Vulnerable Elders Survey (VES-13) predicts for functional decline or death in elderly patients with colorectal cancer
Secondary aims:
-To ascertain if the VES-13 score predicts for severe chemotherapy toxicity.
-To ascertain if any other components of a modified CGA predict for functional decline or death at one year and also severe chemotherapy toxicity

Methods

Patients aged 65 and over, newly diagnosed with localised CRC were eligible to take part in this prospective cohort study. Study invitation letters were posted to their home address 4-6 weeks after they had undergone surgical resection of their primary CRC. They were recruited from three hospitals within the Sussex Cancer Network, UK.

A modified CGA was undertaken within 3 months of definitive surgery.
The baseline assessment comprised:
-Patient and tumour demographics
-Performance status (ECOG-PS)
-VES-13 and G8 scores
-Activity of Daily Living (ADL) & Instrumental Activities of Daily Living (IADL) scores
-Mini Mental State Examination (MMSE-30),
-Hand grip strength,
-Charlson Co morbidity Index Score.
-Weight, height, BMI,
-Mini Nutritional Assessment (MNA®),
-Blood test: Full blood count, serum biochemistry, B12, folate, Thyroid function, Vitamin D levels.

Patients undergoing adjuvant chemotherapy had a baseline assessment performed prior to commencing treatment and then functional status reassessed (PS, ADL, IADL and VES-13 repeated) at the end of treatment. Details of changes in the chemotherapy regime and toxicities were recorded.

Participants are to be followed up at 1,2 and 5 years and functional status and disease status recorded at each assessment point via telephone interview.

Results

112 participants have been recruited over a thirteenth month period. Overall positive response rate to study invite letters was 64.6%. Further participant recruitment is ongoing. Summary results are presented.

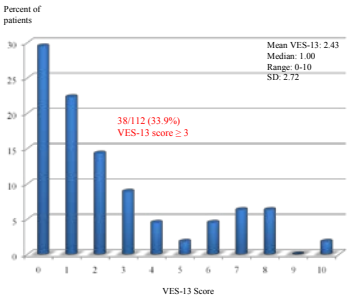
Results

Patient Characteristics	Number of patients	Percent %
Patients assessed	112	100
Age, years		
65-69	24	21.4
≥ 70	88	78.6
Sex		
Female	57	50.9
Male	55	49.1
Marital status		
Married/lives with partner	74	66.1
Widowed	20	17.9
Single	8	7.1
Divorced/separated/other	10	8.9
Household status		
Lives alone	25	22.3
Lives with spouse/relative/other	87	77.7
Colorectal cancer stage		
I	21	18.8
II	48	42.9
III	43	38.4

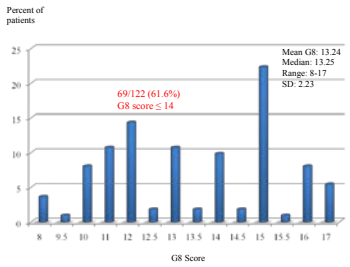
Baseline assessment results:

Performance Status	No. patients n=112 (%)
0	35 (31.3)
1	50 (44.6)
2	21 (18.8)
3	6 (5.4)

Distribution of baseline VES-13 scores



Distribution of baseline G8 scores



Baseline functional assessment:

ADL: 96/112 patients (85.7%) independent in ADLs,
16/112 patients (14.3%) dependent in ≥ 1 ADL domain.
IADL: 73/112 patients (65.2%) independent in IADLs,
16/112 patients (14.3%) dependent in 1 domain
23/112 patients (20.5%) dependent in ≥ 2 IADL domains.

Hand-grip strength:
35/112 patients (31.3%) were classed as frail based on hand-grip strength (adjusted for age, sex and weight)

Results continued…

Assessment domain	Mean score	Median	Standard deviation	Range
Cognition (MMSE)	29.26	30	1.33	20.5 - 30
Charlson co-morbidity score	0.58	0	1.16	0-7
Nutrition-MNA	23.84	24.00	2.56	15.5-29.0
Number of prescription medications	3.86	4.00	2.91	0-14

30 participants received adjuvant chemotherapy
5/30 (16.7%) VES-13 score ≥ 3,
15/30 (50.0%) G8 score ≤ 14.

16/30 (53.3%) did not complete chemotherapy
25/30 (83.3%) had dose modifications
17/30 (56.7%) had a Grade 3 or 4 toxicity
17/30 (56.7%) had a treatment delay and 3/30 (10%) had an unplanned hospital admission.

At end of chemotherapy, performance scores were noted to drop and the number of IADL domains that patients were dependent on increased.

Year One follow up results:

Ninety five patients to date, have been assessed via telephone interview one year on from baseline assessment. One patient was uncontactable but still thought to be still alive. Three patients have died. Functional assessment scores from 91 patients are presented:

Year 1 Performance Status	No. patients n=91 (%)
0	38 (41.8)
1	28 (30.8)
2	16 (17.6)
3	8 (8.8)
4	1 (1.1)

Functional assessment at one year:

ADL: 72/91 patients (79.1%) independent in ADLs
19/91 patients (20.9%) dependent in ≥ 1 ADL domain.
IADL: 67/91 patients (73.6%) independent in IADLs
10/91 patients (11.0%) dependent in 1 IADL domain
14/91 patients (15.4%) dependent in ≥ 2 IADL domain.

Functional decline is defined as a change from no IADL/ADL disability to any ADL/IADL disability, an increase of 2 or more IADL/ADL disabilities or nursing home admission[2]. 19/95 patients (20.0%) had functionally declined or died at 1 year.
Three deaths : Two of cardiac causes. One directly due to recurrent CRC.

Exploratory statistical analysis has not found VES-13 scores to be predictive of functional decline/death at 1 year but follow up and further recruitment is ongoing in order to satisfy the required sample size to meet the primary study aim.

Conclusions

A modified CGA is feasible in this patient population but would not be practical to perform in all patients attending clinic. A screening tool would be more time-efficient.
At one year, 20.0% of patients assessed had functionally declined or died. The predictive ability of VES-13 will be further analysed when study recruitment is completed.
In patients receiving adjuvant chemotherapy, over 50% experienced severe toxicities, treatment delays or did not complete the treatment course. A trend for a fall in functional assessment scores at treatment completion was observed.

References

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2. Saliba D, Elliott M, Rubenstein LZ et al. The Vulnerable Elders Survey: a tool for identifying vulnerable people in the community. J Am Geriatr Soc. 2001 Dec;49(12):1691-9
3. Soubeyran P, Bellera CA, Gregoire F et al. Validation of a screening test for elderly patients in oncology. J Clin Oncol 2008;26 (suppl 20): abstr 20568

G8 AND VES-13 SCORES PREDICT CHEMOTHERAPY TOXICITY IN OLDER PATIENTS WITH CANCER

brighton and sussex medical school

JM Stokoe, J Pearce, R Sinha, A Ring

CIRU Brighton and Sussex Clinical Investigation and Research Unit

Background

- Older patients may be at particular risk of developing chemotherapy related toxicities compared to younger patients
- The objective assessment of health status may be useful in predicting the risk of developing toxicity.
- A short assessment process using specific assessments that patients can self-complete would be advantageous in a busy clinic setting.
- In this study, patients about to commence chemotherapy self-completed three assessment tools: G8 score, Vulnerable Elders Survey (VES-13) and ECOG performance status (PS).
- A low G8 score, ≤ 14, is associated with a high probability of failing a CGA (1, 2).
- A high VES-13 score (≥3) is associated with increased risk of functional decline or death at two years (3).
- PS is commonly used by oncologists to assess patient's general fitness (4).
- We hypothesized that these abbreviated global measures of health and fitness may be predictors of how well patients tolerated chemotherapy

Aims

Primary aim:
To ascertain if the G8 score predicts chemotherapy toxicity.
Secondary aims:
i) To ascertain if the VES-13 score (< 3 vs ≥3) or WHO PS (0,1 vs >/=2) predict severe chemotherapy toxicity.
(ii) To compare the sensitivity and specificity of G8, VES-13 and WHO PS scores as diagnostic tests in predicting risk of chemotherapy toxicity.

Methods

The study population comprised patients referred for cytotoxic chemotherapy at three hospitals within the Sussex Cancer Network, UK.
Patients aged eighteen and over were approached and the results for those aged sixty-five and over are presented here.
Patients were invited, via postal letter, to take part in the study when they received written information regarding planned chemotherapy treatment. Study participants, signed a consent form and returned self-completed baseline questionnaires (G8, VES-13 and PS)) in an envelope. They then received chemotherapy as part of normal care. Baseline tumour, demographic and data regarding adverse outcomes were recorded from patients' medical records.
Severe chemotherapy toxicity was pre-defined as any of the following: toxicity (grade III/IV by CTCAE version 3.0 criteria), treatment delay, chemotherapy dose reductions, death within thirty days of chemotherapy administration and unplanned hospitalization.
Ethical approval was obtained from the local ethics committee. Data was recorded and analysed using Microsoft Excel and Access Databases and statistical package SPSS Version 18.0.

Results

At the time of this analysis, five hundred and six questionnaires were returned, two hundred and two from patients' aged ≥ 65.

Results

Of the ≥ 65 year olds, one hundred and eighty five responses were analysed (seventeen did not meet eligibility criteria). Mean age was 71.3 years (range 65-84 years, median 70.0, SD 4.78). Patient and tumour demographic information were recorded:

Patient Characteristics	Number of patients	Percent %
Patients assessed	185	100
Age, years		
65-69	83	44.9
≥ 70	102	55.1
Sex		
Female	93	50.3
Male	92	49.7
Diagnosis		
Lower Gastrointestinal	51	27.5
Lung	31	16.7
Breast	23	12.4
Gynaecological	21	11.3
Urological	20	10.8
Upper Gastrointestinal	17	9.1
Other	22	11.8
Stage		
I	6	3.2
II	22	11.9
III	71	38.4
IV	74	40.4

Treatment intent:
47.6% (88/185 patients) received palliative chemotherapy, 24.3% (45/185) adjuvant, 18.4% (34/185) neoadjuvant and 9.7% (18/185) primary chemotherapy.

Completion of self-assessments:
All patients were able to self-complete the PS scores. Twenty-three (12.4%) patients did not answer all the VES-13 questions and twenty (10.8%) patients did not fully complete the G8 questions, to enable total scores to be calculated.

Summary of results from study questionnaires:

Assessment score	Number of patients Total n=185	Percent %
Performance status		
0	77	41.6
1	58	31.4
2	43	23.2
3	7	3.8
VES-13 score		
< 3	124	67.0
≥ 3	38	20.5
Missing	23	12.4
G8 score		
> 14	65	35.1
≤ 14	100	54.1
Missing	20	10.8

Chemotherapy toxicity:
153 patients (82.7%) were commenced on full dose chemotherapy.
62 (33.5%) had dose reductions after initiation of treatment.
47 (25.4%) patients had a delay in a planned cycle of chemotherapy.
49 (26.5%) had documented Grade III/IV toxicities.
43 (23.2%) patients had an unplanned hospital admission during treatment.
61 (33.0%) patients – treatment was stopped early.
4.3% (8) of patients died within thirty days of their last chemotherapy cycle.

Results

Does the G8 score predict chemotherapy toxicity?
Our hypothesis was that a low G8 score (≤ 14), previously associated with a high probability of failing a CGA, would identify and predict a population of patients who are at risk of severe chemotherapy toxicity.

Patients with a low G8 score ≤14 were more likely to experience severe chemotherapy toxicity than those with a high G8 score: 64.6% vs. 46.9% (χ^2 = 5.029, p=0.025).

Does the VES-13 score predict chemotherapy toxicity?
A high VES-13 score (≥3) has previously been associated with increased risk of functional decline or death.

Patients with high VES-13 scores ≥3 were more likely to experience severe chemotherapy toxicity than those with a low VES-13 score: 76.3% vs. 54.1% (χ^2 = 5.929, p= 0.015).

Does performance status predict chemotherapy toxicity?

There was no significant difference between PS score groups (PS 0/1 vs. ≥ 2) and likelihood of developing severe toxicity (χ^2 = 0.996, p=0.318). Sensitivity and specificity of the three tools was explored.

Sensitivity and specificity of G8, VES-13 and PS in predicting severe chemotherapy toxicity in the study population:

	G8 score (≤14 vs >14)	VES-13 score (<3 vs ≥3)	PS score (0,1 vs ≥2)
Sensitivity	68.0%	30.5%	30.0%
Specificity	49.3%	86.2%	76.7%

Receiver operator characteristic (ROC) curves did not identify any suitable alternative cut-off values for any of the three scores in predicting chemotherapy toxicity

Conclusions

In this study, 59.5% of older patients experienced severe chemotherapy toxicity. The majority were able to self-complete the questionnaires. ECOG PS was not a good predictor of the likelihood of patients developing severe chemotherapy toxicity. Both the G8 and VES-13 scores identified a subset of patients at higher risk of severe chemotherapy toxicity.
The results are promising and further work could explore whether certain components of the G8 and VES-13 scores or additional measurements such as functional assessment scores or particular blood tests may be useful in assessing and predicting older patients' risk of chemotherapy-related adverse events and toxicities.

References

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