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Screening measures to detect cognitive and auditory dysfunctions in (older) cancer patients

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To Florence

“It always seems impossible until it’s done”

Nelson Mandela

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LIST OF ABBREVIATIONS

A

ABVD	doxorubicine, bleomycine, vinblastine, dacarbazine
AC	adriamycine
ACE-27	Adult Comorbidity Evaluation
AD	Alzheimer's disease
ADL	Activities of Daily Living
APOE	alipoproteine E
ARHL	age-related hearing loss
ASCO	American Society of Clinical Oncology
ASHA	American Speech-Language-Hearing Association
AUC	area under the curve

B

BBB	blood-brain barrier
BOMT	Blessed-Orientation Memory Test

C

C+	patients receiving chemotherapy
C-	patients not receiving chemotherapy
CARG	Cancer and Aging Research Group
CCI	Charlson Comorbidity Index
CDT	clock drawing test
CFT	complex figure test
CFQ	cognitive failure questionnaire
CGA	comprehensive geriatric assessment
CI	confidence interval
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
COWA	controlled oral word association
CRCI	cancer-related cognitive impairment
CVD	cardiovascular disease

D

DART	Dutch adult reading test
dB	decibel
DBI	drug burden index
DDI	drug-drug interactions
DNA	deoxyribonucleic acid
DOR	diagnostic odds ratio
DPOAE	distortion product oto-acoustic emission
DSM-IV	Diagnostic and statistical manual of mental disorders – version IV
DT	distress thermometer

E

ECOG	Eastern Cooperative Oncology Group
EFT	emotional freedom techniques
EORTC	European Organization for Research and Treatment of Cancer

F

FACIT	Functional Assessment of Chronic Illness Therapy
FEC	fluorouracil, epirubicine, cyclofosfamide
FF	free-field
FU	fluouracil

G

G-8 or G8	G8-questionnaire
GA	geriatric assessment
GDS	Geriatric Depression Scale
GG	general geriatric

H

HADS	Hospital Anxiety and Depression Scale
HDL	high density lipoprotein
HHIE	Hearing Handicap Inventory for the Elderly
HHIE-S	Hearing Handicap Inventory for the Elderly – short form
HL	hearing level
HNCA	head and neck cancer

I

IADL	Instrumental Activities of Daily Living
ICCTF	International Cognition and Cancer Task Force
IL	Illinois
ISO	International Organization for Standardization
IQ	intelligence quotient

K

KPS	Karnofsky's performance status

M

MCI	mild cognitive impairment
MMSE	mini mental state examination
MNA	mini nutritional assessment
MoCA	Montreal cognitive assessment
MRI	magnetic resonance imaging

N

NA	not applicable
NAT2	N-acetyltransferase 2
NCCN	National Comprehensive Cancer Network
NCs	no-cancer controls
NEG	negative
NHTSA	National Highway Traffic Safety Administration
NIHL	noise-induced hearing loss
NPV	negative predictive value
NY	New York

O

OAE	oto-acoustic emission
OG	oncogeriatric
OS	operating system

P

POS	positive
PROMs	patient-reported outcome measures
PS	performance status
PTA	pure tone average
PTS	permanent threshold shift
PPV	positive predictive value

Q

Qol	quality of life

R

RAVLT	Rey's auditory verbal learning test
RCHOP	rituximab ,vincristine, adriamycine, cyclofosfamide, prednisone
RCI	reliable change index
RNA	ribonucleic acid
ROC	receiver operating characteristics
ROS	reactive oxygen species

S

S or Se	sensitivity
SD	standard deviation
SE	standard error
SIOG	Société Internationale d'Onco Gériatrie
SNP	single-nucleotide polymorphism
Sp	specificity
SPIN	speech-in-noise test
SPL	sound pressure level
SPSS	Statistical Package for the Social Sciences

T

T0	time 0 - baseline assessment
T1	time 1 – assessment six months after treatment initiation
TEOAE	transient evoked oto-acoustic emission
TMT	trail making test
TTS	temporary threshold shift
TUG	timed up and go

U

UK	United Kingdom
US or USA	United States (of America)

V

VEP	visual evoked potential
VES-13	Vulnerable Elders Survey-13

W

w/o	without
WAIS	Wechsler Adult Intelligence Scale
WDR	word delayed recall
WRAT-3	Wide Range Achievement Test-3
WVT	whispered voice test

SUMMARY

Clinicians have started to pay more interest to the psychosocial problems that are related to a cancer diagnosis and cancer treatment. Hearing loss and cognitive dysfunctions are two conditions that may seriously interfere with the patient's ability to deal properly with all aspects of their cancer disease and may drastically affect the patient's quality of life. Therefore, proper screening of those conditions is essential in order to optimize the patient's comfort during and after treatment. This thesis focusses on screening tools that could enable health care providers to easily detect hearing loss and cognitive deficits in (older) cancer patients.

In older cancer patients, cognitive and hearing loss were addressed as part of a Comprehensive Geriatric Assessment (CGA), a multidisciplinary evaluation in which multiple health domains are assessed in order to develop a coordinated care plan. In case of cognition, the Freund Clock Drawing Test (CDT) was evaluated for use within the CGA and compared to the well-known Mini-Mental State Examination (MMSE). One of the main problems with the CDT was its lack of a proper scoring system and cut-off score in an oncogeriatric population. After establishing a cut-off score of ≤4, results showed an excellent diagnostic accuracy and reduced assessment time when compared to the MMSE.

Cancer-related cognitive impairment (CRCI) is currently a hot topic within the field of psycho-oncology. Many patients may experience subjective cognitive complaints and only little is known about its existence. Initially, CRCI was considered as a consequence of treatment with chemotherapy. However, although some cytotoxic agents may induce cognitive changes, most chemotherapeutics cannot cross the blood-brain barrier. Psychosocial factors, on the contrary, have been recently suggested as possible cofounders of CRCI. In this thesis, the distress thermometer (DT) was used as a screening tool to detect cognitive impairments six months after treatment initiation. Although, the DT failed to screen for objective CRCI, results did indicate that the DT could be used to screen for subjective cognitive complaints. Further, screening for fatigue may even be more suitable to detect subjective cognitive difficulties in cancer patients. Our findings also indicated that receiving chemotherapy did not influence neuropsychological test results when comparing patients with and without chemotherapy.

Assessing hearing loss is mostly omitted when conducting a CGA. In this thesis, uHear™ - an iOS-based application - was examined as a screening tool to detect hearing loss in older cancer patients. Initial results indicated that uHear™ was not feasible when using a scoring method based on the Pure Tone Average. A follow up trial, investigating uHear™ with a pass or fail screening cut-off based on hearing grades improved the diagnostic accuracy of the test, but results did not meet the validation criteria.

In conclusion, this work presents screening tools that could aid clinicians to screen for hearing loss and cognitive dysfunctions in (older) cancer patients. The Freund CDT has shown excellent results and can be directly implemented in routine geriatric oncology practice. In case of screening for hearing loss and CRCI, more research is necessary before the tools investigated here can be used in routine practice. In terms of screening for CRCI, this work provides a first insight into the use of psychosocial measures to screen for cognition. As psychosocial factors are highly related to the amount of subjective cognitive complaints that patients experience, more research in this specific area is necessary in order to optimize the patient's quality of life after treatment. As we failed to validate uHear™, more research is warranted in order to select the proper screening tool for hearing loss within the CGA. Nevertheless, it should be noted that addressing hearing loss in older cancer patients is essential, as patients may not admit they have a hearing problem and it is crucial to know if patients are able to hear the given information.

SAMENVATTING

Artsen besteden meer aandacht aan de psychosociale problemen die gepaard gaan met de diagnose en behandeling van kanker. Gehoorverlies en cognitieve disfuncties zijn twee condities die ernstig kunnen interfereren met de manier waarop de patiënt omgaat met alle aspecten van de ziekte. Daarnaast kunnen ze ook de levenskwaliteit van de patiënt negatief beïnvloeden. Bijgevolg is een adequate screening van deze condities essentieel om de levenskwaliteit van de patiënt tijdens en na de behandeling te optimaliseren. Deze thesis focust zich op screening tools die gezondheidsprofessionals in staat stelt op een eenvoudige manier gehoorverlies en cognitieve problemen op te sporen bij (oudere) kankerpatiënten.

Bij de oudere kankerpatiënten worden geheugen- en gehoorverlies opgespoord in het kader van een uitgebreide geriatrische beoordeling (CGA). Dergelijke CGA kan omschreven worden als een multidisciplinaire evaluatie van meerdere gezondheidsdomeinen met als doel een gecoördineerd zorgplan op te stellen. Om cognitieve problemen op te sporen werd de Freund kloktekentest (CDT) onderzocht en vergeleken met de welgekende Mini-Mental State Examination (MMSE). Een van de grootste problemen van de CDT is het gebrek aan een adequaat scoresysteem en gevalideerde cut-off score in een oncogeriatrische populatie. Bij gebruik van een gepredefinieerde cut-off score van ≤4, werd aangetoond dat de CDT in minder tijd kan afgenomen worden dan de MMSE alsook toont de test excellente diagnostische eigenschappen.

Kanker-gerelateerde cognitieve disfuncties (CRCI) zijn een hot topic binnen de oncopsychologie. Hoewel veel patiënten cognitieve problemen ervaren, is slechts weinig gekend over het ontstaan ervan. Initieel werden deze problemen dikwijls toegeschreven aan de chemotherapeutische behandeling. Hoewel sommige cytotoxische producten cognitieve veranderingen kunnen teweegbrengen, zijn er heel wat die de bloed-hersenbarrière niet kunnen doorkruisen. Recent bleek dat ook psychosociale factoren een rol kunnen spelen in het ontstaan van CRCI. In deze thesis werd nagegaan of de distress thermometer (DT) kon gebruikt worden om CRCI op te sporen zes maanden na de start van de behandeling. Dit bleek niet het geval. Wel werd aangetoond dat de DT subjectieve cognitieve klachten kon opsporen. Daarnaast toonde screenen naar vermoeidheid nog betere resultaten om dergelijke klachten te detecteren. De toediening van chemotherapie had geen invloed op het resultaat van de neuropsychologische testen.

Gehoorverlies wordt vaak niet opgespoord binnen een CGA. In deze thesis werd uHear™, een iOS-applicatie, onderzocht om gehoorverlies op te sporen als onderdeel van de CGA. De eerste resultaten toonden aan dat uHear™ niet gebruikt kon worden wanneer het scoresysteem gebaseerd was op de Pure Tone Average. Een follow-up studie werd opgezet waarbij een scoringsmethode onderzocht werd die zich baseert op graden van gehoorverlies. Hoewel deze scoringsmethode verbeterde diagnostische eigenschappen met zich meebracht, bleek dit niet voldoende om de test te valideren.

We kunnen besluiten dat dit werk screening tools aanreikt die gezondheidsprofessionals kunnen helpen om gehoor- en cognitief verlies op te sporen bij (oudere) kankerpatiënten. De Freund CDT gaf excellente resultaten en kan meteen geïmplementeerd worden in de dagelijkse praktijk. Betreffende CRCI biedt dit werk een eerste inzicht in het gebruik van psychosociale vragenlijsten om cognitieve klachten op te sporen. Gezien de sterke correlatie tussen psychosociale factoren en subjectieve cognitieve klachten, zou vervolgonderzoek zich hierop moeten focussen zodoende de levenskwaliteit van de patiënt te verbeteren. Meer onderzoek is nodig om een geschikte screeningtool inzake gehoorverlies te selecteren voor gebruik binnen de CGA. Niettemin blijft het wel belangrijk gehoorverlies op te sporen aangezien patiënten dergelijke problemen vaak verzwijgen en het toch essentieel is te weten dat de patiënt de gegeven informatie gehoord heeft.

CHAPTER 1

Introduction

PART I

The assessment of the older patient with cancer

Based on

Integration of geriatric oncology in daily multidisciplinary cancer care: the time is now
Lycke M et al. *European Journal of Cancer Care*. 2015

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INTRODUCTION

Due to growth of the ageing population and a prolonged exposure to carcinogens, cancer has become an important disease in older people [1, 2]. It has been reported that individuals aged 65 or older have an 11-fold higher risk of developing cancer compared to their younger counterparts. Further, they have a 15 percent greater cancer-related mortality rate [2]. In the European Union, an approximate 14% increase of the total projected cancer incidence is estimated to occur from 2009 to 2020 [3, 4].

Cancer is a very serious health problem at any age, however, combined with increasing age, it creates even more challenging situations for health care providers. Decreasing physiologic reserves, leading to distinct variations in functional status, cognition and co-morbidity may affect life expectancy in an individualized manner. As a consequence, their chronological and functional age may not correspond [5]. The spectrum of impairment ranges from more independent individuals, to those who are at moderate risk of health deterioration, to patients who have a high risk at functional decline or mortality [6]. Therefore, proper patient selection is an important step to administering a safe and effective cancer treatment [7].

Medical and radiation oncologists are faced with another challenge since evidence-based data of the risks and benefits of cancer treatments in older patients are lacking. Currently applied tools describing the patient's functional status, such as the Eastern Cooperative Oncology Group (ECOG) performance status (PS) and Karnofsky (K) PS, have proven to be insensitive in estimating the functional capabilities of an older patient [8]. Consequently, as a result of doubts concerning the patients' fitness and their ability to tolerate treatment, physicians are less likely to provide appropriate and curative life-saving therapies to older patients when compared to their younger counterparts [9, 10]. For this reason, a Comprehensive Geriatric Assessment (CGA) has become the cornerstone in modern geriatric oncology care [11, 12].

THE INTEGRATION OF GERIATRIC PRINCIPLES IN ONCOLOGY

The initial geriatric assessment was developed in 1930 by Marjory Warren. She established the first geriatric care unit in the UK in which ill older patients were more adequately managed through assessment of a CGA. A CGA can be defined as "a multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described and explained, if possible, and in which the resources and strengths of the person are catalogued, need for services assessed, and a coordinated care plan is developed to focus interventions and long-term follow up on the person's detected vulnerabilities" [13, 14]. Since those first steps of Marjory Warren, a CGA has been the advised approach in the evaluation and treatment of general geriatric patients and has been applied all over the world as it is known to have multiple advantages (Table 1) [15, 16].

Table 1. Overview of the advantages of performing a CGA in oncology

Advantage	Reference
Guides treatment decision	17-19
Predicts and improves survival	20, 21
Prevents functional decline	22, 23
Predicts and improves quality of life	24, 25
Predicts the risk on chemotherapy toxicity	7, 26

These geriatric principles have found their way into oncology practice since the nineties, when Monfardini and colleagues made a first attempt to adapt the CGA for use in cancer patients [27]. Their adapted CGA has later been prospectively validated by the Italian Group of Geriatric Oncology [28]. Around the year 2000, several research groups indicated the value of using a CGA in routine oncology practice [29, 30]. In an ideal situation, a CGA should be performed by a multidisciplinary geriatric team, which includes a geriatrician, nurse, social worker, pharmacist, dietician and an occupational therapist [31]. However, other approaches, including for example a geriatric oncology nurse, have also been proposed as they are more feasible in an ambulatory oncology practice [32].

Extermann and Terret were the first to report that a CGA could detect multiple problems in older breast and prostate cancer patients respectively [21, 33]. Many papers followed describing different health problems in distinct cancer populations [6, 19, 34-37]. Further, Repetto et al. suggested that a CGA has an added value to ECOG PS and KPS [25, 28].

THE CONTENT OF A CGA

In oncology, a CGA is described as a multidisciplinary, in-depth evaluation to assess the risk of morbidity and mortality [29, 38]. It aims at identifying vulnerabilities in different age-related domains such as functional status, physical performance, cognition, nutrition, social state, emotional status, co-morbidity and polypharmacy. Though only a limited number of oncology trials could be found that examined the psychometric properties of CGA as a whole, researchers generally agreed about the CGA's feasibility, reliability and validity [37, 39-41]. Hamaker reported a median number of seven examined domains within a CGA, resulting in a different estimation of vulnerability prevalence (ranging from 28% to 94%) [42]. Moreover, for each health domain, a plethora of validated tools is in use and no consensus exists as to which one is most suited. International oncology societies such as the National Comprehensive Cancer Network (NCCN) (http://www.nccn.org), the International Society for Geriatric Oncology (http://www.siog.org) and the European Organization for Research and Treatment of Cancer (EORTC) (http://www.eortc.org), have published guidelines suggesting those core domains that should be incorporated within a CGA and that could be assessed by a multidisciplinary geriatric oncology team including geriatric oncology nurses, dietitians, psychologist, oncologist, geriatricians and other health care professionals (Table 2) [39, 43-45].

Assessing the functional and physical status are cardinal components of geriatric care. Cancer is considered to be life changing in all its aspects because it induces major changes in the living patterns of older adults [46]. Further, there is evidence that the level of dependence in daily activities influences survival in older patients [47]. The most commonly used instruments to screen for functional dependence are the Activities of Daily Living (ADL) and the Instrumental Activities of Daily Living (IADL) [48, 49]. The ADL rates the patient's ability to fulfil basic activities of daily living including bathing, dressing, toileting, transferring, continence and feeding. The IADL looks at activities that require a higher level of cognition and judgement such as cooking, shopping, transportation and others [50]. Ideally, grip strength and an evaluation of gait, balance and risk of falls should also be included as a direct measure of the patient's physical status [39].

Another essential domain within a CGA is the assessment of the patient's cognitive function. Studies have shown that up to 50% of patients can present with cognitive abnormalities that need further attention. It is further shown that a cognitive disorder can impact the ability to weigh the risks and benefits of the suggested treatment plan and that it may cause difficulties in recognising signs of adverse effects that warrant closer observation [29]. Cognitive functioning

within a CGA is mostly evaluated with the well-known Folstein Mini-Mental Status Examination (MMSE) [51]. Although validated in multiple populations, others have encountered difficulties when having to perform the MMSE in older cancer patients. Therefore, other measures such as the MoCA and Mini-Cog have been proposed [52, 53].

Table 2. Overview of the principle domains within a CGA (Adapted with permission from Pottel, 2014 [54])

Principal domains	Description	Most commonly applied validated tools
Functional status	Assessment to estimate patients self-sufficiency, as well as their ability to live independently and function in the community	Katz' Activities of daily living (ADL)[48], Barthel-index[55], Lawtons' instrumental activities of daily living (IADL)[49]
Physical performance	Mobility, gait, balance, muscle strength	Tinetti Balance and Gait test[56], Timed up and go (TUG)[57], Grip strength[58]
Cognition	Assessment of patient's cognitive performance	Mini Mental State Examination (MMSE)[51], Montreal Cognitive Assessment (MoCA)[52], Mini-Cog[53]
Nutrition	Assessment of patient's nourishment, weight changes	Mini Nutritional Assessment (MNA) [59]
Emotional state	Assessment of the patient's emotional status	Geriatric depression scale (GDS)[60]
Co-morbidities	Rating of the number and severity of co-existing morbidities	Charlson Comorbidity Index (CCI)[61], Cumulative Illness Rating Scale for Geriatrics (CIRS-G)[62], Adult Comorbidity Evaluation (ACE-27)[63]
Polypharmacy	Assessment of the number of medications, possible drug-drug and drug-disease interactions, medications contraindicated in older patients (principles of geriatric pharmacology)	Online drug interaction tool[64], Drug burden index (DBI)[65], Beers criteria [66]

Nutrition is another crucial element included in a CGA. Several studies have demonstrated the importance of weight loss as a prognostic factor for survival in patients with cancer [29]. Up to 40% of general geriatric patients are found to be at risk for malnutrition, and without proper nutritional support, an intensive cancer treatment could induce cachexia. Nutrition can be assessed through the Mini-Nutritional Assessment (MNA) which is frequently used to identify geriatric patients at risk of malnutrition [59].

The emotional status should be assessed within a CGA, as up to 50% of older patients have been found to show signs of a depression [13, 28]. Depression in older adults has been associated with increased risk for resource requirements and informal care giving needs. An assessment of the older patient's psychological state is becoming increasingly important as the care of oncology patients is primarily moving to the outpatients settings, with an increased reliance on caregivers to assist with symptom management and daily activities [29]. The Geriatric Depression Scale (GDS) is a commonly used tool to screen for depression in older patients [21]. The GDS was originally developed and included 30 questions, however, shorter versions exist as well [60, 67].

The relative incidence of comorbidities increases with age. Research has shown an association between the presence of comorbidities and the older cancer patient's prognosis [68]. Further, it is stated that concomitant diseases not only influence survival but that they also may influence the behaviour of the cancer itself. Therefore, screening for comorbidities forms an

essential part of the CGA [29]. Comorbidities can be assessed through the Charlson Comorbidity Index which includes 19 diseases weighted from one to six points [61] or through the Cumulative Illness Rating Scale for Geriatrics [62].

Another element included in the older cancer patient's assessment is polypharmacy, which can be defined as the administration of five or more drugs and may lead to an increased risk of side-effects and drug-drug interactions [69]. Although the reported prevalence of concomitant drug use in the elderly ranges widely and is dependent on the population under study [68], it is known that medication intake increases as patients receive cancer treatment [69]. Further, as the number of medications increases, older patients may have difficulties with treatment compliance and may need more help with their medication intake. Poor treatment adherence may negatively impact the patient's health and quality of life. Further, it may lead to increased visits to the emergency room and drug-related hospitalization [70]. Therefore, a medication review as part of the CGA is essential [71].

A final important aspect to consider when approaching older cancer patients is the social state of the patient. Social isolation in older adults leads to psychological distress and the absence of social support is a predictor of mortality, independent of the age of the patient [29, 72]. To examine the social state of the patients, specific questions can be asked regarding their marital status, living situation, number of children, etc.

CGA IN ROUTINE PRACTICE

When the CGA was first introduced into oncology, the assessment could take up to two hours, without incorporating the time needed to review the data, score the patient's health status and develop an individualized care plan. To overcome this limitation, researchers have focused on a two-step approach in which older patients are first assessed with a brief screening tool, followed by a more comprehensive geriatric assessment for those who screen positive (Figure 1) [73].

Hamaker and her colleagues provided an overview of the screening tools, such as the G8-questionnaire (G8), Vulnerable Elders Survey (VES)-13 and others, that have been investigated for use in oncogeriatric patients. All of these screening tools assess functional status and most of those, also address psychosocial functioning. However, the inclusion of other geriatric domains was observed to vary widely among the different screening methods. Further, the use of different contents and cut-off scores leads to a large discrepancy in sensitivity and specificity to identify vulnerability. Nevertheless, the G8-questionnaire remains the most favourable screening tool for use as it has a strong prognostic value for functional decline and overall survival [24, 74, 75].

In case the patient screens positive and a full CGA is performed, the multidisciplinary geriatric oncology team can make a conclusion of the patient's fitness which can be categorized into 'fit', 'vulnerable' or 'frail' (Figure 1.) according to the criteria applied. Balducci was the first to publish three classes of fitness in the older patient, based on the presence of co-morbidities, geriatric syndromes (e.g. incontinence, distress, delirium, ...) or functional dependence [76]. Further, some have included parameters such as muscle weakness, weight loss and other [77, 78]. At present, an impairment on a CGA is defined as meeting the cut-off scores for impairment in at least one [34] or at least two [6, 35, 36, 79] domains within CGA, based on the finding that deficits in two or more of the CGA scales indicate an increased risk of disability or death [80, 81]. In this thesis, the latter will be used to define vulnerability on the CGA.

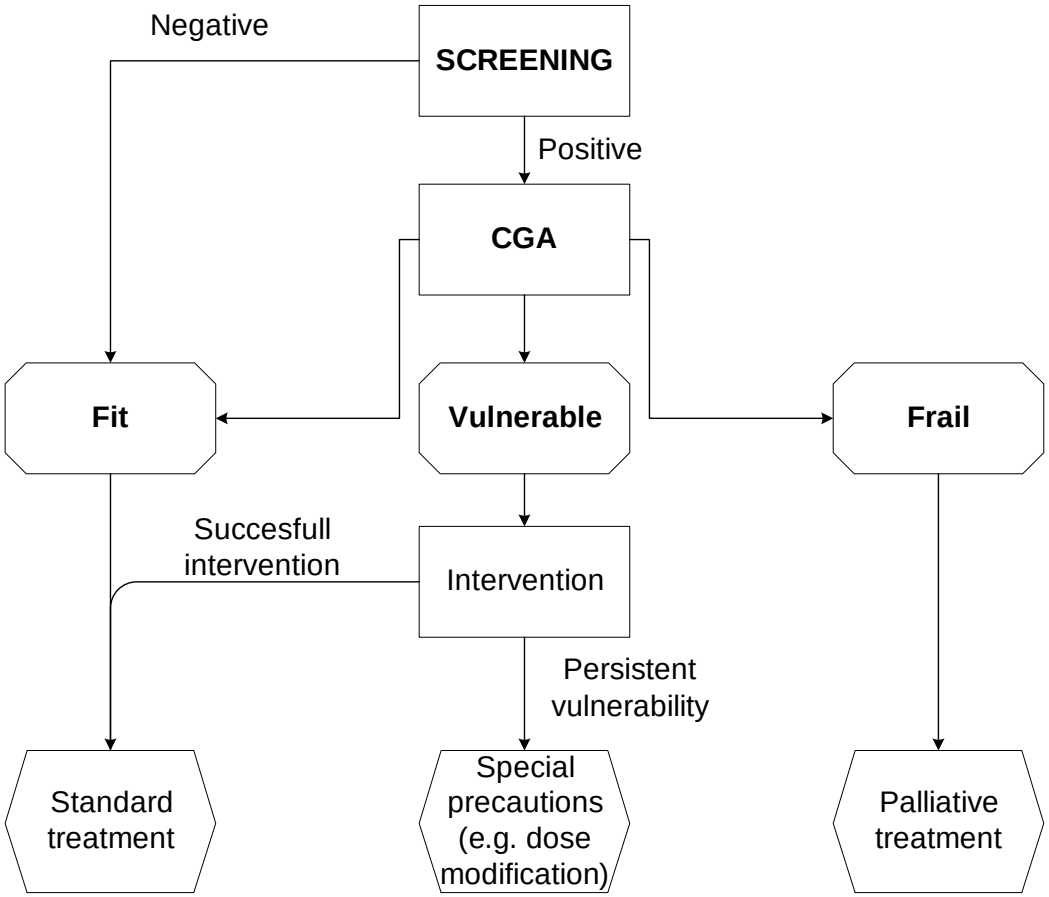


Figure 1. Schematic overview of CGA approach in oncology

It should be noted that conducting a CGA alone does not add any value to the patient's treatment plan without tailored interventions. Based on the CGA, problems or vulnerabilities in the several health domains can be detected. Therefore, when such vulnerability is detected, a proper referral should be made in order to decrease the risk on morbidity and mortality. For example, when a patient shows limited mobility, which influences the patient's ability to perform daily activities, a referral to the geriatric day clinic could be made so that the patient can be assessed by the geriatric team and proper interventions, such as cleaning help or the delivery of meals or physical therapy, can be arranged. Ideally, the results of the CGA are discussed with a geriatrician and are presented at the multidisciplinary oncologic consult, when a multidisciplinary team decides on the patient's treatment. In vulnerable patients, serial CGA should be performed to re-evaluate the patient's status during or after treatment [82].

CHAPTER 1

Introduction

PART II

Pre-existing cognitive dysfunctions in older cancer patients

INTRODUCTION

When growing older, adults are aware that memory loss occurs more frequently than in their younger years. Their mental speed slows down, they have more difficulties in adjusting to newer technologies and they find it harder to remember recent events or peoples' names [83]. On the contrary, cognitive ageing does not affect all aspects of cognition. For example, the so-called crystallized intelligence, such as our knowledge and vocabulary, is stable across the lifespan [83, 84]. In general, the magnitude of normal cognitive decline as a result of the ageing brain tends to be small and does not impair a person's ability to carry out activities of daily living [85]. Although this process develops in all subjects as a result of ageing, it shows an individual pattern and may evolve more rapidly in some persons than in others [83]. Further, in cancer patients, cognitive impairment can interfere with the patient's ability to understand a cancer diagnosis and its treatment. As a result, the NCCN Guidelines in Older Adult Oncology advise to assess the patient's cognitive abilities and to screen for delirium, mild cognitive impairment and dementia [86].

Although delirium lays not within the scope of this thesis, this is addressed briefly, as it remains poorly understood. Delirium can be defined as an acute decline of the patient's cognitive function [87]. It is characterized by disorganized thoughts, incoherent speech and attention deficits and can manifest itself as agitation or hypo-activation [88]. In cancer patients, delirium is associated with an increased morbidity, an increased mortality and prolonged hospitalization [89, 90]. The condition is often unrecognized in both cancer and non-cancer patients and even when it is diagnosed, it remains untreated or inappropriately treated in many patients. Treatment exist of both pharmacological and non-pharmacological interventions [91].

A mild cognitive impairment (MCI) can be described as a transitional state between normal ageing and dementia. It is characterized by a cognitive decline greater than expected according to the person's age and educational level, but has no severe impact on the person's daily functioning [92]. People who suffer from an MCI experience cognitive complaints, that can be objectively measured but do not meet the criteria for dementia [93]. It is estimated that up to 19% of adults over the age of 65 suffer from MCI. In some, the MCI may remain stable over the years, although it progresses into dementia in more than half [92]. Further, it has a greater progression in females than in males [94]. When diagnosing MCI, it is crucial to exclude conditions that may induce cognitive complaints such as depression, alcohol or drug abuse, learning disabilities, anxiety or other conditions, through clinical and psychological examinations. Although evidence is lacking, it is said that detecting an MCI has several benefits as early treatment may prevent progressing to dementia [95]. Further, it is stated that MCI is associated with a lack of appreciation and understanding of consent materials for medical treatments, poorer decision-making and difficulties with financial issues such as counting money and writing checks [96].

Dementia is a progressive neurodegenerative condition that interferes with the ability to perform daily activities [86]. The prevalence of dementia increases with age, ranging from 1.3% between the ages of 65 – 69, up to 32.5% in persons over 95 years old in developed countries. In developing countries, prevalence rates tend to be lower. Possible explanations may be that there are fewer risk factors for dementia, that early detection of dementia is lower and that fewer individuals reach the age of 65 in some very poor countries. Prevalence rates are higher in women than in males and are not influenced by racial differences [97]. Although there are several forms of dementia, Alzheimer's disease (AD) is without doubt the most frequently occurring cause of pathologic cognitive ageing, accounting for up to 70% of all dementia cases [98, 99].

Since both dementia and cancer have age as a common risk factor, older cancer patients pose unique challenges to healthcare professionals. As a result, Solomons et al. (2013) recently published a review on the genetic link between both mechanisms. They state that it is not surprising that various pathways and genes involved in cell-cycle regulation may link dementia and cancer, since the fundamental biologic of cancer is an uncontrolled cell proliferation and/or prolonged cell survival, while dementia involves neuronal cell degeneration and cell death. Some of the possible genetic factors include tumour suppressor genes, peptidyl-propyl cis/trans isomerase, DNA repair genes, miRNA genes and genes on chromosome 21 [100].

ASSESSMENT AS PART OF A CGA

As previously mentioned, one of the domains covered within a CGA is the patient's cognitive functioning. Presenting with both cancer and a cognitive impairment may lead to functional dependence, higher risk on depression and higher mortality rates [101]. Further, having cognitive difficulties may influence the patient's ability to weigh the risks and benefits of the proposed cancer treatment. The NCCN Guidelines in Older Adult Oncology state that cognition, as part of the CGA, can be assessed by the Blessed Orientation-Memory Test (BOMT), the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) or the Mini-Cog [102].

Katzman et al. (1983) have originally developed the BOMT. The BOMT is a 6-item screening tool that allows health care providers to screen for dementia in older adults. Scores range from zero to 28 with a cut-off score of ≥9 indicating a positive test. The test can also be administered by non-clinicians and has shown to discriminate among mild, moderate, and severe cognitive deficits. Although advised by the NCCN Guidelines in Older Adult Oncology, the BOMT is a rather unknown screening tool that has been rarely used within the CGA given the other more validated and more well-known tests that are available [103].

The Folstein MMSE is a brief 30-point questionnaire that is used to screen for cognitive impairment and is considered the gold standard to screen for dementia. It is validated in several patient populations and available in multiple languages. The MMSE assesses orientation, memory, attention, language, planning and visuoconstruction, and can be administered in a time span of approximately ten minutes. It is further stated that the MMSE can estimate the severity of the cognitive impairment at a given point in time, making it an effective way to document an individual's response to treatment. However, the ability to detect little and subtle changes in cognitive function is limited with this screening tool and it cannot predict future decline [29, 51]. Further, it has been reported that the MMSE is influenced by education age [104].

The MoCA was recently developed by Nasreddine et al. (2005) as a brief screening tool to detect cognitive impairments in several clinical settings and is available in multiple languages. Scores range from 0 to 30 with scores of 26 or higher indicating a normal test [52]. The MoCA assesses visuo-spatial abilities by a clock drawing test, executive functioning, attention, memory, concentration, language and orientation. Testing time is set to an average of ten minutes. As it has a test–retest reliability of 0.92 and validity of 0.87 to MMSE, the MoCA seems to be superior to the MMSE to detect MCI. The main difference between both screening measures is that the MoCA also includes tasks assessing executive function and abstraction. Fewer points are given for orientation in time and place while extra weight is given on tasks including recall, attention and calculation [105]. Further, it has also been stated that the MoCA is a superior prognostic indicator to the MMSE in patients with brain metastases [102, 106].

As both the MMSE and MoCA take at least ten minutes to assess, the NCCN Guidelines in Older Adult Oncology also advise the Mini-Cog as a possible alternative cognitive screening tool [102]. The Mini-Cog assesses visuo-spatial abilities by a clock drawing test, combined with

the three word delayed recall test as used in the MMSE, assessing short-term memory [53]. Combining these two tasks would lead to psychometric properties that are comparable to those of the MMSE [107]. While the Mini-Cog has shown good diagnostic accuracy for detecting dementia, it has a rather low sensitivity for detecting MCI [108, 109]. The Mini-Cog can be easily administered by a wide range of healthcare professionals and is not influenced by the educational level or health literacy of the patient. In comparison with other screening tools proposed within the CGA, the Mini-Cog only takes two to three minutes to administer. Scores range from zero to five with scores of two or less indicating a cognitive impairment [110].

CHAPTER 1

Introduction

PART III

Acquired cognitive dysfunctions in cancer patients

INTRODUCTION

Over the years, advances in the early detection of cancer and its treatment have resulted in a longer life expectancy in patients of all ages who are diagnosed with cancer. Although survival rates have increased, many patients suffer from treatment-related side effects that may adversely affect their health-related quality of life. Along with the changes in therapeutic strategies, physicians have paid more attention to the psychosocial problems secondary to cancer as it is well recognized that the diagnosis of cancer and its treatment are extremely stressful and emotional for the cancer patient [111]. Whereas some of these side effects are well recognized, well understood and effectively managed, others are more subtle and not as clear. The improvements in cancer treatments have led to substantial long-term side effects such as fatigue, pain and cognitive alterations which are associated with an anti-cancer treatment or in some cases with the cancer itself [112].

Cancer-related cognitive impairment (CRCI) was first described as chemobrain or chemofog, as it was a common concern among breast cancer patients receiving chemotherapy, which is also the most studied group with regard to this symptom [113]. In paediatric patients on the contrary, neurocognitive adverse effects of chemotherapy and brain radiotherapy have long been recognized as a major concern in long-term survivors [114]. Later however, it became clear to researchers that psychosocial elements such as distress and fatigue also play a role in the development of CRCI and that chemotherapy may not be the sole cause of cancer-related side effects [115]. Nonetheless, a clear understanding of CRCI is critical, as there is a growing group of malignancy survivors who often want to return to their former occupational, scholastic and other social activities [116]. Research into CRCI is rather new within the field of cancer studies and can still be considered as a hot topic.

EFFECT OF CANCER TREATMENT

Chemotherapy is a widely used treatment strategy in the management of cancer. It can be given in a neoadjuvant or adjuvant setting, or in a combination of both. Common side effects of a chemotherapeutic treatment include nausea, vomiting, anorexia, hair loss, neutropenia, skin rashes, peripheral neuropathy, fragile nails, impaired sexual function, early-onset induced menopause in women and other [117, 118]. First studies into CRCI in breast cancer patients also found evidence that chemotherapy may disrupt the central nervous system as women receiving an adjuvant treatment with chemotherapy reported alterations in memory, thinking clearly and concentration. Further, those patients reported significantly more troubles than breast cancer controls who did not receive any chemotherapeutic regimen [117, 119, 120]. Other common changes in cognitive functioning due to chemotherapy include executive functioning, processing speed, working memory, and organizational skills. Chemotherapy-induced impairment of language ability, concentration, memory and/or attention can have a detrimental effect on a patient's quality of life, influencing one's ability to use complex thinking in making treatment decisions [120-122].

While initial studies were criticized by their lack of including a baseline cognitive assessment and their retrospective design, recent prospective research has indicated that CRCI occurs in a substantial number of patients. Studies in breast cancer patients have reported prevalence rates affecting up to 40% of patients, while other longitudinal studies in adult cancer survivors report that cognitive alterations are more commonly found than anticipated with incidence numbers ranging from 15% to 80% of patients being affected [114]. The perceived cognitive problems can persist throughout the whole illness trajectory and in some domains, complaints maintain long after the treatment has ended. A recent meta-analysis by Jim et al. (2012) suggests that breast cancer patients can experience deficits in verbal and visuospatial ability

up to six months and more after the chemotherapy has ended [123]. Furthermore, these problems may even persist 20 years post treatment [124].

Though initial trials focused on breast cancer patients, these last years it has become clear that other cancer patients also experience cognitive difficulties following cancer treatment. It has been reported by several researchers that androgen deprivation therapy, which is used in case of prostate cancer, adversely affects verbal memory, visuomotor function, attention and executive function [125, 126]. CRCI has also been found in patients with haematological malignancies. Treatment-related cognitive decline was noticed in terms of executive functioning, attention, language, memory, spatial ability and psychomotor speed [127]. Cognitive changes have also been reported in lung cancer [128].

Despite the large number of patients with cancer who receive a chemotherapeutic regimen, cognitive alterations develop and manifest itself on an individual and unpredictable basis. While one person may suffer from serious cognitive deficits, another may not be affected at all. Consequently, researchers began to pay more interest into the etiology of CRCI. While it is known that some cytotoxic drugs such as cisplatin and cytarabine can cross the blood-brain barrier (BBB) and induce neurotoxicity, others cannot cross the BBB and are therefore unable to cause damage to brain cells[114, 129, 130]. As a result, researchers began to wonder whether structural or functional changes to the brain could be detected after a chemotherapeutic treatment. The team of Deprez et al. (2011) evaluated chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer. They compared both imaging and neuropsychological test results of breast cancer patients who received chemotherapy compared to healthy controls. Results indicated that chemotherapy seems to affect the brain's white matter integrity [131]. Further, the research team of Deprez et al. (2013) examined changes in brain activation after chemotherapy. For this study, the team included cancer patients who were scheduled to receive chemotherapy, cancer patients who would not receive chemotherapy and healthy controls. At baseline, no differences in brain activation were detected. After treatment, a significant difference was found between the chemotherapy group who reported more cognitive complaints and showed altered brain activation. These results suggest that changes in brain activity may underlie chemotherapy-induced cognitive complaints and that the observed changes might be related to chemotherapy-induced damage to the brain or to reduced connectivity between brain regions even after controlling for effort and functional strategy [132]. Structural changes in gray and white matter were also found in lung cancer patients after receiving chemotherapy [128].

These findings strongly suggest that cytostatics influence the brain's functioning and that cognitive alterations can be expected after receiving chemotherapy. On the contrary, however, not all trials investigating the role of chemotherapy as an etiology of CRCI could detect changes after the treatment had ended. A recent meta-analysis by Lindner et al. (2014) reported that in some longitudinal studies, it was found that patients perform better after cancer treatment [133].

PSYCHOLOGICAL AND DEMOGRAPHIC FACTORS

As mentioned, one of the major flaws in initial studies on CRCI was that researchers did not include a baseline neuropsychological assessment. However, a baseline assessment is crucial if one wants to report the degree of cognitive loss following a cancer treatment. When including a baseline assessment, studies have reported high rates of CRCI prior to adjuvant chemotherapy, increasing problems following chemotherapy and a resolution of the findings to baseline levels when performing longer follow-up assessments [134]. Although researchers do not pay a lot of attention to these pre-treatment impairments, some have tried to find a possible explanation as to why cognitive problems are already detected before the administration of any treatment.

In 2012, it was first reported that the term 'chemobrain' might not be fully accurate, because pre-treatment-altered neural activation, coping, fatigue and psychological stress or distress (including worry, sadness and anxiety) can also contribute to cognitive problems [135-137]. Coping, or the way patients deal with cancer, has been reported to negatively influence patients' cognition. Further, ineffective coping mechanisms may lead to an increased perceived psychological stress level [137]. Distress, on the other hand, can be defined as a multifactorial unpleasant emotional experience of psychological (cognitive, behavioural and emotional), social and/or spiritual nature that may interfere with the ability to cope with cancer effectively, its physical symptoms and its treatment. It extends along a continuum ranging from common normal feelings of vulnerability, sadness and fear, to problems that can become disabling such as depression, anxiety, panic, social isolation, and existential and spiritual crisis. Distress can be easily detected through the Distress Thermometer, which is a well-known tool for initial screening that asks the patients how much distress they perceived during the last week. It uses a 11-point rating scale from zero (no distress) to 10 (extreme distress) to represent the amount of distress experienced by the cancer patient [138]. In a more detailed report by Berman et al. (2014), it was stated that worry appears to be a significant contributor to the patient's cognitive functioning, independent of adjuvant treatment for breast cancer as they found lower cognitive performance and lower brain deactivation in patients with breast cancer. Their results suggest that alterations in cognitive function may develop before the administration of chemotherapy and that worry may contribute to reports of CRCI during treatment [139]. Further, it has been found in non-cancer subjects that worry affects working memory capacity [140]. A recent trial by Oh et al. (2016) also reported significant correlations between objective and self-reported cognitive functioning and psychological distress [141]. Another recent study by Moretta et al. (2017) also reported reduced executive functioning and visuospatial learning to be related to psychological distress in a group of non-cancer subjects [142].

Menning et al. (2015) reported the role of fatigue in the cognitive functioning of breast cancer patients prior to adjuvant treatment. The researchers included patients with breast cancer scheduled to receive chemotherapy (C+), patients with breast cancer not scheduled (C-) for chemotherapy and no-cancer controls (NCs). Patients were assessed through neuropsychological testing, imaging with multimodal magnetic resonance imaging (MRI) and self-reported aspects of psychosocial functioning. Lower white matter integrity and higher levels of fatigue and stress were found in both C+ and C- patients when compared to NCs. When combining the cognitive and imaging data, it was found that symptoms of fatigue were associated with the observed abnormalities. These results suggest that cancer-related psychological or biological processes may adversely affect cognition and associated aspects of brain structure and function before the start of adjuvant treatment in breast cancer patients [143]. Another trial by Visovatti et al. (2016) in patients with colorectal cancer found that older age, less education and fatigue can lead to worse cognitive performance and increased self-reported cognitive problems, stressing the importance of evaluating psychosocial factors when looking into CRCI [144].

Lange et al. (2014) examined baseline cognitive function in elderly breast cancer patients. They reported that more than 40% of patients presented with cognitive deficits prior to any adjuvant treatment [145]. The team of Ahles et al. (2010) investigated the impact of age and cognitive reserve in breast cancer patients receiving adjuvant treatment for breast cancer. Their data indicated that age and pre-treatment cognitive reserve is related to the cognitive decline detected post treatment [146]. Mandelblatt et al. (2014), however, could not detect differences in cognitive function between older breast cancer patients and healthy controls before systemic treatment [147]. Nevertheless, older patients with cancer pose a big challenge to health care providers as they can already present with a pre-existing cognitive impairment and can develop cognitive decline by the cancer diagnosis and/or its treatment.

ASSESSMENT/SCREENING

When researchers began to investigate CRCI, there were no assessment guidelines. As a result, every research team implemented their own idea of a good neuropsychological test battery. Although each of those assessments can be considered as adequate for measuring the patients' cognitive functioning, this does make it difficult when one research team wants to compare assessment results with others. Therefore, an International Cognition and Cancer Task Force (ICCTF) was assembled and proposed guidelines to use when investigating CRCI [148].

The ICCTF states that the ideal research design to examine the effect of a certain treatment is a double-blind placebo-controlled, prospective, longitudinal trial including both a baseline and follow-up assessment. However, as in most cases this will not be feasible since cognitive studies are observational, they advise to include an appropriate control group. They further recommend including tests that measure at least learning and memory, processing speed and executive function. If possible, an additional measure assessing working memory and subjective cognitive complaints can be included. Regarding the latter, it is stated that research has shown a stronger association between subjective cognitive complaints and mood or fatigue than between subjective and objective neuropsychological findings [149].

The ICCTF also published recommended criteria to establish the frequency of CRCI. They state that a person can be diagnosed as having a CRCI if the person presents with two or more test scores at or below -1.5 standard deviations (SDs) from the normative mean or if the person presents with one test score at or below -2.0 SDs [148]. Using these criteria could ultimately ease the process in comparing results with other researchers in the field.

The ICCTF further stated that it would be beneficial to use a prespecified Reliable Change Index (RCI) to determine change in cognitive function. The RCI allows evaluation of meaningful changes in test scores following treatment interventions. The RCI addresses whether a found change is of sufficient magnitude to be sure that the change is not the result of a measurement error [148, 150]. While advised by the ICCTF, only few researchers define the RCI in their trial. Mohile et al. (2010) examined the cognitive effects of androgen deprivation therapy in older patients with cancer and defined decline by use of the RCI. Results demonstrated a decline in executive functioning in 38% of patients while an improvement was noticed on measures of visuospatial abilities [150]. Lange et al. (2016) evaluated cognitive decline in older cancer patients with early-stage breast cancer by use of the RCI. About half of patients showed an objective cognitive decline, mainly in terms of working memory, after adjuvant treatment [151]. A reason why many researchers do not define cognitive decline by use of the RCI may be that the RCI defines decline as an absolute score reduction outside a test's standard error. So in order to achieve this absolute score reduction, a patients who has a substantially lower baseline score would need a greater percentage of decrease in the follow-up score, while it has been reported that even small changes can have detrimental effects [152, 153].

CHAPTER 1
Introduction

PART IV
Hearing loss in older cancer patients

PRESBYACUSIS

Older cancer patients are a vulnerable group of individuals as they present with comorbidities that have naturally developed as a consequence of ageing. One of those comorbidities is age-related hearing loss (ARHL), also referred to as presbyacusis or presbycusis. Presbyacusis is the most common cause of hearing loss in adults and refers to a degenerative process that results in a progressive bilateral hearing loss, starting in the higher frequency region [154, 155]. ARHL is characterized by a reduction in hearing sensitivity and decreased ability to understand speech in noise. It also results in a slowed central processing of sound and impaired localization of acoustic stimuli [156, 157].

Although its onset and rate of progression may vary widely among individuals, the prevalence of ARHL increases with age. A review by Roth et al. (2005) indicated that at the age of 70, 20% of European women and 30% of European men present with a loss of at least 30 decibel Hearing Loss (dB HL). At the age of 80, numbers increase to 55% of men and 45% of women being affected [155]. In the United States of America (USA), similar numbers are reported [157]. In male individuals, the first signs of presbyacusis may already be detected around the third to fourth decade when the higher frequency range from 10.0 to 16.0 kHz is affected. During the fourth decade, damage in lower frequencies ranging from 6.0 – 8.0 kHz can be found. In females, ARHL starts later in life. First signs are usually noticed a decade later than in males. Although authors remain inconclusive, some attribute these changes to the more frequently occurring noise exposure in men [158]. Ovarian steroid hormones and cardiovascular diseases, affecting inner ear blood flow, have also been reported to account for the better hearing thresholds in women [159]. In both men and women, decreased hearing sensitivity in the most important region for speech ranging from 0.5 to 4.0 kHz, starts around the sixth life decade [160]. Besides these differences in gender, it is also reported that Caucasian individuals can be more affected by AHRL than their African-American counterparts [161].

Based on post-mortem histological analysis, presbyacusis can be classified into four categories: sensory, neural, metabolic and mechanical [162]. Sensory presbyacusis accounts for only 5% of the total incidence of ARHL and is characterized by the loss of hair cells and supporting cells at the basal end of the cochlea. As it is mostly limited to the most basal end, it affects the higher frequency region, affecting those frequencies vital for speech perception [163, 164]. Sensory ARHL is most likely a result of excessive noise exposure during life and is not believed to be a consequence of ageing [165]. The second type, neural presbyacusis, manifests itself later in life and is marked by a loss of auditory neurons. It becomes apparent for the individual when the number of functional neurons is less than those required for an effective transmission and decoding of neural patterns resulting in poor speech discrimination scores [163]. Metabolic or strial presbyacusis refers to hearing loss caused by atrophy of the stria vascularis leading to sensorineural hearing loss. Gacek & Schuknecht (1969) reported that this type of ARHL is characterized by an equal or nearly equal hearing loss across all frequencies with a slow progression rate and that it has only a minimal effect on speech discrimination. They presume it appears as a result of a biochemical deficiency of the endolymph. Animal studies have indicated a degeneration of the stria vascularis and decreased endolymphatic potential along with hearing loss in gerbil [163, 166] Further, severe degeneration of the spiral ligament was observed in autosomal-dominant non-syndromic hearing loss among genetic hearing loss [167]. Others however, stated that strial presbyacusis is a result of strial atrophy and its associated damage to the stereocilia resulting in a hearing loss that is more pronounced in the higher frequency region [165]. Mechanical ARHL is a slowly progressive variant that appears

without the interference of a disorder in the organ of Corti, auditory neurons or stria vascularis. The audiogram is characterized by an increasing hearing sensitivity with increasing frequency. Mechanical presbyacusis is thought to be caused by a deficiency in the motion mechanics of the cochlear partition such as a stiffened basilar membrane or atrophy of the spiral ligament [163].

ARHL can be influenced by both genetic and environmental factors. Studies investigating ARHL in humans have estimated that – depending on the population under study and the definition of ARHL – at least half of the variation is influenced by a genetic component [168-170]. One of those genes is the apolipoproteine E (APOE) allele. The APOE genotype is known to play a role in the maintenance and repair of neuronal cell membranes and contributes to several age-related diseases including Alzheimer's disease, degeneration of the macula and generalized atherosclerosis [171-173]. Kurniawan et al. (2012) compared audiometry results of 435 participants in relation to APOE-ε4 genotype. They have found that, even after adjusting for cardiovascular disease, stroke, and cognition, the APOE-ε4 allele influence the etiology of ARHL [174]. However, a recent trial conducted by Dawes et al. (2015) could not find an association between APOE-ε4 and presbyacusis [168]. Several single nucleotide polymorphisms (SNP's) have also been identified. Dawes et al. (2015) investigated to role of the N-Acetyltransferase 2 (NAT2) gene. The NAT2 gene codes for an enzyme that metabolizes carcinogens such as hydrazine an arylamine drugs. In previous literature, studies have reported an association of an SNP in the NAT2 gene and ARHL [175-177]. Nevertheless, Dawes et al. (2015) could not reproduce these results in their study [168]. Another SNP was found in the GRM7 gene. The GRM7 gene encodes the metaboprotic glutamate receptor type 7. This receptor is activated through L-glutamate, which is the primary excitatory neurotransmitter in the hair cells of the cochlea [178, 179]. Newman et al. (2012) investigated the role of GRM7 in relation to ARHL and found that GRM7 alleles are primarily associated with peripheral measures of hearing loss. Further, they stated that GRM7 alleles are also associated with speech detection in older adults [180]. Although evidence exist that some individual genetic factors may play a role in the etiology of ARHL, its exact impact in humans remains unclear. Raynor et al. (2009) reported that familial aggregation influences its development. Siblings of participants diagnosed with a hearing loss had a 4.7 times greater odds of having a reduced hearing sensitivity than siblings of individuals without a hearing loss. Further, siblings of those with a hearing loss were 30% more likely to have a hearing loss themselves when compared to the average population [181]. To date, researchers believe that there are probably no major genes involved in the development of ARHL and that presbyacusis is more of polygenic nature. While some can be attributed to SNPs, it is stated that this is partly the result of the small effects of many causal alleles that never reach genome-wide significance [179].

Non-genetic risk factors of ARHL have also been described extensively and can be categorized into either environmental or medical factors. It is not clear whether environmental factors, such as noise exposure, induce an accelerated ageing process in the ear or that they act on specific pathways [182]. Wright et al. (1987) stated that they believe that ARHL is more the result of a sum of minor insults occurring throughout life [183]. Of all the environmental factors reported, noise exposure is the one the most frequently examined. Noise-induced hearing loss (NIHL), comparable to ARHL, occurs in the high frequency region, typically first affecting frequencies from 3.0-6.0 kHz. It is known that excessive noise exposure can result into either mechanical damage in the cochlea due to noise with a high intensity, which induces a temporary threshold shift (TTS). A TTS occurs as the result of the buckling of the pillar bodies and uncoupling of the stereocilia of the outer hair cells from the tectorial membrane. While it is believed that a

TTS recovers, prolonged or frequent noise exposure can lead to permanent threshold shifts [184]. Asides to mechanical damage, metabolic changes, as a consequence of lower noise levels during a longer time span, can also lead to NIHL [185, 186]. Presumably, free radicals and other reactive endogenous substances have an influence in the etiology of this process [182, 187-189]. Emmerich et al. (2000) investigated the impact of industrial noise in guinea pigs and found that industrial noise exposure leads to severe damage of the outer hair cells. Further, it has been noted that noise exposed ears are more prone to develop ARHL. Kujawa et al. (2006) addressed this issue in an animal model and found that pathologic but sublethal changes in the cochlea, initiated by early noise exposure, render the inner ears significantly more vulnerable to aging [190]. Xiong et al. (2006) compared audiometry results of two groups of men where one group had served in the military during the sino-Vietnamese war whereas the other group had no military experience. They have found that the pure-tone thresholds at 4.0, 6.0 and 8.0 kHz of the first group were poorer than those of the men without military experience, concluding that impulse noise exposure accelerates ARHL [191]. As it is known that noise influences hearing thresholds, the International Organization for Standardization (ISO) published reference values regarding the estimation of noise-induced hearing loss (ISO 1999) in older subjects [192]. The formula suggested by ISO 1999 states that the total amount of hearing loss is the sum of the age-related hearing loss and noise induced PTS, minus a compression factor that is used when the threshold shifts exceeds 20-25 dB [193]. Based on the above findings, one would believe that noise exposure accelerates ARHL. Gates et al. (2000) however, examined noise-notches in elderly men. They found a reduced progress of hearing loss over time at 3.0, 4.0 and 6.0 kHz and an accelerated hearing loss in frequency areas adjacent to noise damaged frequencies, especially for 2.0 kHz. These findings suggest that there is less threshold deterioration in a noise-damaged ear in the NIHL frequency region (3.0-6.0 kHz) than in a non-damaged ear, while thresholds increase in adjacent frequencies [194]. Another environmental factor, more frequently investigated in younger individuals than in older adults, is ototoxic medication [182]. Aminoglycosides and drugs containing platinum are the most frequently reported medications that induces ototoxicity. Aminoglycoside drugs damage the outer hair cells in a similar way as noise, causing non-reversible hearing loss in the higher frequencies. Further, aminoglycosides seem to potentiate the effect of noise exposure and vice versa [195]. Ototoxicity from platinum compounds, such as cisplatin and carboplatin, also occurs in the higher frequency region [196]. The cisplatin-induced cochlear toxicity is the result of the production of reactive oxygen species (ROS). Cisplatin-induced hearing loss is dose-dependent and occurs mainly in the high-frequency region. It occurs in about 10–25% of adults receiving the drug, 50% of individuals receiving high doses (>400 mg/m2 cumulative dose) and 41–61% of children [197]. Pre-treatment hearing loss (≥ grade 2) has been proposed as a relative contraindication and predictive factor to define a patients' eligibility for treatment with cisplatin [198, 199]. In addition, cumulative cisplatin dose, cumulative radiation therapy dose and young age were identified as risk factors for increased sensorineural hearing loss due to cisplatin based treatment. However, the pre-treatment hearing threshold at frequencies vital for speech perception proved to be the only independent predictive risk factor for post-treatment hearing capability which means that the more unfavourable the hearing level prior to therapy, the more unfavourable the hearing capability will be after cisplatin-based chemotherapy [200].

Environmental influences are not the only non-genetic factors that accelerate the process of ARHL. Several other mediators such as alcohol and tobacco use and some medical risk factors have been described. In literature, there is no consensus whether alcohol and tobacco use

influence ARHL. It seems that these factors could accelerate ARHL, however, other factors may play a more crucial role [201-203]. A highly reported medical condition possibly influencing ARHL are cardiovascular diseases [182]. It is known that older individuals are more prone to develop some form of cardiovascular disease (CVD) [204]. Although some trials did not detect an association between CVD and ARHL, there is reason to believe that CVD accelerates ARHL given its rich capillary supply to the stria vascularis and its sensitivity to disruptions in the arterial blood supply [205]. Park et al. (2007) found an association between the presence of hearing loss in older adults and low HDL cholesterol levels [206]. Gates et al. (1993) also reported an association between CVD and a predominantly low frequency hearing loss [207]. Helzner et al. (2011) concluded that certain CVD risk factors such as a higher body mass index (BMI) in women and a faster resting heart rate in both males and females are associated with elevated hearing thresholds [205]. Dietary influences, such as type 2 diabetes - often as a result of a high BMI, have also been published as a risk factor for ARHL [208, 209].

AGE-RELATED HEARING LOSS AND QUALITY OF LIFE

Presbyacusis is known to have a serious impact on the patients' daily life. It does not only affect their physical, cognitive and emotional activities, but it also influences patients' social functioning. As patients lose their hearing, they feel left out as they have difficulties communicating with others. Even without hearing loss, it has been reported that listening effort increases with age [210]. As a result, their quality of life deteriorates with various symptoms such as depression, social isolation and lowered self-esteem [211]. Further, ARHL is also associated with a future loss of functional abilities and functional dependence [212]. However, despites its prevalence and morbidity, presbyacusis is often left unrecognised and untreated. It is reported that only 25% of patients who have a hearing loss great enough to be aided with hearing aids, actually receive proper rehabilitation [213]. On the contrary, many people who own hearing aids do not use them on a regular basis and even when they are wearing them, some still have socially disabling levels of hearing loss [214]. There are multiple reasons why patients are somewhat reluctant towards amplification. The process of accepting the need of hearing aids, selecting, trying and purchasing them and using them afterwards is challenging for many patients. The most common barrier however, is the dissatisfaction with its performance [215]. Patients often believe that wearing hearing aids can be compared to wearing glasses. Once you put them on, you hear as you heard before. During the adaptation process, they often feel discouraged as the device does not exactly performs as they had hoped. Conversations in noisy environments remain difficult and are often unpleasant due to the excessive noise. As a result, the hearing aids disappear in their closets and are almost never used [216, 217].

Despite these difficulties, in cancer patients, who already have a lower quality of life, optimization of such condition is crucial. Therefore, the NCCN guidelines in Older Adult Oncology recommend an assessment of sensory functions such as vision and hearing [131] as part of a CGA. Within the CGA, it is not the main objective to diagnose patients as having a significant hearing loss and to refer them to a hearing aid specialist. The purpose is merely to select those patients who show signs of decreased hearing sensitivity so that proper measures can be taken. One of those measures can include a referral to the otolaryngologist for a full examination or a referral to a hearing aid specialist. Others can include taking notes, a more pronounced articulation, etc.

ASSESSMENT

Pure-tone audiometry is known as the gold standard to assess hearing loss since its introduction as a clinical tool more than seventy years ago. A necessary requirement for optimal testing is a controlled test environment with ambient noise levels as close to 0 dB sound pressure level (SPL) (ISO 8253) [218]. In that way, it is prevented that environmental noise masks hearing thresholds at this level [219]. Therefore, pure-tone testing is usually performed in a sound-isolated room or sound booth. Both the American Speech-Language-Hearing Association (ASHA) and the British Society of Audiology (BSA) have published similar guidelines on how to perform pure-tone audiometry [220, 221]. The ASHA distinguishes three types of pure-tone threshold audiometry: manual or conventional audiometry, automatic or Békésy audiometry and computerized audiometry. Diagnostic standard pure-tone threshold audiometry usually includes manual air-conduction measurements at the conventional octave frequencies including 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 kHz. Bone conduction threshold may be established in order to provide the type of hearing loss (sensorineural, conductive or mixed). High frequency audiometry, including frequencies from 9.0 to 16.0 kHz, may be performed in some cases including ototoxicity monitoring and noise-induced hearing loss [220, 222, 223]. Thresholds are usually established by the Hughson-Westlake technique using a simple 10 dB down and 5 dB up approach [224]. Based on the results of the pure-tone threshold audiometry, the physician can give an overview of the patient's hearing degree, calculated as the pure-tone average or PTA. The PTA is calculated as the average air-conduction threshold found at 0.5, 1.0 and 2.0 kHz. The ASHA distinguishes seven degrees of hearing loss ranging from normal hearing with PTA from -10 to 15 dB, to a profound hearing loss when a PTA of more than 90 dB is found [225]. A downside on using the ASHA-regulations for calculating the PTA is that it does not include those frequencies that are most affected by ARHL. Including 4.0 kHz could in part solve this issue. Further, though pure tone audiometry is considered as the gold standard to asses a person's hearing, it is less suited to implement within the CGA as it requires a transfer to the audiology department and may be cumbersome for patients who are bedridden or who have a limited mobility due to their intravenous infusion.

Another method to define the patient's hearing is by use of a speech-in-noise (SPIN) test as these give more accurate results in terms of speech intelligibility. SPIN tests give an idea of the patient's ability to understand meaningful sentences in noisy situations and provide valuable information as listeners find themselves surrounded by background noise multiple times a day. Although commonly used to assess the patient's speech intelligibility, there are up to today no Dutch eHealth applications available that include SPIN tests and can therefore not be used as a screening method within the CGA [226, 227].

Other measures, such as oto-acoustic emissions (OAEs), could also be used to evaluate the patient's hearing. OAEs are an objective and fast measure to establish the function of the outer hair cells within the cochlea. It is widely used as a neonatal screening method and to establish an audiological diagnosis. When conducting the test, brief acoustic stimuli are produced into the external ear canal. As a result, OAEs can be measured, which are low-volume sounds that originate from the cochlea [228]. OAEs can be divided into transient-evoked (TEOAE) and distortion-product (DPOAE) OAEs, based on the type of stimuli that is presented to the patient. TEOAEs are measured within the 0.5 to 4.0 kHz frequency range and use a brief pure tone stimulus while DPOAEs include frequencies up to 8.0 kHz and uses two pure tones that are produced simultaneously [229, 230]. Although it is known that the amplitude of OAEs decreases

with increasing age and increasing hearing thresholds, OAEs are not optimal to use within the CGA as the test is highly influenced by environmental noise [231, 232].

The NCCN Guidelines in Older Adult Oncology recommend using a quick and simple screening tool. The test is performed by whispering the sentence “What is your name?” while standing behind the patient and occluding one ear. The patient fails if he does not hear the sentence. The test is repeated for the contralateral ear [131, 233]. Free-field voice testing was one of the easiest methods to get an idea of someone’s hearing and was used as the standard method before clinical audiometers became available in the 1940s. The test proposed by the NCCN is not validated and therefore several issues arise. Nonetheless, several researchers have published reliable forms of whispered voice testing [234-236]. All of the proposed tests use more or less the same methodology. The examiner has to stand behind the patient in order to remove the ability of speechreading. In addition, the non-tested ear has to be excluded to rule out interference. The easiest way to mask the non-tested ear is to gently occlude the external auditory canal with a finger while rubbing it in a circular manner. Whispering is done after the examiner exhaled completely. This set up is similar in all types of whispered voice tests. The distance between the patient and the examiner, and the words expressed to the patient may differ. Swan et al. (1985) described a whispered voice test (WVT) to identify those individuals who may benefit from management of their hearing loss. In their test, the patient needed to repeat a combination of three numerals and letters. A new combination was expressed when the patient repeated an incorrect combination or if he or she did not repeat anything at all. The researcher did not mention the distance between the patient and the examiner [234]. Macphee et al. (1985) investigated whether the WVT could be implemented for use in a group of patients admitted to a geriatric unit. They performed the test in multiple conditions: conversational voice at 6 inches and at 2 feet from the ear, and whispered voice at 6 inches and at 2 feet from the ear. Results indicated that using a whispered voice at 2 feet was the most discriminant test with a sensitivity of 100% and specificity of 84% [235]. Eekhof et al. (1996) compared the WVT to other screening measures. The first was the Pat-225, which is a handheld device that produces mixed noise with frequencies ranging from 0.5 kHz to 4.0 kHz at 30 dB HL. The second was the Audioscope-3, an otoscope with a built-in screening audiometer that produces pure tones at 0.5 kHz, 1.0 kHz, 2.0 kHz and 4.0 kHz. Eekhof and his colleagues considered an inability of hearing tones at 40 dB HL as having a hearing loss of 40 dB or greater. The last instrument was a screening audiometer called the Micromate-304, which could only generate tones at 2.0 and 4.0 kHz at 40 dB HL. Patients passed the test if they could hear both tones. Results indicated that the WVT was the best tool to use. Although the WVT showed promising results, they were the first to report that they had found a broad variation between outcomes of several examiners [236]. The problem with the WVT is that the words are pronounced live and are not pre-recorded. Therefore, it is difficult to standardise the technique, to control the pitch of the whisper and to control the background noise. Further, different acoustic environments may also play a role in the outcome of the test [236-238]. A recent trial investigated the effect of experience on the sensitivity and specificity of the WVT. They have found that the sound intensity of the whispered voice of experienced examiners is 8 to 10 dB higher than the whisper of an examiner without experience. They state that this problem can be addressed by training through voice measurement in order to ensure an nearly equal loud intensity of the whispers [239].

As the WVT has many problems when accounting for the interrater-reliability, researchers have examined other, more objective measures to screen for hearing loss. A popular objective tool is the Audioscope (Welch Allyn Medical Products, Skaneateles Falls, NY) [240]. The Audioscope

is a handheld otoscope that is able to generate a set of pure tones at 0.5, 1.0, 2.0 and 4.0 kHz with an intensity of either 25 or 40 dB HL. It also enables an inspection of the tympanic membrane and auditory canal. The examiner needs to hold the Audioscope directly into the external auditory canal. A probe tip on the device occludes the canal. The listener is asked to indicate whether the given tone is heard. For screening purposes, a pass is given when the patient hears the pure-tone at 40 dB. Although the Audioscope has an excellent diagnostic accuracy, the device provided by Welch Allyn is rather expensive as it may cost up to €600 [213, 241-243].

Since its development in 1982 by Ventry and Weinstein, the Hearing Handicap Inventory for the Elderly (HHIE) has gained a lot of interest in terms of screening for hearing loss in an older population [244]. The HHIE is a self-assessment tool containing 25 items on emotional and situational problems that are associated with hearing loss. The HHIE guides in determining the need for rehabilitation and assists in the planning and implementation of an aural rehabilitation program. Weinstein et al. (1986) reported that the test-retest reliability for the questionnaire was high for both face-to-face as well as for paper-and-pencil administration [245]. Ventry & Weinstein published a shortened version of their self-administering questionnaire including 10 items [246]. Per question, a score of maximum four is given leading to a total of 40 points. Final scores of at least 26 indicate an 84% probability of having a hearing impairment and moderate to severe handicap [243, 247]. Lichtenstein et al. (1988) examined the diagnostic performed of the HHIE-Screening version (HHIE-S) against different definitions of hearing loss. Sensitivity ranged from 53% to 72%, whereas specificity reached a maximum of 84%. They concluded that the HHIE-S was a robust and valid test for identifying older individuals with a hearing impairment, irrespective of the definition used to define the patient's hearing status [248]. Over the years, the HHIE-S has gained interest and has been translated and subsequently validated in several languages [249-251]. The HHIE-S is easy and straightforward. However, it should be noted that it measures functional and not physical hearing loss, therefore resulting in poor sensitivity results [213].

In our developing world, eHealth applications are gaining more and more interest. Using information and communication in healthcare, can result in improved healthcare access and improved quality of service delivery [252]. In a systematic review by Swanepoel et al. (2010), several eHealth applications in audiology are described [253]. The most interesting tools, however, are those developed for use on mobile phones running on Android, iOS or other operating systems (OS), since mobile phones are small and can easily be carried around. EarTrumpet and uHear™ both run on iOS devices such as an iPod, iPad or iPhone. EarTrumpet (PraxisBiosciences, Irvine, California) was released in the iTunes Store in 2010 and is calibrated with standard Apple earbuds. The test is performed according to the Hughson-Westlake technique and allows basic (0.5, 1.0, 4.0 and 8.0 kHz), comprehensive (0.25 - 8.0 kHz) or custom testing. Test tones are pulsating with a 0.8 seconds duration while the silence interval varies between one and two seconds. Masking is done automatically when a difference of at least 35 dB is found between both ears. In a quiet room, 94% (95% confidence interval (CI): 87-100%) of the thresholds detected with EarTrumpet were within 10 dB of the pure-tone threshold obtained through conventional audiometry [254]. Derin et al. (2016) confirmed that Eartrumpet gives reliable results [255]. Kam et al. (2012) developed a computerized self-administered hearing test that can be used on iOS devices. An iPhone 3GS with iOS4 software and standard iPhone earbuds were used. Although the application seemed promising, it is not freely available in the iTunes Store [256]. uHear™ on the other hand, is a freely available iOS-based application that is more frequently examined by several

independent researchers in the field. uHear™ was developed by Unitron (Kitchener, Ontario, Canada) by Don Hayes, the director of the audiology department. It offers three tests: (1) a hearing sensitivity test that takes approximately five minutes to administer, (2) a one-minute speech-in-noise test and (3) a 12-item questionnaire in order to create a hearing profile. Of all the available tests, the hearing sensitivity test is most examined. Pure-tone air conduction thresholds at 0.25, 0.5, 1.0, 2.0, 4.0 and 6.0 kHz are established. Results are presented in a graphic display [257-260]. Szudek et al. (2012) were the first to report on the diagnostic performance of the tool. They evaluated 100 adult subjects and compared the results of the uHear™ app to conventional audiometry based on the PTA. With a sensitivity of 98% and a specificity of 82%, they concluded that uHear™ could be used as a screening to rule out moderate hearing loss [257]. Khoza-Shangase et al. (2013) determined the accuracy of uHear™ in young children with a mean age of 9.0 years old. They stated that the screening tool was not as accurate as conventional audiometry in determining pure-tone thresholds in school-aged children. They attributed the differences between both test to the ambient noise levels that were present during uHear™ testing and the lack of calibration of the tool [258]. Peer et al. (2015) tested 50 ears in three environments: a waiting room, a quiet room and a soundproof room. Sensitivity was excellent (100%) in all conditions. Specificity differed and was 88% in the soundproof room, 73% in the quiet room and 68% in the waiting room [259]. The most recently published trial on the performance of uHear™ was conducted by Abu-Ghanem et al. (2016) in older patients. They included 26 subjects with a mean age of 84.4±6.7 years and detected a sensitivity of 100% and specificity of 60% compared to conventional audiometry. They also evaluated the hearing questionnaire included in the app, however, results were less accurate than those of the hearing sensitivity test [260]. Swanepoel et al. (2014) developed the hearScreen™ application on an inexpensive Android OS cell phone. The application was validated in a group of schoolchildren. The idea behind the screening is somewhat similar to that of the Audioscope. The children hear a specific frequency (1.0, 2.0 or 4.0 kHz) at an intensity level of 25 dB HL. A pass or fail score is given. HearScreen™ showed similar results to those of screening with conventional audiometry [261]. Wenjin et al. (2014) evaluated the Smart Hearing app in schoolchildren. Smart Hearing runs on Android OS and is able to deliver pure tones (1.0, 2.0 and 4.0 kHz) at an intensity level ranging from 20 dB HL to 60 dB HL. The pass or fail screening cut-off was set at >30 dB HL. Results indicated a low sensitivity of 37.5% and a high specificity of 92.6%. They concluded that further improvements of the app needed to be undertaken in order to improve the sensitivity of the test [262]. Na et al. (2014) developed a screening tool that runs on Android software. Although their test is not yet available for public use, it showed some promising results. The researchers used the built-in microphone of the smartphone to measure the surrounding environmental noise. As a result, the known threshold shift was much lower than it is in other mobile hearing screening apps [263]. Other apps, such as Hearing Test for Android users, have also been described. However, no accuracy results have been published [264].

THE RELATION BETWEEN HEARING LOSS AND COGNITION

Though not within the scope of this thesis, it is interesting to briefly discuss the interaction between hearing and cognition as it has been shown that persons with impaired hearing score worse on psychological tests examining working memory and selective attention [265, 266]. Further, verbal tests were more impaired than non-verbal assessments [267]. Communication is a process that involves more than solely the peripheral auditory functions. Once a sound reaches the concha and is transferred through the external ear canal to the auditory nerve and

further on, multiple cognitive processes including selectively attending sound sources, storing information in memory, using context information to improve understanding, resolving ambiguities and generating appropriate responses, are set in motion [268]. Consequently, researchers started to realise that a reduced hearing may negatively affect cognition and that it may not only influence cognition at a certain time but that it also may enhance cognitive decline. Lin et al. (2012) for example, examined older subjects at baseline and annually over a six-year period. They reported that older patients with impaired hearing showed poorer test scores on a modified MMSE and in terms of executive functioning compared to patients with no hearing deficit. Further, impaired hearing led to a greater decline in test scores over the years. It should also be noted that impaired cognitive functioning may lead to miscommunication and could therefore result in poorer hearing test scores. Objective testing, such as OAEs, may offer a solution in these persons [269].

Another frequent studied variable regarding the interaction between hearing loss and cognition is listening effort. Listening effort can be described as the energy patients have to put into understanding speech. For persons experiencing hearing loss, listening is often reported to be exhausting. As a logical consequence, they may complain of fatigue caused by the greater amount of concentration that is required to understand speech in everyday listening environments [270]. Commonly used measures to report listening effort include self-reported measures, single- and multi-task paradigms and clinical measures such as imaging and pupillometry [271]. While examining the patient's hearing status through the listening effort offers useful information, it is less suited as a screening tool for use within the CGA as it does not provide results on what patients can hear but rather on the amount of work the patient has to put into listening.

CHAPTER 2
Aim and Outline

Based on the findings of the introduction, it can be noted that there is a need to validate screening tools that can detect cognitive dysfunctions and hearing loss in cancer patients, as both may impact adequate treatment selection. For both cognitive and hearing disorders, screening tools have been developed. However, they have not been validated in the target population. Therefore, the aim of this thesis is to explore screening measures to examine screening tools to detect cognitive dysfunctions in both young and older cancer subjects to detect hearing loss in older cancer patients. An overview of the main research questions are presented in Table 1.

In older cancer patients, not being able to understand what physicians and other health care workers are saying, can seriously affect the patients' quality of life. In line with the NCCN Guidelines in Older Adult Oncology, many hospitals in Belgium have started to implement a comprehensive geriatric assessment (CGA) in which multiple health domains are evaluated. The CGA has been a cornerstone in the management of older cancer patients for many years and gives physicians a clear understanding of the patient's abilities in order to select the most optimal treatment plan. The most frequent used tool to assess cognitive functioning within the CGA is the well-known and widely validated Mini Mental State Examination (MMSE). It is considered the gold standard within the CGA in most institutions in Belgium and is therefore selected for use within this thesis. Although the MMSE has multiple benefits, it takes rather long to assess in an already exhausting list of screening tools that are assessed within the CGA. Further, as the majority of older cancer patients have a good cognition, it is not that well accepted. The more rapid Clock Drawing Test (CDT), developed by Dr. Barbara Freund, has recently been proposed as a quick and easy screening tool and could be more optimal for use within this population [272]. It was selected above other measures such as the MoCA, as it reduces total CGA assessment time while still providing sufficient information. However, a fast and simple scoring system was lacking. Further, while the scoring system of Dr. Freund had been reported as easy and straightforward, cut-off scores for use in a geriatric oncology population are not provided. Therefore, in Chapter 3, Part I, a cut-off score for the Clock Drawing Test, when using the Freund scoring system as part of the CGA is determined. In Part II, this retrospectively determined cut-off score is validated in a new set of subjects.

Though the CGA assesses existing age-associated cognitive functioning, both young and older cancer patients can develop cancer-related cognitive impairments (CRCI). However, the exact pathophysiology remains unclear. Chapter 4, Part I, addresses this issue and evaluates if there are variables that can be attributed to baseline CRCI as CRCI has been reported to occur even before the treatment has started. Further, while CRCI was first ascribed as a result of the chemotherapy treatment, resulting in a term coined chemobrain; recent findings suggest that other conditions, such as psychological factors, may cause CRCI, as problems may already be present upon the first presentation with the medical or radiation oncologist. While the way a patient copes with cancer may be one the most prominent psychological variables, distress – which is a result of coping, can be easily assessed by the NCCN's developed Distress Thermometer (DT). Therefore, Chapter 4, Part II, examines whether the DT can be used to predict long-term CRCI.

In case of hearing in older cancer patients, the NCCN proposes a screening measure that uses a whispered voice. Though this test did not seem to be validated, it has several similarities to the Whispered Voice Test (WVT). The WVT uses a whispered voice and has shown good sensitivity and specificity results, but problems arise when accounting the interrater variability, caused by the difference in loudness of the examiners' voices. With the upcoming mobile

health systems, using smartphone or tablets could be an interesting way of screening the patient's hearing in a hospital room. Although several applications have been developed, most validation studies did not include older subjects; therefore limiting the use of those within the CGA. The uHear™ application, originally designed by Don Hayes, runs on iOS devices and shows promising results in youngsters and in older adults. Data in a large subset of older cancer subjects, however, is lacking and the application itself does not give the person a pass or fail result. Further, uHear™ was chosen above other screening tools given its accessibility and use in multiple clinical trials. Chapter 5, Part I, examines whether uHear™ can be used within the CGA when using a cut-off score based on the PTA or if the scoring method needs to be adjusted. The latter is addressed in Chapter 5, Part II.

Table 1. Overview of the chapters, research papers and main research questions

Focus	Population	Chapter	Research paper	Main research questions
Cognition	**Older adults** *≥70 years* *Cancer or no cancer* *No cancer treatment, curative or palliative cancer treatment*	**Chapter 3.** The use of the Freund Clock Drawing test as a screening tool for cognitive dysfunctions in a geriatric oncology population	**Part I.** Use of the Freund clock drawing test within the mini-cog as a screening tool for cognitive impairment in older patients with or without cancer	What is the most optimal cut-off score Freund clock drawing test as a screening tool to detect cognitive dysfunctions in older cancer patients as part of a CGA?
			Part II. Validation of the Freund clock drawing test as a screening tool to detect cognitive dysfunction in older cancer patients undergoing comprehensive geriatric assessment	Can the retrospectively determined cut-off score for the Freund clock drawing test be used for use within older cancer patients as part of a CGA?
	All adults *≥18 years* *All cancers* *Curative treatment only*	**Chapter 4.** The use of the Distress Thermometer as a screening tool for cognitive dysfunctions in a general cancer population undergoing curative treatment	**Part I.** Predictors of baseline cancer-related cognitive dysfunctions in cancer patients undergoing a curative cancer treatment	Which factors predict baseline cancer-related cognitive impairment in a group of general cancer patients scheduled for a curative treatment?
			Part II. The Distress Thermometer predicts subjective, but not objective, cancer-related cognitive complaints six months after treatment initiation in cancer patients receiving a curative cancer treatment	Can the distress thermometer predict long-term cancer-related cognitive impairment? Can the distress thermometer predict subjective cognitive complaints? What amount of cognitive decline can be detected six-months after treatment initiation? Is there a difference in cognitive functioning between patients who did and patients who did not receive chemotherapy?

Focus	Population	Chapter	Research paper	Main research questions
Hearing loss	**Older adults** *≥70 years* *All cancers* *Curative and palliative treatment*	**Chapter 5.** The use uHear™ as a screening tool for hearing loss in a geriatric oncology population	**Part I.** Evaluation of uHear™ - an iOS-based application to screen for hearing loss - in older cancer patients undergoing a comprehensive geriatric assessment	Can uHear™ screen for hearing loss in older cancer patients as part of a CGA when used in its current form?
			Part II. The use of uHear™ - by use of a new scoring method based on hearing grades - in older cancer patients undergoing a comprehensive geriatric assessment	Can uHear™ screen for hearing loss in older cancer patients as part of a CGA when using a new retrospectively determined pass or fail screening cut-off?

CHAPTER 3

The use of the Freund clock drawing test as a screening tool for cognitive dysfunctions in a geriatric oncology population

PART I

Use of the Freund clock drawing test within the mini-cog as a screening tool for cognitive impairment in older patients with or without cancer

Based on

Use of the Freund clock drawing test within the mini-cog as a screening tool for cognitive impairment in elderly patients with or without cancer

Ketelaars L, Pottel L, Lycke M et al. *Journal of Geriatric Oncology*. 2013

Abstract

OBJECTIVE

We aimed to determine an optimal cut-off score for the Clock Drawing Test (CDT), scored by the scale of Freund, for efficient screening for cognitive impairment in older (cancer) patients within a Comprehensive Geriatric Assessment (CGA) and to compare the Freund CDT to the Mini-Cog.

METHODS

Data of 221 older (≥ 70 years) patients, comprising of an OncoGeriatric (OG) and General Geriatric (GG) group, were retrospectively reviewed. All patients were evaluated with both the CDT and Mini Mental State Examination (MMSE) as the gold standard. Receiver Operating Characteristics (ROC) analysis was used to determine diagnostic performance. A pre-established algorithm was applied to retrieve Mini-Cog results through a combination of the CDT and the 3-word delayed recall (3-WDR) test (included within MMSE).

RESULTS

Data of 105 OG and 116 GG patients were evaluated. Potential cognitive impairment (MMSE ≤ 23) was detected in 29.5% and 65.8% of patients, respectively. The CDT showed good diagnostic accuracy in the OG (0.88±0.03) and GG (0.85±0.03) group, based on the Area Under the ROC Curve (AUC ± SE). CDT (cut-off ≤ 4) provided good sensitivity (80.7%) and specificity (81.1%) in the OG group and excellent sensitivity (89.6%) and moderate specificity (51.3%) in the GG group. Addition of the 3-WDR test, to form the Mini-Cog, resulted in similar positive and negative predictive values for the OG group and higher negative predictive value for the GG group.

CONCLUSION

These data suggest that the Freund CDT, at the cut-off score of ≤ 4, is promising for use within a CGA. The Mini-Cog might be preferable in the GG population.

INTRODUCTION

Older persons have an eleven times greater risk of developing cancer than their younger counterparts. Up to two-thirds of persons affected by cancer are aged ≥ 65 years. A Comprehensive Geriatric Assessment (CGA) is one of the procedures designed to improve the health-related outcome of this population, and its use has in recent years been suggested as a key component in the treatment approach of older patients with cancer [273, 274]. A CGA is a multidimensional evaluation in which problems in different health domains are uncovered and a coordinated individualised treatment plan is developed [275].

Cognitive status is one of the domains that is examined within a CGA. Some studies have demonstrated that up to 50% of older patients with cancer have cognitive abnormalities that warrant further evaluation. Cognitive function influences the diagnosis and treatment of older adults with cancer [276]. It determines if patients have the decisional capacity to consent to a proposed therapeutic plan and reflects if patients are predisposed to delirium and are at high risk for concomitant depression. Because effective measures exist to reduce complications associated with impaired cognitive function in patients undergoing intensive treatment, careful attention should be paid to identify patients at risk [277, 278].

The Folstein Mini Mental State Examination (MMSE) is a validated cognitive screening instrument, which is widely used in an older population and often included within a CGA. It is designed to detect moderate to severe dementia, yet it has shown to lack sensitivity to detect mild cognitive impairment (MCI) [279]. Moreover, even though it is not a comprehensive diagnostic test, it is rather time consuming. [280, 281]. Recently, the Clock Drawing Test (CDT) has been proposed as a more acceptable and time-efficient cognitive screening instrument [282-284]. In addition, it has been combined with the 3-word delayed recall (3-WDR) test, a crucial element within MMSE, to form the Mini-Cog, which was proven to have comparable psychometric properties to the MMSE [285, 286]. The reliability and validity of the CDT has been extensively reported [287-290], but the majority of these studies were based on relatively small sample sizes, focusing solely on a general geriatric population [283]. Additionally, over the past two decades, more than a dozen scoring systems for the CDT have been developed, but no international consensus has been reached [291]. Moreover, validated cut-off scores for use in different patient populations are still lacking, significantly limiting the utility of CDT in clinical and research settings [292]. The recently developed Freund scoring system has been reported in literature as a fast screening tool, and is easy and trustworthy to score as demonstrated by its high interrater reliability [272].

This study was initiated to determine if the CDT can be used as a screening tool for cognitive impairment in an oncogeriatric population within a CGA, if the Freund scoring system is a reliable method to score the CDT in both a geriatric and oncogeriatric population, to determine the most optimal cut-off scores for use in these populations, and to establish the added value of the 3-WDR test to the Freund CDT, that are combined to form the Mini-Cog.

METHODS

Patient selection

We retrospectively reviewed the case records of 221 patients, aged 70 and older, referred to the Oncology or Geriatric Departments at the General Hospital Groeninge or Ghent University Hospital, between January 2011 and January 2012, and whose data were registered within the scope of two observational trials or as part of routine clinical care, respectively. The

population comprises two different patient groups. The OncoGeriatric (OG) group consists of 105 community-dwelling older patients, newly diagnosed with a solid tumour or a haematological malignancy. All patients were assessed with a full Comprehensive Geriatric Assessment (CGA) prior to therapy start and were treated with palliative or curative intent. Eighty-three percent of patients were obtained from the PROGERCAN-trial, an observational study registering clinical data from older general oncology patients. In this patient group, a CGA is conducted upon positive screening with the Vulnerable Elders Survey-13 (VES-13) or G8, or upon specific request by the treating physician [293]. The remaining seventeen percent of OG patients were included from the OMGIANT-trial, an observational study recruiting head and neck cancer patients undergoing radiotherapy with curative intent, with or without systemic treatment. In this trial, all patients underwent a full CGA [294]. Both studies were approved by the institutional review boards.

The General Geriatric (GG) group consists of 116 hospitalised geriatric patients without a known cancer diagnosis, who had been referred to the General Hospital Groeninge by general practitioners or family members because of symptoms of functional decline. All patients (community-dwelling elderly, institutionalized patients, and elderly admitted to nursing homes at discharge from the hospital) had received a cognitive evaluation, comprising of both the Mini Mental State Examination (MMSE) and Clock Drawing Test (CDT), at the time of admission.

Cognitive Measures

All patients were evaluated with both the CDT and MMSE, as the gold standard, by an occupational therapist, a clinical psychologist or a research associate, depending on the department of presentation. The latter two had received a training from the occupational therapist, enabling them to conduct and score the MMSE, according to standardized guidelines [280, 295]. Patients scoring 23 or less on the MMSE were defined as potentially cognitively impaired [280]. Assessment of this screening tool took approximately 10 to 15 minutes.

For assessment of the CDT, patients were given a pre-drawn circle (10 cm in diameter) and were verbally instructed to place all the numbers in the correct position on the clock. Consequently, patients were requested to place the hands at ten past eleven, which has been reported in the literature to be the most sensitive place for detecting neurocognitive dysfunction [272]. Patients were allowed to self-correct, however, no clues were given. All clock drawings were scored by the method of Freund, using a 7-point scoring scale, with 0 and 7 indicating potentially poor and excellent cognitive status, respectively. The scoring system is divided into three categories, namely the ability to correctly reproduce all numbers, to position them accurately in the clock and to appropriately replicate the hands at a predefined time (Figure 1, Table 1) [272]. Although no administration times were recorded, all raters agreed that this test never took longer than 5 minutes to complete. The scoring was done by the assessor who conducted the test, and afterwards independently by another investigator, to examine interrater reliability.

Freund Mini-Cog results were obtained by combining the three-word delayed recall (3-WDR) test performance with the individual CDT results, using an adapted version of the pre-established algorithm, developed by Borson et al. (Figure 2) [53]. Individual 3-WDR test performance was obtained by scoring the simple three-item delayed memory task within the corresponding MMSE evaluation.

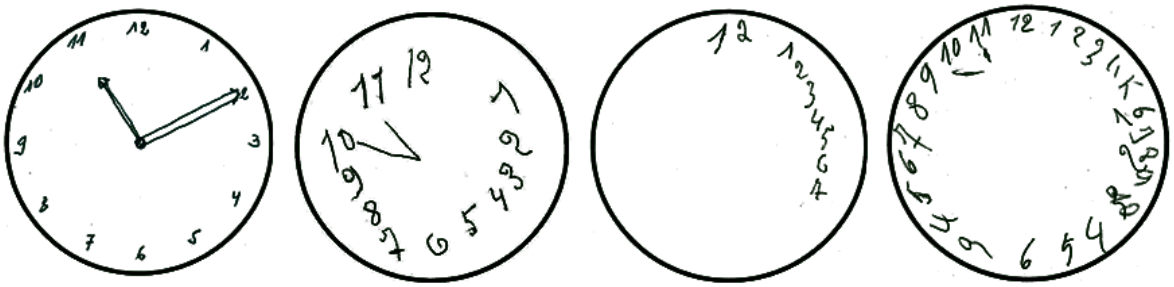


Figure 1. Examples of the Clock Drawing Test

Table 1: Freund scoring system for the Clock Drawing Test[272]

Time (0-3)	- One hand points 2 (or symbol representative of 2) - Exactly two hands - Absence of intrusive marks, e.g., writing or hands indicating incorrect time, hand points to number 10, tic marks, time written in text
Numbers (0-2)	- Numbers are inside the clock circle - All numbers 1-12 are present, no duplicates or omissions
Spacing (0-2)	- Numbers spaced equally or nearly equally from each other - Numbers spaced equally or nearly equally from the edge of the circle

Statistical analyses

Descriptive statistics were performed to present patient characteristics, CDT, Mini-Cog, and MMSE results. Mann-Whitney U tests and a Pearson Chi-square test were performed to examine potential statistical differences in cognitive status (scored by CDT, MMSE, and Mini-Cog, respectively) between patients in both groups. Potential differences in respectively age and gender between (OncoGeriatric versus General Geriatric) and within (based on CDT, MMSE, and Mini-Cog performance) both groups were determined with unpaired t-tests and Pearson Chi-square tests. For oncogeriatric patients, Pearson Chi-square statistics were applied to examine potential statistical differences in screening scores between patients with respectively early and advanced disease and curative and palliative treatment intent. A Kappa score was calculated for both groups to determine interrater reliability for CDT. Receiver Operating Characteristic (ROC) curves were drawn for each group to evaluate the discriminatory accuracy of the screening tool, in determining the presence of cognitive impairment compared with MMSE, as the gold standard. Sensitivity (S) and specificity (Sp) with 95% confidence intervals (95% CI) of the CDT were calculated at different cut-off scores, with reference to the gold standard. The optimal cut-off score, enabling highest S and Sp, which could be used for the CDT, was determined for both populations under study. S and Sp of the dichotomous Mini-Cog were calculated, based on the applied algorithm (Figure 2), enabling comparison of these results with the CDT results. Positive (PPV) and negative predictive values (NPV) were also determined. Subsequently, odds-ratios were calculated for both screening tools. All analyses were conducted using Prism® software (GraphPad Prism 5, Inc., La Jolla, CA) and IBM SPSS v.19 (SPSS Inc., Chicago, USA).

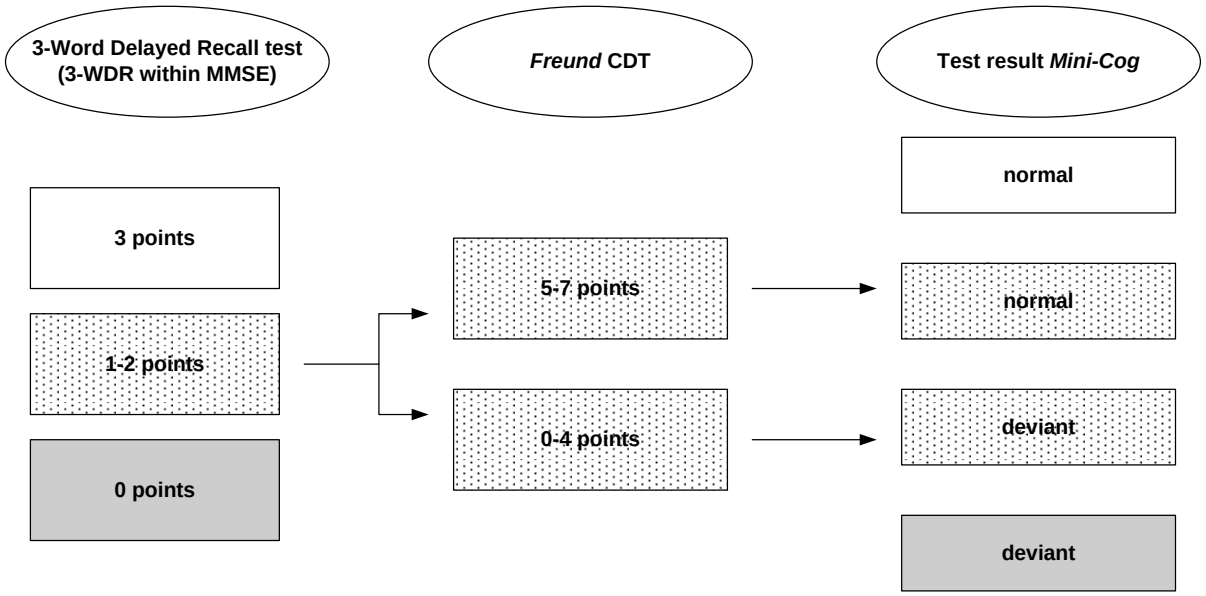


Figure 2. Applied algorithm, adapted from Borson et al. [53] to derive Mini-Cog scores from a combination of the 3-Word Delayed Recall (3-WDR) test within MMSE and the Freund CDT score. White, dotted, and grey colour codes relate to normal, potentially impaired, and impaired cognitive status, respectively.

RESULTS

Patient characteristics

Medical records of 221 older patients (40.3% men), with a mean age of 81.2 years (range: 70-96), were reviewed. The OncoGeriatric (OG) group consisted of 105 patients (mean age 78.3 years, range: 70-91). Patients presented with following tumours: head and neck (19.0%), gynaecological (18.1%), urological (15.2%), breast (13.3%), haematological (12.4%), digestive system (9.5%), lung (5.7%), melanoma (2.9%), other (1.9%) and unknown primary (1.9%). Half of patients were treated with curative intent (50.5%) (Table 2). Potential cognitive deficits were identified in 29.5% of patients, scoring 23 or less on the Mini Mental State Examination (MMSE). Median Clock Drawing Test (CDT) and MMSE scores were 5 and 25, respectively, with a median score of 2 on the 3-word delayed recall (3-WDR) test. The General Geriatric (GG) group counted 116 patients (mean age 83.8 years, range: 72-96), of which 66.4% scored possibly cognitively impaired according to the MMSE. Median CDT, MMSE, and 3-WDR score were 3, 21 and 0, respectively (Figure 3). The GG group comprised a significantly older (p<0.001), and mainly female population (p<0.05), compared to the OG group. In the GG group, significantly more cognitive impairments were identified with the MMSE as the gold standard (p<0.001) (Table 3).

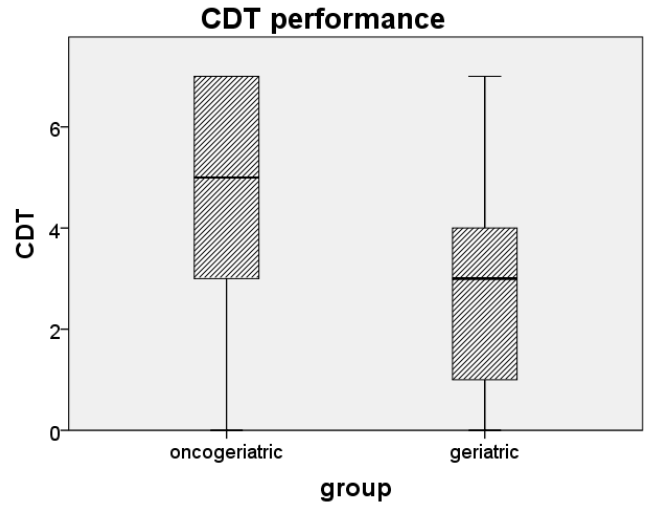
Table 2: Cancer types and treatment intent

Disease and treatment characteristics	n (n=105)	(%)
Cancer types		
Head and neck	20	(19.0)
Gynaecological	19	(18.1)
Urological	16	(15.2)
Breast	14	(13.3)
Haematological	13	(12.4)
Digestive system	10	(9.5)
Lung	6	(5.7)
Melanoma	3	(2.9)
Other	2	(1.9)
Unknown primary	2	(1.9)
Treatment intent		
Curative intent	53	(50.5)
Palliative intent	52	(49.5)

Table 3: Demographic and cognitive characteristics of both groups under study

	OncoGeriatric (OG) group (n= 105)	**General Geriatric (GG) group** (n=116)	**Comparison between both groups**
Age (mean±SD)	78.3 ± 5.1	83.8 ± 4.7	t(219)=8.215, p<0.001
Gender (% male)	51.4%	30.2%	χ^2=10.352, p<0,05
MMSE score (0-30)			
Median	25	21	U=3225, p<0.001
Interquartile range	23-28.5	14-5	
Impairment (%)	**29.5**	**66.4**	
Mini-Cog			
CDT score (0-7)			
Median	5	3	U=2970, p<0.001
Interquartile range	3-7	1-4	
Impairment (%)	**37.1**	**75.9**	
3-word-recall (0-3)			
Median	2	0	χ^2=47.884, p<0,001
Interquartile range	2	1	
Impairment (%)	**35.2**	**81.0**	

A)



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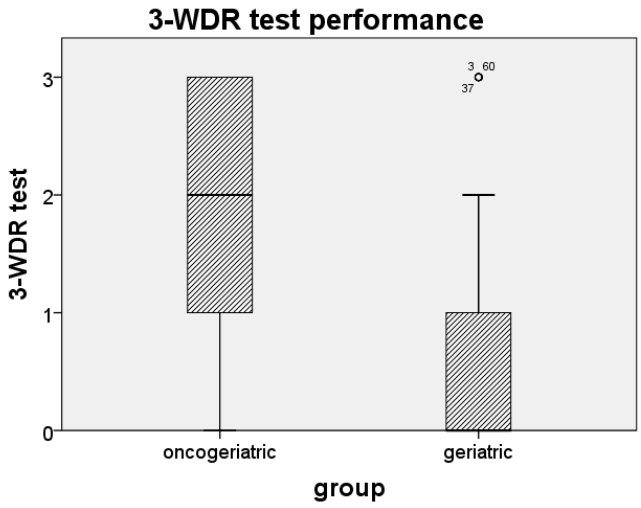

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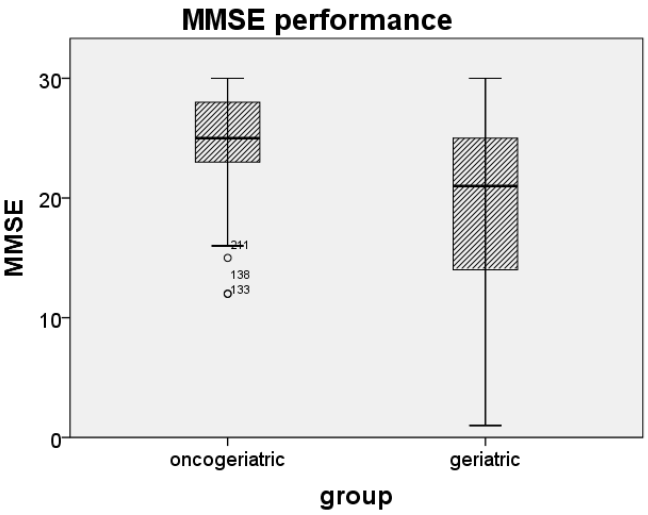

Figure 3. Cognitive characteristics of both the OG group and the GG group presented as boxplots, graphically displaying median, inter-quartile range and minimum and maximum data values. A) CDT performance, B) 3-WDR test performance, C) MMSE performance

As presented in Table 4, within-group analyses revealed no significant age differences between patients with normal and impaired cognitive function, according to MMSE, CDT and Mini-Cog performance, except for CDT performance in the GG group where cognitively impaired patients were significantly younger (p<0.01). Pearson Chi-square analyses revealed no differences between the percentage of cognitive impaired male versus female GG patients, whilst in the OG group men performed significantly better than women according to MMSE, CDT, and Mini-Cog (p<0.005, p<0.01, and p<0.05 respectively). Patients with an advanced cancer (stage IV), or treated with palliative intent did not screen significantly different on the CDT (p=0.277; p=0.192), Mini-Cog (p=0.935; p =0.760) or MMSE (p=0.432; p=0.342) as compared to patients diagnosed with an early stage cancer (stages I-III) or treated with curative intent, respectively.

Table 4: Exploratory within group analyses

OncoGeriatric (OG) group (n=105)					
	Screening tool	Screening tool performance		Difference	*p*-value
Age (mean±SD; years)		**Normal**	**Impaired**		
	MMSE	78.0±0.53	79.3±1.09	t(103)=1.208	0.230
	CDT	77.8±0.58	79.3±0.89	t(103)=1.437	0.154
	Mini-Cog	78.3±0.55	78.4±0.98	t(103)=0.147	0.884
Gender (% impaired)		**Male**	**Female**		
	MMSE	20.4	39.2	χ^2=4.477	0.034*
	CDT	22.2	52.9	χ^2=10.601	0.001*
	Mini-Cog	25.9	45.1	χ^2=4.225	0.040*
Staging (% impaired)		**Stages I-III**	**Stage IV**		
	MMSE	27.1	25.0	χ^2=0.031	0.859
	CDT	33.3	25.0	χ^2=0.459	0.498
	Mini-Cog	31.3	25.0	χ^2=0.266	0.606
Treatment intent (% impaired)		**Curative**	**Palliative**		
	MMSE	28.8	30.2	χ^2=0.023	0.342
	CDT	30.8	43.4	χ^2=1.793	0.181
	Mini-Cog	30.8	39.6	χ^2=0.902	0.342
General Geriatric (GG) group (n=116)					
	Screening tool	Screening tool performance		Difference	*p*-value
Age (mean±SD; years)		**Normal**	**Impaired**		
	MMSE	84.9±0.81	83.2±0.51	t(114)=1.843	0.068
	CDT	85.9±0.69	83.1±0.52	t(114)=2.845	0.005*
	Mini-Cog	84.2±0.98	83.6±0.49	t(114)=0.526	0.600
Gender (% impaired)		**Male**	**Female**		
	MMSE	62.9	67.9	χ^2=0.279	0.093
	CDT	65.7	80.2	χ^2=2.819	0.093
	Mini-Cog	80.0	81.5	χ^2=0.035	0.852

* $p<0.05$

CDT and Mini-Cog compared to the gold standard MMSE

The corresponding areas under the Receiver Operating Characteristic (ROC) curves (AUC ± SE) of CDT for the OG group (0.88 ± 0.03) and the GG group (0.85 ± 0.03) showed good diagnostic accuracy (Figure 4).

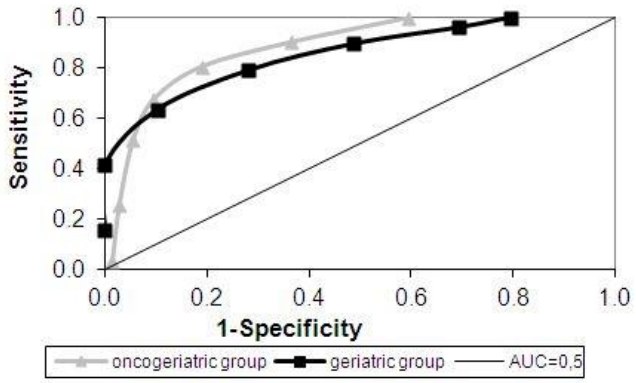

Figure 4. Receiver Operating Characteristics (ROC)-curve of both the OG group and the GG group. AUC: Area Under the (ROC)-Curve

ROC analysis revealed an optimal cut-off score of ≤ 4 on CDT for both groups (Figure 5). As presented in tables 3 and 5, a cut-off score of ≤ 4 identified 37.1% of OG and 75.9% of GG patients as in need of further cognitive evaluation, with a sensitivity (S) of 80.7% (95% CI [61.9-91.9]) and 89.6% (95% CI [80.0-95.1]), and a specificity (Sp) of 81.1% (95% CI [70.0-88.9]) and 51.3% (95% CI [35.0-67.3]), respectively. Combination of the CDT, with 3-WDR test performance resulted in Mini-Cog outcomes. At the determined optimal cut-off score for CDT, Mini-Cog results showed an S and Sp of 80.7% (95% CI [61.9-91.9]) and 83.8% (95% CI [73.0-91.0]) for the oncogeriatric patients, similar to S and Sp for CDT alone. In the GG-population, the Mini-Cog showed a slightly higher S of 97.4% (95% CI [90.1-99.5]) and a similar Sp of 51.3% (95% CI [35.0-67.3]), compared to CDT results alone. In the OG group, the PPVs and NPVs were 64.1% (95% CI [47.2-78.3]) and 90.9% (95% CI [80.6-96.3]) for the CDT, and 67.6% (95% CI [50.1-81.4]) and 91.2% (95% CI [81.1-96.4]) for the Mini-Cog, respectively. In the GG group, the PPV's of the CDT and the Mini-Cog (combination of 3-WDR and CDT, cut-off ≤ 4) were 78.4% (95% CI [68.1-86.2]) and 79.8% (95% CI [70.0-87.1]), respectively. The NPV's, on the contrary, were 71.4% (95% CI [51.1-86.0]) for the CDT and 90.9% (95% CI [69.4-98.4]) for the Mini-Cog. The odds ratios for the CDT and the Mini-Cog were 17.9 (95% CI [6.2-51.8]) and 21.5 (95% CI [7.3-63.7]) for the OG group. In the GG group an odds ratio of 9.1 (95% CI [3.5-23.8]) and 39.5 (95% CI [8.5-183.8]) was calculated for the CDT and for the Mini-Cog, respectively.

The Kappa score, evaluating CDT interrater reliability, for the OG and GG group was 0.84 and 0.86, respectively, indicating high agreement between both raters, in classifying patients as cognitively normal or potentially cognitively impaired.

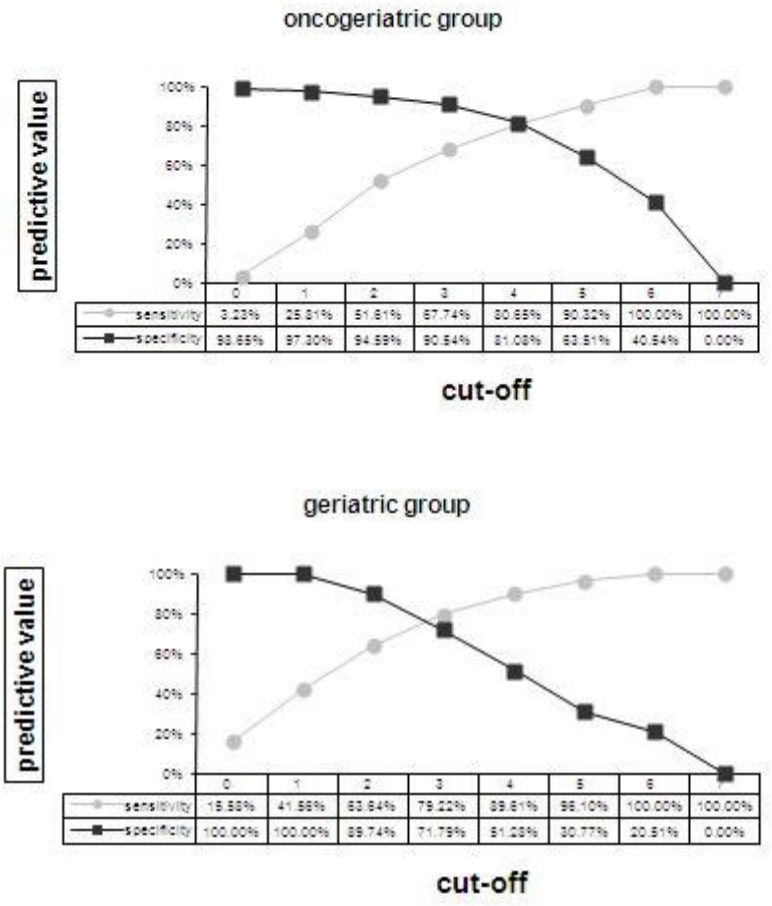

Figure 5. Sensitivity and specificity values graphically displayed for different cut-off scores for the OG group and GG group.

Table 5: Comparison of predictive value between the CDT and the Mini-Cog for both groups

Predictive value	**CDT (cut-off ≤4) [95% CI]**	**Mini-Cog (CDT: cut-off≤4; 3-WDR) [95% CI]**
OncoGeriatric (OG) group (N=105)		
S	80.7% [61.9-91.9]	80.7% [61.9-91.9]
Sp	81.1% [70.0-88.9]	83.8% [73.0-91.0]
PPV	64.1% [47.2-78.3]	67.6% [50.1-81.4]
NPV	90.9% [80.6-96.3]	91.2% [81.1-96.4]
DOR	17.9 [6.2-51.8]	21.5 [7.3-63.7]
General Geriatric (GG) group (N=116)		
S	89.6% [80.0-95.1]	97.4% [90.1-99.5]
Sp	51.3% [35.0-67.3]	51.3% [35.0-67.3]
PPV	78.4% [68.1-86.2]	79.8% [70.0-87.1]
NPV	71.4% [51.1-86.0]	90.9% [69.4-98.4]
DOR	9.1 [3.5-23.8]	39.5 [8.5-183.8]

CDT: clock drawing test; S: Sensitivity; Sp: Specificity; PPV: positive predictive value; NPV: negative predictive value; DOR: diagnostic odds ratio

DISCUSSION

The Clock Drawing Test (CDT) has in recent years been widely suggested in literature as a cognitive screening tool with clinical utility, as it shows good correlation with the Mini Mental State Examination (MMSE) [284]. However, the lack of an easily applicable universal scoring system and available cut-off scores for use in different patient populations limits its use in routine clinical practice. In this retrospective study, we evaluated the use of the CDT -scored by the system of Freund- as a screening tool for potential cognitive impairment in older patients with and without cancer. The most optimal cut-off scores of the Freund CDT were determined, and CDT results were compared with the Mini-Cog.

These results indicate that the Freund CDT shows good diagnostic accuracy, based on the area under the ROC curve, in both populations under study. Moreover, at the optimal cut-off score of ≤ 4, the CDT showed high and intermediate negative predictive value (NPV) for the OncoGeriatric (OG) and General Geriatric (GG) group, respectively. Addition of the 3-word delayed recall (3-WDR) test, as applied in the Mini-Cog, resulted in negative predictive values in the 90% range for both populations. In the GG group a cut-off score of 4 was preferable to a cut-off score of 3, since the former shows higher sensitivity (>80%). High sensitivity and NPV are mandatory characteristics for a good screening tool in an older population, as it reduces false negative results, or thus false reassurance about the absence of vulnerability, rather than certifying that cognitively competent patients do not receive an unnecessary MMSE.

Twenty-nine percent of the OG patients were considered cognitively impaired, based on the MMSE. These results are in line with literature, reporting cognitive problems in 25% to 50% of older patients with cancer, who were evaluated with a MMSE within a full Comprehensive Geriatric Assessment (CGA) [276, 296]. The GG group, however, comprised more patients with cognitive deficits –indicated by positive screening on MMSE- than reported in literature (66.4% vs. 17% to 40%) [287, 297-299]. This could be partly explained by the fact that our GG patients consisted of a highly impaired population, as they had all been referred for a thorough geriatric evaluation because of signs of functional decline, and cognitive impairment has been reported as a possible determinant of functional disability [300]. In contrary, the OG population consisted of less frail patients, as they were significantly younger than their general geriatric counterparts and comprised of mainly ambulatory (64.8%) patients.

Determination of cognitive impairment by the CDT required the choice of an appropriate scoring system and adequate cut-off score. Out of a variety of possible scoring systems, we considered the system developed by Freund to be the most suitable for clinical practice. Its use is recommended by the National Highway Traffic Safety Administration (NHTSA), as a primary component in the assessment of driving safety among older adults [301]. Moreover, a lot of clock-drawing errors that are critical for dementia, as determined by Lessig et al. (2008), have been taken into account in the scoring manual [302]. Additionally, Shulman (2000) suggested the use of a simple scoring system, as he found that the more complicated scoring systems do not appear to add significant value to the clinical utility of this test [303]. Finally, Hubbard et al. (2008) reported the Freund scoring system not to be influenced by sex, race or education level, and requiring the least amount of time for scoring, compared to other scoring systems such as the Mendez and Cahn scale [292].

Although age, gender and cognitive status of both groups differed significantly, our data suggest an optimal cut-off score of ≤ 4 for identification of cognitive problems in both GG and OG patients. Moreover, the same cut-off score was established in the original paper by Freund

for the driving evaluation of older drivers [272]. This suggests robustness of the cut-off score and applicability in various settings.

At the defined cut-off score, the Freund CDT identified more potentially cognitively impaired patients compared to the MMSE. This is in line with literature, reporting that disturbances in executive functioning, which are detected by the CDT, often precede the memory decline, and people with executive cognitive dysfunction can have a normal MMSE score [288]. Moreover, this could also explain the high number of false positives (specificity: 51.3%) that was found in the GG group. Previous studies did indicate a wide range of sensitivity (50-80%) and specificity (65-90%) values for the clock scoring methods to screen cognitive impairment [304]. Exploratory analyses revealed that cognitively impaired GG patients, as defined by CDT, were significantly younger. This result could be due to the small number of cognitively normal (n=28/116) patients. Male OG patients performed significantly better on all cognitive measures; however, this could be attributed to their significantly younger age. Moreover, male patients might have received a higher education. However, the significant result of the Freund CDT does not correspond to the argumentation that CDT is unaffected by educational level, as reported by Hubbard et al. [292].

Addition of the 3-WDR test, to form the Mini-Cog, seems to add some value to the CDT score in the GG group, lowering the number of false negatives (NPV: 71.4% vs 90.9%). This seems to be confirmed by an improvement of the odds ratio (9.1 vs. 39.5). Moreover, our results are in line with those of the Capita test (S: 90%, Sp: 50%), a Mini-Cog version that is currently the standard for cognitive screening in our geriatric departments. The Capita test classifies CDT performance as normal or deviant without use of standardized scoring guidelines, such as the Freund method [305]. In contrast, our results do not support the use of the Mini-Cog over the CDT alone in the OG group.

The results of this study should be interpreted with some caution due to some limitations in the design. First, although the MMSE is considered the gold standard for detection of cognitive impairment, it is not a diagnostic test. As mentioned earlier, cognitive function detected by the CDT might be different from that detected by the MMSE [288]. For that reason, it is important to emphasize that these tools are merely screening instruments and should always be followed by a diagnostic evaluation (i.e. neuropsychological tests and physician diagnosis) [288, 306]. Second, the Mini-Cog was not directly assessed. It was calculated using an algorithm that combined the CDT performance with the 3-WDR as evaluated within the MMSE. Immediate sequential assessment of both the CDT and the Mini-Cog separately would lead to strong recall bias. Moreover, unlike the currently often applied Capita test, we used a pre-drawn circle for conduction of the CDT, as described by Freund [272]. A pre-drawn circle prevents participants from possibly drawing a circle not large enough to contain the numbers and hands, or from not being symmetrical, which might affect the spatial arrangement of the numbers [307]. Third, the interrater reliability is probably underestimated, since the blinded investigator could not take into account immediate patient corrections that were observed during the assessment. Fourth, the educational level of patients was not taken into account, while the MMSE has been proven to be influenced by this factor [308]. However, Hubbard et al. reported the Freund scoring system not to be affected by education level [292]. Though, for participants with a higher education, the CDT is possibly too simple and in the early stages of cognitive decline these patients may retain a minimal level of ability to complete the CDT successfully [309]. Fifth, since the screening tools under study require verbal insight, memory, visuo-spatial abilities and constructive qualifications of the patient, chronobiology and mood could influence test results [310]. Moreover, an alternative test would be required for screening visually impaired patients. Last, both the

GG and OG population might not be representative of an actual reference population, as they comprise a significantly compromised geriatric population, and a selected cancer population resulting in an unequal distribution of cancer types. These results can therefore not be extrapolated and further confirmation in a more comprehensive cancer population is warranted.

In conclusion, our results suggest that the Freund CDT at the optimal cut-off score of ≤ 4 is a reliable tool for identification of cognitive problems in older patients with a cancer diagnosis, and could lead to a more time-efficient CGA, eliminating the need for a MMSE in 62.9% of OG patients undergoing CGA. The Freund CDT within the Mini-Cog is possibly the screening tool of preference for use in the GG population. A prospective trial is planned for validation of the cut-off score of the Freund CDT in a larger multicentre OG sample.

ACKNOWLEDGEMENTS

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CHAPTER 3

The use of the Freund clock drawing test as a screening tool for cognitive dysfunctions in a geriatric oncology population

PART II

Validation of the Freund clock drawing test as a screening tool to detect cognitive dysfunctions in older cancer patients undergoing a comprehensive geriatric assessment

Based on

Validation of the Freund clock drawing test as a screening tool to detect cognitive dysfunction in elderly cancer patients undergoing comprehensive geriatric assessment

Lycke M et al. *Psycho-Oncology*. 2014

Abstract

OBJECTIVE

We aimed to validate the Freund Clock Drawing Test (CDT), with its predefined cut-off score of ≤ 4, as a screening tool to detect older cancer patients in need of a more in-depth cognitive evaluation within a Comprehensive Geriatric Assessment (CGA).

METHODS

Patients aged 70 or above with a histologically confirmed diagnosis of cancer were evaluated with a full CGA, including CDT and Folstein Mini Mental State Examination (MMSE) as gold standard. Validation of the Freund CDT was defined in terms of diagnostic accuracy of the test through Receiver Operating Characteristics (ROC)-analysis. To accept the Freund CDT as a screening tool, we estimated that the Area Under the ROC-curve (AUC) had to differ significantly from 0.70 with an AUC of at least 0.85.

RESULTS

Two hundred older cancer patients with a mean age of 79.0 years were included. Four patients were excluded from the analyses due to invalid results. Potential cognitive impairment (MMSE ≤23) was observed in 27.0% of patients. Based on the AUC±SE, the Freund CDT showed excellent diagnostic performance (0.95±0.17). Furthermore, it provided excellent sensitivity (94.3%) and high specificity (87.4%).

CONCLUSION

Our results indicate that the Freund CDT can be used as an initial screening tool to detect older cancer patients in need of a more in-depth cognitive assessment within CGA, instead of the MMSE.

INTRODUCTION

As a result of the ageing of populations, there is currently a demographic evolution particularly in Western countries. These demographic changes have triggered an increased interest in the multidisciplinary management of older patients since the latter is a heterogeneous group that is in need of a more individualized treatment approach [311, 312]. Tailored care can be facilitated through a Comprehensive Geriatric Assessment (CGA), which has been the cornerstone in the management of geriatric patients for years [313]. A CGA is a multidisciplinary evaluation assessing medical, psychosocial and functional capabilities and limitations in older cancer patients. It aims at predicting the functional age of patients including the risk on morbidity and mortality through assessing a wide range of domains including functional status, cognition, nutrition, emotional status, polypharmacy, comorbidities and geriatric syndromes, each evaluated with a commonly used validated tool [19, 37, 312, 314]. In addition, it reveals unknown problems, predicts toxicity from treatment and quality of life. During the past years, efforts have been made to implement a CGA in an older oncology population, with success, as it has now been proposed as the key treatment approach [315, 316].

The Folstein Mini Mental State Examination (MMSE) is a standard validated measure to screen cognitive function within a CGA. Studies have noted that up to 40% of older cancer patients present with cognitive abnormalities that warranted further evaluation. Cognitive dysfunctions can influence the ability to weigh the risks and benefits of cancer therapy, comply with the suggested treatment plan, and decreases the ability to recognize the symptoms of toxicity that need medical attention [29]. The MMSE can be used to screen for dementia and to estimate the severity of cognitive impairment in a general population and in older cancer patients [51, 317, 318]. However, in an oncogeriatric population, where the majority of patients has a normal cognitive function, such assessment can be experienced as tedious and time-consuming, as it may take up to 10-15 minutes to carry out [281, 319]. More recently, the Clock Drawing Test (CDT) has been proposed as a quick and simple screening tool to assess cognitive dysfunction as it can be completed in only five minutes [320]. The CDT evaluates multiple domains of cognition including memory, comprehensive and executive function, visuo-spatial ability and abstract thinking [286, 290]. Furthermore, when given a predrawn circle, the CDT is not influenced by education age [292]. Although the CDT has the characteristics of an attractive screening tool, an easy and straightforward scoring method and validated cut-off scores were still lacking. Therefore, our research group retrospectively reviewed the Freund scoring system, as it has been reported in literature as a fast, easy and trustworthy scoring method [292]. A retrospective analysis on 105 older cancer patients at the General Hospital Groeninge showed that a cut-off score of ≤ 4 for the CDT had a good Area Under the Curve (AUC), sensitivity (S) and specificity (Sp). The same cut-off score appeared optimal in a general geriatric population. Furthermore, the Freund scoring system demonstrated high interrater-reliability [272, 318].

In this prospective trial, our primary endpoint was to prospectively validate the Freund CDT, with its predefined cut-off score of ≤4, as a screening tool to detect cognitive deterioration in older cancer patients within a comprehensive geriatric assessment.

METHODS

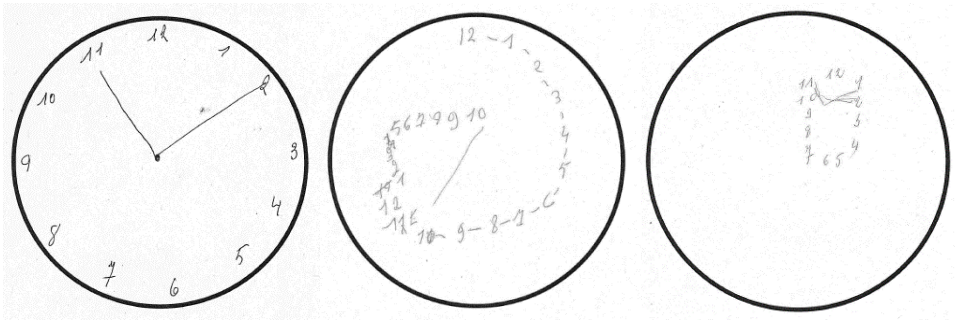
Patient selection

This prospective study (PROACTIVE trial, ClinicalTrials.gov identifier: NCT01749995) was conducted from November 2012 till December 2013 in patients aged 70 or above with a histologically confirmed diagnosis of a solid cancer or haematologic malignancy at all four sites of the General Hospital Groeninge (Kortrijk, Belgium). Patients, receiving their primary oncology care (surgery, course of (neo)adjuvant or palliative chemotherapy, radiotherapy, targeted therapy, palliative care, experimental treatment as part of a clinical trial, ...) could be included before or at the start of a line of treatment, but not during a line of treatment. Eligible patients were screened with the G8-questionnaire before or after they had received their cancer diagnosis, as part of routine clinical practice [321]. Patients who screened positive on the G8 (cut-off ≤14) were evaluated with a full CGA and were subsequently invited to participate in this trial. In a limited number of cases, a CGA was performed irrespective of the G8 test score due to a referral by the treating physician based on clinical suspicion of vulnerability or frailty. This trial was approved by the ethical committee of the General Hospital Groeninge (Kortrijk, Belgium).

CGA and cognitive assessments

Cognitive function was assessed as part of a routine oncogeriatric assessment or CGA. The CGA comprised several domains, each assessed with a standard validated measure: nutrition (Mini Nutritional Assessment - Short Form [322]), functional status (Activities of Daily Living, Instrumental Activities of Daily Living [48, 49]), physical status (falling past year [323]), depression (Geriatric Depression scale – 15 [60]), cognition (MMSE, Freund CDT [51, 272]), polypharmacy (number of drugs) and comorbidities (Charlson Comorbidity Index [324]). In accordance with previous reports, patients were classified into either having a fit or vulnerable profile. Patients were deemed vulnerable if they presented with impairments in two or more domains within the CGA [6, 313]. The CGA, including MMSE and Freund CDT, was conducted by an oncopsychologist or research associate with experience in the field of oncogeriatrics. Both had received training from an occupational therapist, enabling them to conduct and score the Folstein MMSE according to international guidelines [295]. Patients were considered to be potentially cognitively impaired if they presented with a test score of 23 or less [319]. Potentially cognitively impaired means that a patient has to be referred to a neurologist or memory clinic for a more in-depth cognitive assessment. For the CDT, patients were given a predrawn circle and were verbally instructed to put all the numbers of a clock on it and set the time at ten past eleven, as this has been reported to be the most sensitive for detecting neurocognitive impairments [325]. The Freund scoring system uses a 7-point rating scale ranging from 0 to 7, indicating a potentially very poor to excellent cognitive function respectively. The scoring system is divided into three categories, namely the ability to correctly reproduce all numbers, to position them accurately in the circle and to appropriately replicate the hands at the indicated time (Table 1). For every item, one point can be awarded [272, 318]. According to our predefined cut-off score, patients were considered to be potentially cognitively impaired if they had a score of 4 or less [318].

Table 1: Clock Drawing Test: Freund scoring system [272] and examples

Time (0-3 points)	– One hand points 2 (or symbol representative of 2) – Exactly two hands – Absence of intrusive marks, e.g., writing or hands indicating incorrect time, hand points to number 10, tic marks, time written in text
Numbers (0-2 points)	– Numbers are inside the clock circle – All numbers 1-12 are present, no duplicates or omissions
Spacing (0-2 points)	– Numbers spaced equally or nearly equally from each other – Numbers spaced equally or nearly equally from the edge of the circle
Examples	 Excellent clock drawing followed by two poor drawings

Statistical analyses

All statistical analyses were performed by use of SPSS software (version 21; IBM SPSS Statistics, Chicago, IL). Descriptive statistics were conducted to present patient and tumour characteristics, and CGA and cognitive test results. Scatter graphs were plotted to evaluate if a linear relationship was present between education age and MMSE and CDT test scores. Based on the linearity of this association, Pearson or Spearman correlation coefficients were calculated to examine the association between age, education age and MMSE and CDT test scores. Education age can be defined as the number of years that patients went to school, starting from primary education. In advance sample size calculations were based on the hypothesis of equality with 0.70 of the area under the Receiver Operating Characteristics (ROC) curve (ClinicalTrials.gov identifier: NCT01749995). In our scenario, a sample with an unequal allocation ratio of four, consisting of a sample of at least 32 from the positive group, and at least 128 from the negative group would achieve at least 80% power to detect a difference of 0.15 between the area under the ROC curve under the null hypothesis of 0.70 and an AUC under the alternative hypothesis of 0.85 using a two-sided z-test at a significance level of 5%. ROC curves were plotted to evaluate the diagnostic performance, in terms of AUC, of the Freund CDT in determining patients who are potentially cognitively impaired compared to the Folstein MMSE as gold standard. The cut-off for determining impairment was defined as having a MMSE score of 23 or less [319]. Sensitivity and specificity with 95% confidence intervals (95%CI) were calculated at our predefined cut-off score of ≤4. Positive and negative predictive values were also determined (PPV and NPV, respectively).

RESULTS

Patient characteristics

During the inclusion period, 490 patients were evaluated with a routine oncogeriatric screening at General Hospital Groeninge. Of those, 320 (65%) patients needed an additional full CGA. Two hundred older cancer patients consented to participate in this trial. Four patients were excluded from analyses due to an incomplete cognitive assessment. Patients presented with a mean age of 79.0 years (range: 70.0-93.0 years) and a mean education age of 10.3 years (range: 4.0-22.0 years). The study population comprised slightly more male patients (52.6%). Patients presented with cancer of the following regions: digestive (30.6%), genitourinary (22.4%), gynaecologic (13.3%), breast (8.7%), haematological malignancies (8.7%), thorax (5.6%), head and neck (5.6%), skin (2.0%), musculoskeletal (2.0%) and central nervous system (1.0%). More than half of patients were treated with curative intent (55.1%) (Table 2).

Table 2. Patient and tumour characteristics

Characteristic (n=196)	Mean (range)	n (%)
Age	79.0 (70.0-93.0)	
Gender		
Male		103 (52.6)
Female		93 (47.4)
Marital Status		
Single		13 (6.6)
Married		107 (54.6)
Divorced		3 (1.5)
Widow-er		69 (35.2)
Other		4 (2.1)
Level of education		
Age	10.3 (4.0-22.0)	
Less than primary education		2 (1.0)
Primary education		11 (5.6)
Lower secondary education		109 (55.6)
Higher secondary education		51 (26.0)
Higher education		23 (11.8)
Cancer site		
Digestive		60 (30.6)
Genitourinary		44 (22.5)
Gynaecologic		26 (13.3)
Breast		17 (8.7)
Hematologic malignancies		17 (8.7)
Head and neck		11 (5.6)
Thorax		11 (5.6)
Skin		4 (2.0)
Musculoskeletal		4 (2.0)
Central nervous system		2 (1.0)
Treatment intent		
Curative		108 (55.1)
Palliative		77 (39.3)
No active treatment		11 (5.6)

CGA and cognitive measures

Three patients (1.5%) screened negative on the G8-questionnaire (cut-off ≤14) and were evaluated with a full CGA based on a referral from their treating physician. Mean and median scores per screening tool assessed within the CGA and the percentage of patients vulnerable per test are shown in Table 3. Based on the CGA outcome, 89.8% of patients were deemed vulnerable as they presented with a potential impairment in two or more domains. Potential cognitive deficits were identified in 27.0% of patients according to the MMSE. To meet the criteria of the power analysis, at least 32 patients needed to have a potential cognitive impairment based on the MMSE and at least 128 patients needed to score above the cut-off. The MMSE selected 53 (27.0%) patients with a potential cognitive impairment, whereas 143 were marked as having a good cognition. Median MMSE and CDT scores were 27 and 5, respectively (Table 3). Scatter graphs did not detect a linear association between age, education age and MMSE test scores, nor was this the case for the CDT test results. Spearman correlation coefficient showed a significant negative correlation between MMSE and age (p<0.01; r_s=-0.23) and a significant positive association between MMSE scores and the years of education (p<0.01; r_s=0.24). We did not find a significant association between age, education age and CDT test results (p=0.07; r_s=-0.13 and p=0.07; r_s=0.13, respectively) (data not shown). At our predefined cut-off score of ≤4, the area under the ROC-curve (AUC±SE) of the CDT showed excellent diagnostic accuracy (0.95±0.17) (Figure 1). Furthermore, it provided a sensitivity of 94.3% (95% CI [83.4-98.5]) and specificity of 87.4% (95% CI [80.6-92.2]). The PPV and NPV were 73.5% (95% CI [61.2-83.2]) and 97.7% (95% CI [92.8-99.4]), respectively (Table 3). When subdividing patients into groups by age and education age according to Crum et al. (1993), the cut-off remained optimal (data not shown) [308].

Table 3. Overview of median scores and percentage of vulnerable patients per tool (n=196)

Domain	Test	Range	Median	Mean	% vulnerable
Nutrition	MNA-SF	0-14	10	9.6	82.1
Functional status	ADL	0-24	7	8.9	87.2
	IADL	0-8	5	4.7	
Physical status	Falls past year	NA	NA	NA	38.3
Depression	GDS-15 (n=195)	0-15	2	2.6	15.8
Cognition	MMSE	0-30	27	25.5	27.0
	CDT	0-7	5	4.9	NA
Polypharmacy	Number of drugs	NA	7	6.6	72.4
Comorbidities	CCI	0-37	2	2.3	23.5

MNA-SF: Mini Nutritional Assessment-Short Form, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, GDS: Geriatric Depression Scale, MMSE: Mini Mental State Examination, CDT: Clock Drawing Test, CCI: Charlson Comorbidity Index, NA: Not applicable

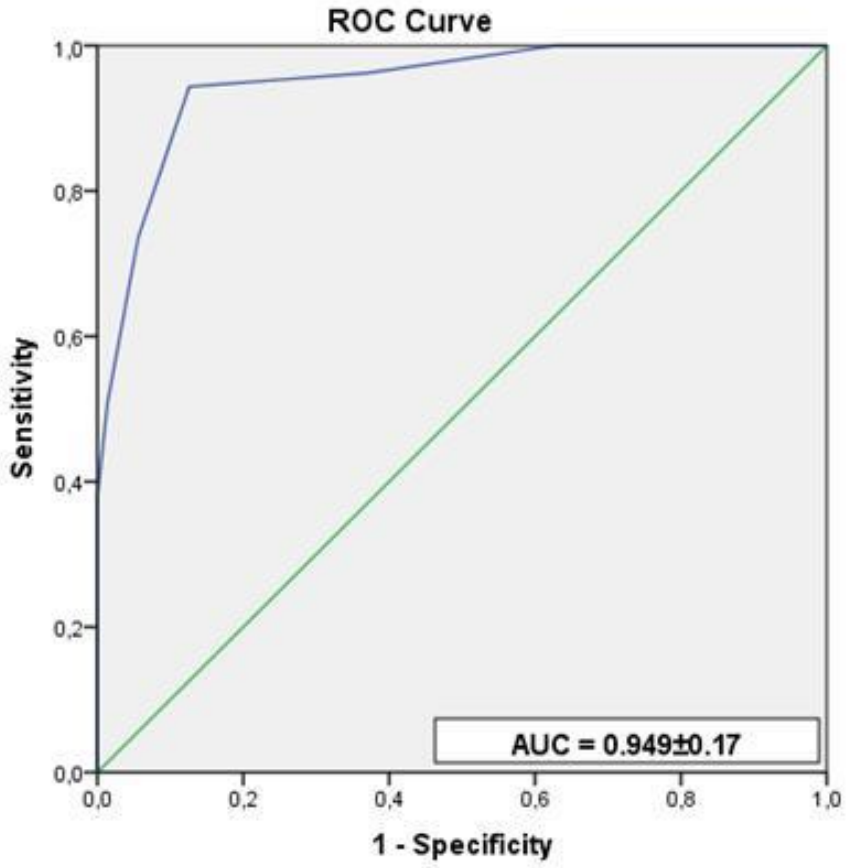


Figure 1. Receiver operating characteristics (ROC) curve of the Clock Drawing Test compared with the Mini Mental State Examination as gold standard. AUC, area under the (ROC) curve

DISCUSSION

Assessing cognitive function provides health care workers valuable information on the mental reserve of the patient as patients presenting with a memory impairment can have difficulties understanding treatment instructions and may not be attentive for the signs and symptoms of treatment related toxicities that need further evaluation [13]. The Folstein MMSE is a commonly used instrument to screen for dementia and is validated for use in several patient populations. Nevertheless, the MMSE is time-consuming and confronting in the many cognitively fit patients that undergo a CGA as part of their cancer care. Previous work from our group suggested that the Freund CDT with a cut-off score of ≤4 could replace the MMSE within the CGA resulting in gain in time for health care providers and increased comfort for patients [318]. The current study was able to prospectively validate the retrospectively identified cut-off score and could therefore be practice changing.

A good screening tool needs a high sensitivity and high NPV as it reduces the number of false negative cases. Our results show that the Freund CDT, with a cut-off score of ≤4, has indeed the properties of an excellent screening instrument as we have found a sensitivity of 94.3% and NPV of 97.7%. Further, the Freund CDT provided a high specificity of 87.4%. In this trial, our primary endpoint was to validate the CDT based on the diagnostic accuracy of the test. We stated that a sample with an unequal allocation ratio of four, consisting of a sample of at least 32 from the positive group, and at least 128 from the negative group would achieve at least 80% power to detect a difference of 0.15 between the AUC under the null hypothesis of

0.70 and an AUC under the alternative hypothesis of 0.85 using a two-sided z-test at a significance level of 5%. In our sample, results show an AUC (AUC±SE) under the ROC-curve of 0.95±0.17. Hereby we can accept the alternative hypothesis as an AUC under the ROC-curve of at least 0.85 was achieved. As this cut-off score was also determined in our previous retrospective study (in oncogeriatric and general geriatric patients) and in the original paper by Barbara Freund et al. (2005), we can assume the robustness of this cut-off score [272, 318]. Further, we can state that the cut-off score of ≤4 is the most optimal cut-off score for use in an oncogeriatric population.

In our sample, 27.0% of patients presented with a potential cognitive deficit that needed further evaluation based on the MMSE. This is in line with previous research reporting cognitive deterioration in up to 50% of patients [29]. Further, it has been noted that the Folstein MMSE can be influenced by education age, whereas the CDT is less dependent of education age when given a predrawn circle [292, 308]. Spearman correlation coefficients showed a significant statistical association between MMSE test scores and education age. This was not the case for the Freund CDT.

Initially, it was our objective to validate the Freund CDT as a pre-screener within a CGA. Since results show such an excellent AUC of 0.95 with sensitivity of 94.3% and specificity of 87.4%, we could assume that an assessment with the MMSE may be redundant and that results on both screening tools will be nearly equal. However, McNemar test revealed a significant difference between both test outcomes disputing the latter statement (p<0.005; data not shown). This highly significant result reflects a minor discordance in 21 out of 196 patients of which 18 are considered fit by MMSE and classified vulnerable by CDT, and 3 out of 196 who were considered vulnerable by MMSE and classified as fit by CDT. Nevertheless, selecting the Freund CDT above the Folstein MMSE has some advantages. First, the Freund CDT defined more patients as vulnerable leading to a more sensitive test. Second, within a CGA, we try to select those domains that can influence and increase the risk on morbidity and mortality. As it is not our intention to diagnose patients but merely to detect potential vulnerabilities, we need a screening tool that gives us valuable information in less time. The Freund CDT can be administered in approximately five minutes and has been previously reported as a good screening tool in other populations that can be carried out in very little time [320]. Third, the Freund scoring system is user-friendly and has been reported with a high interrater-reliability [272, 318]. Fourth, in our and other patient populations, the MMSE can be experienced as tedious and annoying, whereas the CDT has been described previously as a non-threatening cognitive assessment [326]. Last, it has been noted that the MMSE can be influenced by education age whereas the CDT - when given a predrawn circle - is not influenced by education age [292, 308]. Our results support this statement.

The results of this trial need to be interpreted with caution due to some limitations. We considered the Folstein MMSE as the gold standard against the Freund CDT. Although the MMSE is a commonly used validated measure, it is not a diagnostic test. Cognitive malfunction detected by the CDT may slightly differ from that detected by our gold standard. Therefore, it is important to remember that both MMSE and CDT are screening tools and that they should always be followed by an intensive diagnostic neuropsychological assessment when a potential cognitive impairment is detected [288]. Further, the MMSE cut-off of ≤23 may not be sufficient for detecting mild cognitive impairment nor may it be sufficient for detection dysfunctions in patients with less than 9 years of education [308, 327]. Although our population has a mean education age of 10.3 years, 6.6% of patients received less than lower secondary education (Table 2). However, in our study we did not intend to diagnose patients but to select those who may present with a potential vulnerability that needs closer evaluation. Next, this

study was conducted in oncogeriatric patients receiving a routine oncogeriatric assessment. Most patients consenting for this trial had been assessed with a CGA due to a positive test score on the G8-questionnaire. In our clinic, patients deemed fit - based on their G8 screening score - are only evaluated with a CGA when required by the physician. Therefore, this trial includes only a minority of fit patients. The cut-off score achieved may thus not be representative for patients who screened negative on the G8 or patients who are evaluated with other screeners such as VES-13. However, the G8-questionnaire contains seven items from the Mini Nutritional Assessment and age. One of the items included in the G8-questionnaire concerns cognition and depression. This item has previously shown to correlate with MMSE test scores [34, 328]. Last, we did not consider the chronobiology [329]. However, in our sample, as patients were seen throughout the day, we suggest a minimal bias by biological rhythms.

Overall, we can conclude that in this prospective trial, we were able to validate the Freund CDT with a cut-off score of ≤4 as a screening tool to detect cognitive dysfunction in older cancer patients undergoing a Comprehensive Geriatric Assessment. Our results indicate that it could potentially replace the MMSE as a stand-alone screening instrument, leading to a more time-efficient CGA.

ACKNOWLEDGEMENTS

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CHAPTER 4

The use of the Distress Thermometer as a screening tool for cognitive dysfunctions in a general cancer population undergoing curative treatment

PART I

Predictors of baseline cancer-related cognitive dysfunctions in cancer patients undergoing a curative cancer treatment

Based on

Predictors of baseline cancer-related cognitive dysfunctions in cancer patients undergoing a curative cancer treatment

Lycke M et al. *Psycho-Oncology*. 2017

Abstract

OBJECTIVE

Recent research in the field of cancer-related cognitive impairments (CRCI) has shown CRCI presentation prior to treatment initiation. Some have attributed these problems to worry and fatigue whereas others have suggested an influence of age, IQ and other psychosocial and medical factors.

METHODS

Patients (≥18 years) with a histologically confirmed diagnosis of a solid cancer or haematological malignancy, scheduled for a curative treatment, were evaluated with a baseline neuropsychological assessment including patient-reported outcome measures (PROMs). PROMs entailed distress, anxiety and depression, fatigue and cognitive complaints. The neuropsychological assessment comprised several cognitive domains such as premorbid IQ, attention, processing speed, flexibility, verbal and visual episodic memory and verbal fluency.

RESULTS

Cross-sectional data of 125 patients were collected. Patients had a mean age of 60.9 years (range: 30.0-85.0) and comprised primarily females (65.6%). Patients presented with cancer of following sites: breast (44.0%), digestive (28.8%), urological (11.2%), gynaecologic (8.0%), haematologic malignancy (4.8%) or lung (3.2%). Patients presented with a premorbid IQ of 105.3 (range: 79.0–124.0). In 29.6% of patients, a CRCI was detected. Binary logistic regression analyses showed that a lower premorbid IQ (β=-0.084, p<0.01) and a higher level of fatigue (β=-0.054, p<0.05) predicted baseline CRCI. Premorbid IQ also predicted performance on individual cognitive domains. Some domains were also influenced by age, gender, having a breast cancer diagnosis and an active treatment for hypertension.

CONCLUSION

Premorbid IQ and fatigue are important predictors of baseline CRCI. Therefore, we advise researchers to implement a short IQ test when conducting clinical trials on CRCI.

INTRODUCTION

Improved cancer treatments have led to increased survival rates and a growing number of cancer survivors presenting with persistent treatment-related side effects. Cognitive malfunctioning is one of the most frequently reported adverse events and poses a big challenge for patients who want to return to their former lives. Patients may suffer from concentration problems, distractibility, forgetfulness, difficulties in remembering names or numbers and a lack of mental sharpness [123, 124, 134, 330, 331].

Researchers ascribed these problems at first to chemotherapeutic treatments, resulting in a term called 'chemobrain'. Initial trials focused on breast cancer patients, as they reported symptoms even long after their treatment had ended [123, 124]. Recent research, however, indicates that chemotherapeutic agents may not be the sole cause of cancer-related cognitive impairments (CRCI). Studies have shown that radiotherapy, external to the brain region, and hormonal treatments can also induce CRCI [332-334]. Further, prospective studies, including neuropsychological assessments before treatment administration but after cancer diagnosis – and most often after cancer surgery, have reported high rates of CRCI prior to adjuvant chemotherapy. They report increasing problems following chemotherapy and a resolution of the findings to baseline levels when performing longer follow-up assessments [134].

Although the majority of studies now include a baseline assessment that shows that some patients present with a CRCI before adjuvant treatment initiation, little is known about why these impairments occur. A trial by Schilder et al. (2010) investigated baseline cognition in a group of postmenopausal breast cancer patients and found that an individual cognitive domain can be influenced by age, IQ and other medical factors [334]. Others have suggested that psychosocial factors such as worry and fatigue may enhance the risk of presenting with a CRCI at baseline in patients diagnosed with breast or colorectal cancer [139, 143, 144].

Although more research has been conducted into the pathophysiology of baseline CRCI, sufficient evidence is lacking. Further, studies have mainly been focussing on how breast cancer patients experience these problems. It is only until more recently that researchers have broadened their landscape and started to examine CRCI in other cancer types. Another shortcoming in current literature is that only few researchers implement some form of IQ assessment when investigating CRCI, although it is known that IQ can predict neuropsychological assessment results [335].

In this paper, we tried to closing the gap in some of these shortcomings by performing a cross-sectional analysis in which we aimed at identifying predictors of baseline CRCI in a group of general cancer patients who were scheduled for a treatment with curative intent.

METHODS

Participants

Patients were invited to participate in the CONCEPT-trial (ClinicalTrials.gov Identifier: NCT01846260) between May 2013 and September 2015. Baseline data were collected as part of an ongoing longitudinal trial in which we aimed to examine whether the distress thermometer can predict long-term CRCI (Chapter 4, Part II). All patients were recruited in the Kortrijk Cancer Centre (Kortrijk, Belgium). Eligible patients were 18 years or older and natively Dutch speaking or bilingual. All patients had a histologically confirmed diagnosis of a solid tumour or haematological malignancy, in an early or advanced stage. Patients were scheduled to receive a treatment with curative intent. Patients receiving surgery as a sole treatment were excluded.

Other exclusion criteria entailed: being diagnosed with primary brain tumours or brain metastases, having a prior history of cancer -with or without chemotherapy or radiotherapy- during the last five years, suffering from an organic brain syndrome, showing signs of mental deterioration or being diagnosed with dementia (DSM-IV criteria), having an untreated or unstable major medical condition, being alcohol or drug dependent, presenting with a condition other than cancer in which fatigue is a prominent symptom (such as chronic fatigue syndrome) and having a major psychiatric or neurologic disorder that could potentially invalidate assessment; a prior or current diagnosis of a depressive or anxiety disorder was allowed. All patients gave written informed consent. The trial was approved by the ethics committee of the General Hospital Groeninge, Kortrijk, Belgium.

Measures

Patients were evaluated by a baseline neuropsychological assessment (Table 1) including patient-reported outcomes (PROMs). All assessments were performed by either a neuropsychologist or study trial coordinators trained to perform these measurements.

Table 1. Neuropsychological assessment

Cognitive domain	**Test**	**Item**	**Outcome measure**	**Range**
Premorbid intelligence	Dutch Adult Reading Test (DART)	IQ estimation	IQ estimation	≥ 0
Episodic memory				
Visual	Rey's Complex Figure Test (CFT)	Delayed recall	Total score	0 – 36
Verbal	Rey's Auditory Verbal Learning Test (RAVLT)	Delayed recall	Total score	0 – 15
Executive functions				
Flexibility	Trail Making Test (TMT)	Condition 4 (number-letter sequencing)	Time needed to complete in seconds	≥ 0
Semantic word fluency	Controlled Oral Word Association Test (COWA)	Animals	Number of correctly produced words in 60 seconds	≥ 0
Phonetic word fluency	COWA	letter N	Number of correctly produced words in 60 seconds	≥ 0
Processing speed	TMT	Condition 2 (number sequencing)	Time needed to complete in seconds	≥ 0
	WAIS-III Digit Symbol		Number of correct items	≥ 0
Working memory				
Attention	WAIS-III Digit Span	Forward and backward span	Total score	0 – 30

WAIS: Wechsler Adult Intelligence Scale

The neuropsychological assessment included standardized neuropsychological tests assessing several cognitive domains as advised by the International Cognition and Cancer Taskforce (ICCTF) [148].

The Dutch Adult Reading Test (DART) is the Dutch version of the National Adult Reading Test (NART). It consists of a list of 50 words with an irregular pronunciation, which have to be read aloud. The DART estimates premorbid intelligence and is relatively insensitive to brain dysfunctions and mild dementia [336, 337].

The Rey-Osterrieth Complex Figure Test (CFT) assesses both visuoconstruction and visual memory [338, 339]. It consists of three conditions: a copy task, an immediate and a delayed recall task. The CFT has been a useful tool for measuring visual episodic memory that is mediated by the prefrontal lobe [340].

The Rey Auditory Verbal Learning Test (RAVLT) measures verbal learning ability and verbal memory. Patients are asked to repeat and remember a list of 15 words. It entails both an immediate and delayed recall task [341].

The Trail Making Test (TMT) provides information on a patient's visual scanning and searching abilities, processing speed, mental flexibility and executive function [342]. D-KEFS TMT consists of five conditions instead of two on the original test. Patients are asked to draw lines sequentially connecting encircled numbers or letters distributed on a sheet of paper. The most important conditions concerning executive functioning comprises a number and a number-letter sequencing task [343].

The Controlled Oral Word Association test (COWA) is one of the most commonly used measures of verbal fluency. This rapid and organized word retrieval task is a sensitive indicator of brain dysfunctions. Verbal fluency tests typically employ a word-list generation procedure and are divided in two forms. Semantic fluency tasks require the patient to generate a list of words according to a certain category. Phonemic fluency tasks require that words be generated according to a letter of the alphabet [344-346].

The Digit Span subtest of Wechsler Adult Intelligence Scale-III (WAIS-III) measures attention, concentration and working memory, and entails a forward and backward repeating task. The score is the total number of correctly repeated sequences before two failed attempts in each condition [347, 348]. The WAIS-III Digit Symbol measures cognitive and perceptual-motor processing speed. The subject is given a code that pairs symbols with digits. The patient is asked to match as many series of digits as possible to their corresponding symbols as possible in a fixed time span of 120 seconds [348, 349].

PROMs entailed an assessment of distress (Distress Thermometer including 38-item Problem list[350]), anxiety and depression (Hospital Anxiety and Depression Scale (HADS) [351]), fatigue (FACIT-fatigue [352]), cognitive complaints (Cognitive Failure Questionnaire (CFQ) [353]) and quality of life (EORTC QLQ-C30 [354]).

Statistical considerations

Statistical analyses were conducted by use of SPSS software (version 23; IBM SPSS Statistics, Chicago, IL). Descriptive statistics were performed to present patient and tumour characteristics and neuropsychological assessment results. Overall, cognitive impairment was calculated by the definition of the ICCTF. Patients were marked as having a CRCI if they either presented with two or more test scores at or below -1.5 standard deviations (SDs) from the normative mean or if they presented with one test score at or below -2.0 SDs [148]. Published

normative data, adjusted for gender, age and/or education, were used to convert raw test scores into standardized z-scores (mean=0; SD=1). Curves based on the binomial probability distribution were used to determine that in our test battery, including eight independent test, approximately 17% of patients would perform 2SDs below the normative mean on a single test [355]. A binomial test was performed to examine whether our data differed from the binomial probability distribution. Data from questionnaires were converted according to standard scoring rules, if applicable.

Independent Student's t and Chi-square tests were performed to examine patient and clinical characteristics between impaired and non-impaired subjects. Binary logistic regression analysis was used to examine potential predictors of overall CRCI. Multiple regression analysis were used to examine predictors of individual cognitive domains. Models were selected through forward and backward analyses. Models were not controlled for age, gender or premorbid IQ, as we wanted to evaluate the effect of these variables in our target population. Both binary and linear regression analyses included 14 covariates: age, gender, premorbid IQ, distress, fatigue, cognitive complaints, days since diagnosis, days since surgery, active treatment for diabetes mellitus, active treatment for hypertension, active treatment with anxiolytics/antidepressants/antihypnotics, having a prior or current diagnosis of depression or anxiety, stage (early vs. late stage) and diagnosis (breast cancer or not). Variables were included in the model if they were significant at the $p<0.05$ level.

RESULTS

Patient characteristics

In total, 125 patients were included in the trial. Patients had a mean age of 60.9 years (range: 30.0-85.0). The study population comprised primarily female individuals (65.6%). The majority of patients finished high school or higher (71.2%). Patients presented with cancer of following sites: breast (44.0%), digestive (28.8%), urological (11.2%), gynaecologic (8.0%), haematologic malignancy (4.8%) or lung (3.2%). Most patients were diagnosed in an early stage (62.4%). Eighty-six patients underwent surgery prior to the baseline assessment. On average, there were 38.1 days (range: 13-106) between the day of surgery and the day of the assessment. Five patients were included with a prior history of diagnosed depression or anxiety disorder. No patient was included with a current diagnosis of any of these conditions. Of all patients, 22.4% were prescribed antidepressants, antihypnotics and/or anxiolytics. Only few patients received an active treatment for diabetes mellitus (6.4%) whereas almost half of patients were on antihypertensive drugs (42.4%) (Table 2).

Neuropsychological outcomes

One patient was excluded from the analyses as not all neuropsychological test were completed. Table 3 shows mean raw scores, Z-scores and SDs for each cognitive test. Patients had a mean premorbid IQ of 105.5 (range: 79.0 – 124.0). Based on the definition of the ICCTF, 29.6% of patients presented with an overall CRCI. Thirty patients scored below 2SDs from the normative mean on a single test (24.2%, Binomial test $p<0.001$). Independent Student's t-tests did not detect differences between impaired and non-impaired patients for age, education age, distress, anxiety, depression, fatigue, subjective cognitive complaints and days between surgery and baseline assessment, nor did the Chi-square test show any differences between both groups for gender, active treatment with anxiolytics/antidepressants/antihypnotics, having a prior or current diagnosis of depression or

anxiety , stage (early vs. late stage) or cancer type (breast cancer vs. other cancer type) (data not shown). A significant difference was found for premorbid IQ (p<0.01). Non-impaired patients presented with a mean premorbid IQ of 107.0 (range: 79.0 – 124.0) whereas the mean premorbid IQ of impaired patients was calculated as 101.5 (range: 82.0 – 116.0).

Table 2. Demographic and clinical data (n=125)

Demographics	**n (%)**	**mean (range)**
Age		60.9 (30.0-85.0)
Gender		
Female	82 (65.6)	
Male	43 (34.4)	
Highest education		
Primary education	0 (0)	
Lower secondary education	36 (28.8)	
Higher secondary education	49 (39.2)	
Higher education	35 (28.0)	
Other	5 (4.0)	
Clinical data		
Diagnosis		
Breast cancer	55 (44.0)	
Digestive cancer	36 (28.8)	
Urological cancer	14 (11.2)	
Gynaecologic cancer	10 (8.0)	
Haematologic malignancy	6 (4.8)	
Lung cancer	4 (3.2)	
Stage		
Early (I-II)	78 (62.4)	
Advanced (III-IV)	47 (37.6)	
Surgery		
Number of patients who received surgery before baseline assessment	86 (68.8)	
Days between surgery and baseline assessment		38.1 (13-106)
Medication		
Active treatment diabetes mellitus	8 (6.4)	
Active treatment hypertension	53 (42.4)	
Active treatment with anxiolytics/antidepressants/antihypnotics	28 (22.4)	

Table 3. Mean raw and z-scores and SDs per cognitive test score (n = 124)

Cognitive test	**Raw score Mean (SD)**	**z-score Mean (SD)**
DART	105.3 (9.1)	NA
CFT Delayed Recall	19.6 (5.1)	0.07 (0.76)
RAVLT Delayed Recall	10.3 (3.8)	-0.26 (1.48)
TMT condition 4: number-letter sequencing	104.7 (53.9)	0.06 (1.10)
COWA Semantic Word Fluency	21.7 (7.0)	0.01 (1.09)
COWA Phonetic Word Fluency	10.0 (5.0)	0.00 (1.22)
TMT condition 2: number sequencing	43.8 (22.1)	0.20 (1.09)
WAIS-III Digit Symbol	63.6 (20.4)	0.28 (1.21)
WAIS-III Digit Span	14.3 (3.5)	0.10 (1.04)

DART: Dutch Adult Reading Test, CFT: Complex Figure Test, RAVLT: Rey's Auditory Verbal Learning Test, TMT: Trail Making Test, COWA: Controlled Word Association, WAIS: Wechsler Adult Intelligence Scale, SD: standard deviation, NA: not applicable

All regression analyses started with a list of 14 covariates as mentioned previously. Results of the binary logistic regression analyses indicated that overall CRCI, according to the definition of the ICCTF, was predicted by a lower premorbid IQ ($\beta = -0.084$, $p<0.01$) and lower score on the FACIT-Fatigue scale representing a higher level of fatigue ($\beta = -0.054$, $p<0.05$). Individual cognitive domains were evaluated through multiple regression analysis (Table 4.). Results revealed that all cognitive domains can be predicted by premorbid IQ, stating that a higher IQ results in a better test score. Premorbid IQ alone predicted up to 27.1% of the explained variance (R^2 adjusted) in a single test domain. Visual and verbal episodic memory, information processing speed, semantic word fluency and flexibility were also influenced by age, favouring younger patients. Including age in the model resulted in an up to 31.7% increase of the explained variance. Verbal episodic memory was further predicted by gender resulting in a total explained variance of 33.2%. Test scores on the WAIS-III Digit Span were, next to premorbid IQ, predicted by an active treatment for hypertension, adding 8.0% to the explained variance of the model. Interestingly, processing speed, as measured by the WAIS-III Digit Symbol was in part predicted by having a breast cancer diagnosis or not.

Table 4. Multiple regression analysis

Models	**R^2 adj.**	**Dependent variables in final models**	**β**	***p*-value**
CFT Delayed Recall				
IQ	0.140	IQ	0.328	<0.001
IQ + age	0.204	Age	-0.270	<0.01
RAVLT Delayed Recall				
IQ	0.223	IQ	0.421	<0.001
IQ + age	0.296	Age	-0.255	<0.01
IQ + gender + age	0.332	Gender	0.204	<0.01
TMT number-letter sequencing				
IQ	0.186	IQ	-0.325	<0.001
IQ + age	0.467	Age	0.544	<0.001
COWA Semantic Word Fluency				
IQ	0.245	IQ	0.456	<0.001
IQ + age	0.283	Age	-0.214	<0.01
COWA Phonetic Word Fluency				
IQ	0.271	IQ	0.526	<0.001
TMT: Number Sequencing				
IQ	0.105	IQ	-0.224	<0.01
IQ + age	0.372	Age	0.531	<0.001
WAIS-III Digit Symbol				
IQ	0.170	IQ	0.272	<0.001
IQ + age	0.487	Age	-0.566	<0.001
IQ + age + having breast cancer or not	0.508	Having breast cancer or not	0.161	<0.05
WAIS-III Digit Span				
IQ	0.179	IQ	0.399	<0.001
IQ + active treatment for hypertension	0.259	active treatment for hypertension	-0.294	<0.001

Covariates: age, gender, premorbid IQ, distress, fatigue, cognitive complaints, days since diagnosis, days since surgery, active treatment for diabetes mellitus, active treatment for hypertension, active treatment with anxiolytics/antidepressants/antihypnotics, having a prior or current diagnosis of depression or anxiety, stage (early vs. late stage) and diagnosis (breast cancer or not). CFT: Complex Figure Test, RAVLT: Rey's Auditory Verbal Learning Test, TMT: Trail Making Test, COWA: Controlled Word Association, WAIS: Wechsler Adult Intelligence Scale.

DISCUSSION

This paper aimed at identifying risk factors for baseline CRCI in a group of general cancer patients scheduled for a curative treatment. Our data highlights the importance of conducting an IQ test when conducting neuropsychological assessments in cancer patients. Results indicated that CRCI, which is defined as presenting with two or more test scores at or below -1.5 SDs from the normative mean or presenting with one test score at or below -2.0 SDs, was predicted by premorbid IQ and fatigue. Further, individual neuropsychological test scores were all influenced by premorbid IQ. Some cognitive domains were also predicted by gender, age, having a breast cancer diagnosis or not and/or by an active treatment for hypertension.

Our results indicate that IQ predicts baseline CRCI. To our knowledge, we are the first to report this finding in case of overall CRCI. Our data also indicate that IQ influences individual cognitive domains. These results are in line with previous literature as the IQ of a patient has been reported as a strong predictor of neuropsychological test scores in both cancer and non-cancer subjects. Diaz-Asper et al. (2004) evaluated the influence of IQ on several individual cognitive tests in 221 normal adults and stated that IQ predicts concurrent neuropsychological performance across the entire spectrum of intelligence [356]. In a group of breast cancer patients exposed to chemotherapy, Ahles et al. (2010) reported that pre-treatment cognitive reserve, assessed by the Wide Range Achievement Test-3 (WRAT-3) was related with post-treatment cognitive decline [146]. Further, the data of Schilder et al. (2010) is in accordance with our findings. They reported IQ to be a predictor of individual cognitive domains in a group of postmenopausal breast cancer patients before the administration of adjuvant systemic treatment [334]. Lange et al. (2014), however, examined baseline cognition in older cancer patients and could not detect any correlations between CRCI and clinical characteristics [145]. When comparing our data to the binomial probability distribution we detected a statistical significant result ($p<0.001$) stating that the number of impaired CRCI can only in part be explained by normal variance.

In our study, overall CRCI was also predicted by fatigue. Although it has been noted that fatigue influences subjective cognitive complaints in cancer patients, most studies have failed to find an association between objective CRCI and fatigue [357-359]. Booth-Jones et al. (2005) examined the cognitive function of patients who underwent a bone marrow transplantation and reported that both objective and subjective cognitive impairments are influenced by the level of fatigue [360]. Further, recent research by Menning et al. (2015) found that symptoms of fatigue were related to observed impairments in breast cancer patients when compared to healthy controls, prior to adjuvant treatment [143].

Our data suggest that age could predict processing speed, executive function, verbal episodic memory and semantic word fluency. This finding is in accordance with the results of Lange et al. (2014) who examined baseline cognition in older breast cancer patients. They reported that more than 40% presented with a CRCI at baseline and that respectively 15%, 16% and 21% of patients presented with an impairment in the domain of processing speed, executive function or verbal episodic memory [145]. Further, age-related decline on cognitive functioning has also been noted in non-cancer subjects [361]. For example, Kramer et al. (2003) stated that older healthy subjects could present with poorer verbal memory results when compared to their younger counterparts [362].

Verbal episodic memory, as measured by the RAVLT delayed recall was also predicted by gender. These findings are in line with Kramer et al. (2003) who found comparable results in a group of healthy individuals. In their study, they have noted that men perform worse on a delayed recall test [362].

Our data further indicates that an active treatment for hypertension predicts in part the outcome on the WAIS-III Digit Span, which measures attention. It is known that hypertension influences cognitive performance. Knecht et al. (2009) reported that hypertension might account for one-tenth of the cognitive impairments found in non-demented community-dwelling subjects [363]. Schilder et al. (2010) confirms this finding in a group postmenopausal breast cancer patients [334]. This finding is a reminder that cancer occurs within the context of multiple comorbidities that could each have its own influence on the patient's cognitive abilities and that it is important to consider these when conducting clinical trials on CRCI.

A breast cancer diagnosis seems to affect performance on the WAIS-III Digit Symbol. Although we could not find evidence to support this finding at baseline, Schagen et al. (1999) reported that breast cancer patients who were treated with chemotherapy (cyclophosphamide, methotrexate and 5-fluorouracil, a somewhat outdated treatment scheme nowadays) performed worse on the WAIS Digit Symbol compared to breast cancer patients who did not receive chemotherapy [364]. As previously mentioned, research on CRCI mainly focusses on breast cancer patients. A possible explanation for this may be that breast cancer patients are more emotionally open and express side effects quicker than others. In our trial, comprising 44% breast cancer patients, we found that – although not statistical significant, breast cancer patients experienced more subjective cognitive complaints compared to other cancer patients. On the contrary, a fewer percentage of breast cancer patients than others were found to have CRCI (not significant, data not shown).

The strengths of this study include several aspects. Firstly, although it is also listed as a limitation, we did include several cancer types. It is known that most research on CRCI is performed in breast cancer patients and that this is a shortcoming in current literature. Although more researchers have gained interest in other cancer types, highlighting that not solely breast cancer patients experience CRCI remains important. Further, as a result of including a high number of breast cancer patients, we were able to use this as a covariate in our analysis making it possible to see if breast or rather other cancer patients are more prone to certain cognitive impairments. Secondly, we used the DART to examine IQ, which is a quick and easy assessment tool. Other trials, investigating mainly post-adjuvant treatment CRCI, used tests such as the Wide Range Achievement Test (WRAT) [146, 365]. Although clinically useful to screen for premorbid intelligence, the WRAT can take up to 45 minutes to administer depending on the age the patient, therefore making it less useful to add to an already exhaustive list of neuropsychological tests. Thirdly, this trial includes a wide range of cognitive domains and implements a number of tests that are advised by the ICCTF [148]. Further, we also chose to use their definition of CRCI in order to facilitate comparing trial results with others. Lastly, our study tried to confirm findings of the few researchers who have reported predictors of baseline CRCI in cancer patients.

The results of our analysis need to be interpreted with caution. First, we did not include a healthy control group. Nevertheless, we compared our findings with the binomial probability distribution. We estimated that approximately 17% of patients would score at least two SDs below the normative mean on a single test score when using a neuropsychological assessment including eight independent tests. Results found a statistical significant difference indicating

that our selected population differs from healthy subjects, thus only in part explaining the influence of IQ, which is a known confounder of neuropsychological tests [335]. Second, we have included patients of all cancer types and did not find a normal distribution across the cancer types. Although we believe that it is necessary to perform these studies in patients diagnosed with all cancer types, it may mask certain differences. Nonetheless, statistical analysis revealed that the cancer type did not influence overall impairment. Having a breast cancer diagnosis did influence the outcome on the WAIS Digit Symbol. Further research is warranted to compare breast and other cancer patients. Third, some neuropsychological tests, such as the RAVLT and CFT, did not provide optimal z-scores for older patients. Z-scores can only be calculated in three age categories (>30 years, 30-50 years, <50 years) which may result in more impairments in older patients due to this shortcoming in the normative data. On the other hand, when conducting the regression analyses, age was included as a covariate. Further, the linear regression analyses used raw test score instead of z-scores. Raw scores were selected in order to be able to compare our results with findings of other researchers. Therefore, the age and IQ effect may be more present in these results. Nonetheless, when using the standardized z-scores, IQ effects remain present in all domains. The influence of age remains present in the RAVLT and both conditions of the TMT (data not shown).

To the best of our knowledge, this paper is the first to report baseline cognition of a heterogeneous group of cancer patients scheduled to receive a curative treatment. Although future research is needed to confirm our findings regarding medical and psychosocial factors such as fatigue in particular, we advise other researchers to include a short IQ evaluation such as the DART, which is quick and easy to administer, when conducting neuropsychological assessments in clinical trials investigating CRCI.

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CHAPTER 4

The use of the Distress Thermometer as a screening tool for cognitive dysfunctions in a general cancer population undergoing curative treatment

PART II

The Distress Thermometer predicts subjective, but not objective, cancer-related cognitive complaints six months after treatment initiation in cancer patients receiving a curative cancer treatment

Based on

The Distress Thermometer predicts subjective, but not objective, cognitive complaints six months after treatment initiation in cancer patients

Lycke M et al. *Journal of Psychosocial Oncology*. 2017

Abstract

OBJECTIVE

Research has indicated that cancer-related cognitive impairments (CRCI) may be influenced by psychosocial factors such as distress, worry and fatigue. Therefore, in this trial, we aimed to validate the distress thermometer (DT) as a screening tool to predict CRCI six months post treatment initiation in a group of general cancer patients.

METHODS

Patients (≥18 years, n=106) with a histologically confirmed diagnosis of a solid cancer or haematological malignancy, scheduled for a curative treatment, were evaluated at baseline (T0) and six months post-treatment initiation (T1) by a neuropsychological assessment including patient-reported outcome measures (PROMs). Assessed cognitive domains included premorbid intelligence, attention, processing speed, flexibility, verbal and visual episodic memory and verbal fluency. PROMs entailed distress (Distress Thermometer (DT), cut-off ≥4, range 0-10), anxiety and depression (Hospital Anxiety and Depression Scale), fatigue (FACIT-fatigue scale) and subjective cognitive complaints (Cognitive Failure Questionnaire).

RESULTS

At T0, 60.4% of patients showed a DT score of ≥4, whereas 50% met this criterion at T1. According to the definition of the International Cognition and Cancer Taskforce, 25.5% and 28.3% of patients presented with a CRCI at T0 and T1, respectively. When evaluating the DT as a screening tool for CRCI at T1, data showed an inverse relationship between the DT and CRCI with an AUC<0.5. ROC-curve analyses evaluating the DT and FACIT-fatigue scale as screening tools for subjective cognitive complaints showed an AUC±SE of respectively 0.642±0.067 and 0.794±0.057.

CONCLUSION

The DT failed to predict objective CRCI at T1 but both the DT and FACIT-fatigue scale showed potential to be used as screening tools for subjective cognitive complaints.

INTRODUCTION

Chemobrain - a term coined to describe cancer-related cognitive impairment (CRCI) - is a common concern among cancer patients receiving chemotherapy [113, 116]. It may influence cognitive functioning such as executive functioning, processing speed, working memory and organizational skills. CRCI can have a detrimental effect on a patient's quality of life (QoL), influencing one's ability to use complex thinking in making treatment decisions [120-122, 330, 366]. CRCI can persist throughout the whole illness trajectory and in some domains, complaints remain present long after therapy has ended [124]. A clear understanding of CRCI is crucial as there is a growing group of cancer survivors who have difficulties resuming their former activities [113].

It has been noted that CRCI can be already observed before the administration of systemic chemotherapy [367]. As a result, some authors suggest an association with psychological risk factors such as distress, worry and fatigue [134, 137, 368, 369]. Distress is defined as a multifactorial unpleasant emotional experience of psychological, social and/or spiritual nature that may interfere with the ability to cope with cancer effectively, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fear to problems that can become disabling such as depression, anxiety, panic, social isolation, and existential and spiritual crisis [370]. Studies have noted that up to 47% of newly diagnosed and recurrent cancer patients presented with a significant level of mental distress, to an extent that they can be diagnosed with a psychiatric disorder [371]. The NCCN Guidelines in Distress Management recommend an early evaluation and screening of distress as it leads to poorer QoL if left untreated. Therefore, the NCCN Distress Management Panel developed the distress thermometer (DT) which uses an 11-point rating scale to identify distress caused by any kind of source, even if unrelated to cancer [351, 372]. Other factors, including hypertension and diabetes mellitus, were also reported as potential confounders of CRCI [373].

In this paper, we present the primary and predefined clinical secondary endpoints of the CONCEPT-trial (ClinicalTrials.gov Identifier: NCT01846260) in which we sought to examine the feasibility of the DT as a screening tool to predict CRCI in a group of general cancer patients receiving a curative treatment. As screening for distress is already implemented in routine care, this would allow a faster identification of patients who are prone to develop CRCI. Further, we analysed objective versus subjective cognitive complaints, examined cognitive changes over time and compared assessment results of patients with (C+) and without (C-) chemotherapy.

METHODS

Participants

Patients were invited to participate in the CONCEPT-trial between May 2013 and September 2015. All patients were recruited in the Kortrijk Cancer Centre, Kortrijk, Belgium. All patients were aged 18 years or above and had a histologically confirmed diagnosis of a solid tumour (lung, gastro-intestinal, GIST, urological, breast, sarcoma or gynaecological cancer) or haematological malignancy, in an early or advanced stage. Patients were scheduled to receive a treatment (radiotherapy, chemotherapy, radiochemotherapy, radiobiotherapy, anti-hormonal, targeted therapy or a combination of the above) with curative intent. Patients receiving surgery as a sole treatment were not allowed to participate. Other exclusion criteria included: a diagnosis with primary or secondary brain tumours, having a prior history of cancer during the

last 5 years, with or without chemotherapy or radiotherapy, suffering from an organic brain syndrome, having an untreated or unstable major medical condition other than cancer, being alcohol or drug dependent, showing signs of mental deterioration based on the investigator's judgement or pre-trial routine assessments, being diagnosed with dementia (DSM-IV criteria), presenting with a condition other than cancer in which fatigue is a prominent symptom (such as chronic fatigue syndrome) and having a major psychiatric or neurologic disorder that could potentially invalidate assessment; a prior or current diagnosis of a depressive or anxiety disorder was allowed since many cancer patients may suffer from this as a consequence of the cancer diagnosis. The trial was approved by the ethics committee of the General Hospital Groeninge, Kortrijk, Belgium and all patients gave written informed consent.

Measures

Patients were evaluated by a neuropsychological assessment (Table 1) including patient-reported outcome measures (PROMs, Table 2) at baseline (T0) and six months post-treatment initiation (T1) [374].

The neuropsychological test battery assessed the following cognitive domains: premorbid intelligence (Dutch Adult Reading Test (DART) [375]), episodic memory (visual: Rey's Complex Figure Test (CFT) delayed recall test [376]; verbal: Rey's Auditory Verbal Learning Test (RAVLT) delayed recall test [341]), executive functions (flexibility: Trail Making Test (TMT) number-letter sequencing [343]; phonetic and semantic word fluency: Controlled Oral Word Association Test (COWA) [344]; processing speed: TMT number sequencing [343] and WAIS-III Digit Symbol [348]) and working memory (attention: WAIS-III Digit Span [348]). An alternative form was used to minimise practice effect in case of the Rey's Auditory Verbal Learning Test (RAVLT) [341]. All assessments were performed by either a neuropsychologist (MSc) or study trial coordinators (MSc, PhD) trained to perform these measurements.

PROMs included an assessment of distress (Distress thermometer (DT) and 39-item Problem List [372]), anxiety and depression (Hospital Anxiety and Depression Scale (HADS) [351]), fatigue (FACIT Fatigue Scale [352]) and subjective cognitive complaints (Cognitive Failure Questionnaire (CFQ) [377]).

Table 1. Neuropsychological assessment

Cognitive domain	Test	Item	Outcome measure	Range
Premorbid intelligence	Dutch Adult Reading Test (DART)	IQ estimation	IQ estimation	≥ 0
Episodic memory				
Visual	Rey's Complex Figure Test (CFT)	Delayed recall	Total score	0 – 36
Verbal	Rey's Auditory Verbal Learning Test (RAVLT)	Delayed recall	Total score	0 – 15
Executive functions				
Flexibility	Trail Making Test (TMT)	Condition 4 (number-letter sequencing)	Time needed to complete in seconds	≥ 0
Semantic word fluency	Controlled Oral Word Association Test (COWA)	Animals	Number of correctly produced words in 60 seconds	≥ 0
Phonetic word fluency	Controlled Oral Word Association Test (COWA)	letter N	Number of correctly produced words in 60 seconds	≥ 0
Processing speed	Trail Making Test (TMT)	Condition 2 (number sequencing)	Time needed to complete in seconds	≥ 0
	WAIS-III Digit Symbol		Number of correct items	≥ 0
Working memory				
Attention	WAIS-III Digit Span	Forward & Backward span	Total score	0 – 30

WAIS: Wechsler Adult Intelligence Scale

Table 2. Patient-reported outcome measures

Measure	Indication	Range	Cut-off
Distress thermometer (DT) and 39-item Problem List	Distress	0-10	≥4
Hospital Anxiety and Depression Scale (HADS)	Anxiety	0-21	≥8
	Depression	0-21	≥8
FACIT Fatigue Scale	Fatigue	0-52	NA (lower score indicates greater fatigue)
Cognitive Failure Questionnaire (CFQ)	Subjective cognitive complaints	0 – 100	≥43

FACIT: Functional Assessment of Chronic Illness Therapy; NA: not applicable

Statistical considerations

Statistical analyses were conducted by use of SPSS software (version 23; IBM SPSS Statistics, Chicago, IL). Descriptive statistics were performed to present patient and tumour characteristics and neuropsychological assessment results. In accordance with the

International Cognition and Cancer Task Force (ICCTF), patients were marked as having a cognitive impairment if they either presented with two or more test scores at or below -1.5 standard deviations (SDs) from the normative mean or if they presented with one test score at or below -2.0 SDs [148]. Published normative data, adjusted for gender, age and/or education, were used to convert raw test scores into standardized z-scores (mean = 0; SD = 1), if applicable. Data from questionnaires were converted according to standard scoring rules.

It was assumed that the neuropsychological assessment was the gold standard against which the DT was compared. Sample size calculations were based on following assumptions. A sample of 21 from the positive group and 63 from the negative group would achieve 81% power to detect a difference of 0.20 between the area under the roc curve (AUC) under the null hypothesis of 0.50 and an AUC under the alternative hypothesis of 0.70 using a two-sided z-test at a significance level of 5%.

Paired-sample T-tests were performed to detect differences between neuropsychological test scores at T0 and T1 for all patients together and for the C+ and C- group separately. Univariate analysis of variance, adjusted for age and IQ, were selected to compare results at T1 between the C+ and C-group. Binary logistic regression analysis was performed in order to find predictive factors of CRCI. Regression analysis included 13 covariates: age, gender, premorbid IQ, distress level, fatigue level, cognitive complaints, days since diagnosis, surgery (yes or no), active treatment for diabetes mellitus, active treatment for hypertension, stage (early vs. late stage), treatment (chemotherapy: yes or no) and diagnosis (breast cancer or not). Variables were included in the model if they were significant at the $p<0.05$ level.

RESULTS

Patient characteristics

In total, 125 patients were included in the trial. Baseline patient characteristics are previously described [367]. Of the 125 patients, 106 (84.8%) completed the second assessment (Table 3). Five patients withdrew from the trial without giving a specific reason, five patients felt too ill, four patients did not want to make the extra travel to the hospital, three patients had died as a consequence of their disease or treatment and two patients declared to have no time. At T0 and T1, respectively one and five patients did not fully complete the PROMs. The mean age of the remaining 106 patients was 59.0 years (range: 30.0-85.0). Patients were more likely to be female (69.8%) and presented with following cancer types: breast (48.1%), gastro-enterological (24.6%), genitourinary (11.3%), gynaecological (9.4%), haematological (5.7%) and lung (0.9%). More patients had an early stage disease (65.1%). Exactly half of patients (50.0%) received (neo)adjuvant chemotherapy with or without radiotherapy and/or hormonal treatment. Other patient characteristics and chemotherapy regimens are presented in Table 3.

Table 3. Demographic and clinical data (n=106)

Demographics	**n (%)**
Gender	
Female	74 (69.8)
Male	32 (30.2)
Highest education	
Primary education	0 (0)
Lower secondary education	25 (23.6)
Higher secondary education	42 (39.6)
Higher education	34 (32.1)
Other	5 (4.7)
Clinical data	
Stage	
Early (I-II)	69 (65.1)
Advanced (III-IV)	37 (34.9)
Surgery prior to T1	95 (89.6%)
Treatment	
Hormonal treatment alone	1 (0.9)
Radiotherapy alone	7 (6.6)
Chemotherapy alone	29 (27.4)
Radiochemotherapy	20 (18.9)
Radiotherapy and hormonal treatment	45 (42.5)
Chemotherapy and hormonal treatment	1 (0.9)
Radiochemotherapy and hormonal treatment	3 (2.8)
Chemotherapy (n=53)	
Folfox	12 (22.6)
Cisplatin w/o other compound	10 (18.9)
Carboplatinum with taxane derivate	9 (17.0)
5FU	8 (15.1)
FEC w/o taxotere	3 (5.6)
Cyclofosfamide with taxane derivate	3 (5.6)
AC with paclitaxel	2 (3.8)
ABVD	2 (3.8)
Gemcitabine	2 (3.8)
RCHOP21	2 (3.8)

FU: fluorouracil, FEC: fluorouracil, epirubicine, cyclofosfamide, AC: adriamycine, cyclofosfamide, ABVD: doxorubicine, bleomycine, vinblastine, dacarbazine, RCHOP: rituximab, vincristine, adriamycine, cyclofosfamide, prednisone

Primary endpoint results

At T0, 60.4% of patients showed a DT score of ≥4, whereas 50% met this criterion at T1. According to the definition of the ICCTF, 25.5% and 28.3% of patients presented with a CRCI at T0 and T1, respectively. When evaluating the DT as a screening tool for CRCI at T1, ROC-curve analysis revealed an AUC <0.5. Binary logistic regression analysis found that less distress at T0 (B=-0.267, p<0.05), having a lower premorbid IQ (B=-0.066, p<0.05), female

gender (B=1.861, *p*<0.05) and no surgery (B=-1.745, *p*<0.05) predicted CRCI at T1. Chemotherapy did not influence the risk on CRCI (B=0.186, *p*=0.666).

CRCI vs. cognitive complaints

At both time points, only a small percentage of patients stated to have cognitive complaints based on a Cognitive Failure Questionnaire (CFQ) score of 43 or higher (14.3% at T0, 16.8% at T1). Fig 1.A and 1.B show the number of patients with a CRCI at T0 and T1 subdivided by a CFQ-score of ≥43. At baseline, the distribution of cognitive complaints was more or less equal in both groups (Fig. 1.A). At T1, more patients experienced subjective cognitive complaints (Fig. 1.B). Surprisingly, the majority of these patients were not diagnosed with a CRCI. ROC-curve analyses evaluating the DT and FACIT-fatigue scale as screening tools for subjective cognitive complaints showed an AUC±SE of respectively 0.642±0.067 and 0.794±0.057 (Fig. 2.A and 2.B).

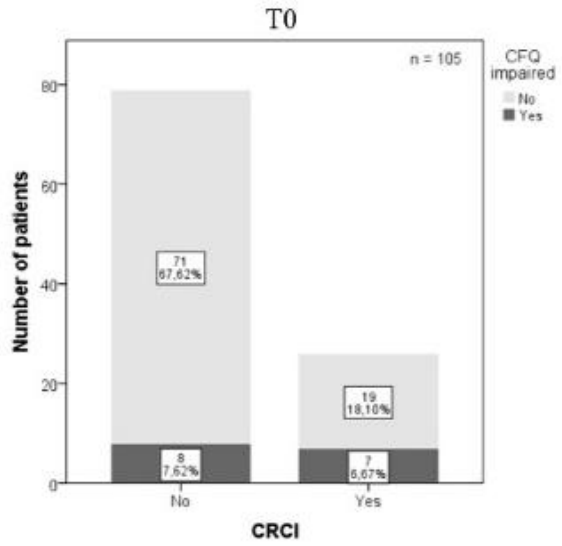

Fig. 1.A Objective versus subjective impairment at T0

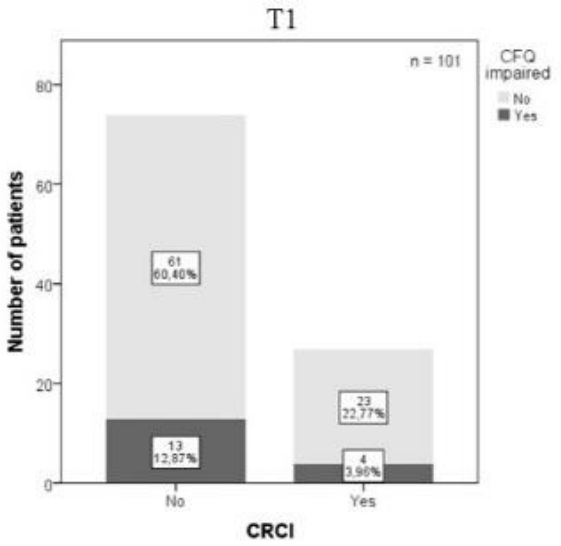

Fig. 1.B Objective versus subjective impairment at T1

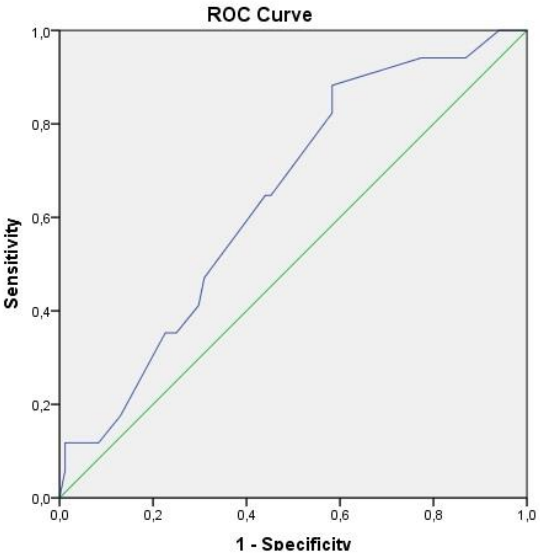

Fig. 2.A ROC-curve of the distress thermometer vs. CFQ score ≥43

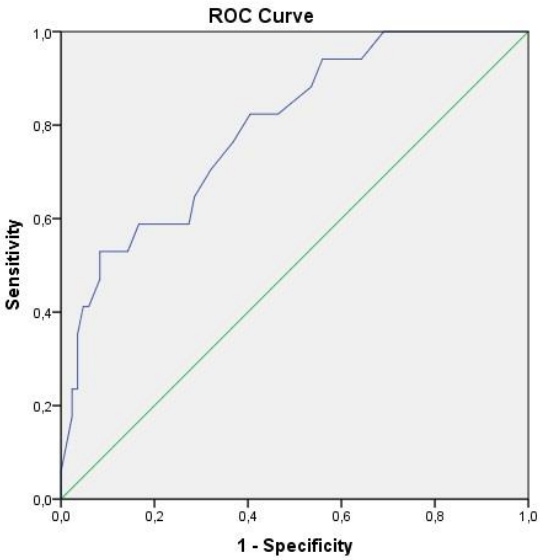

Fig. 2.B ROC-curve of the FACIT-Fatigue scale vs. CFQ score ≥43

Cognitive changes and subgroup analyses

Table 4 and 5 show mean PROM scores and mean raw scores per cognitive test at T0 and T1 for all patients and for the C+ and C-group independently. Paired-samples T-test detected significant differences for the WAIS-III Digit Symbol, RAVLT delayed recall and CFT delayed recall when comparing T0 and T1 in all patients. An improved performance over time was found in all tests except for the RAVLT delayed recall test.

Mean age and mean education age of the C+ group was calculated as 57.8 and 18.7 years, respectively, whereas the C- group had a mean age of 60.2 years and a mean education age of 18.5 years. Mann-Whitney U test did not detect statistical significant differences in terms of age and education age (p=0.459 and p=0.430, respectively). The C+ and C- group both comprised primarily female individuals (58.5% and 81.1%, respectively). However, a significant difference was detected (X^2 test: p<0.05). Table 4 and 5 show mean PROM and neuropsychological test scores, respectively, at T0 and T1 for the C+ and C- group. Distress decreased over time for the C+ group and slightly increased in the C- group. C+ patients also showed significant lower distress at T1 compared to C- patients (p<0.01). Similar results in terms of other PROMs and cognitive changes, compared to all patients together, were found for both the C+ and C-group. A better performance on neuropsychological tests was found at T1 in all domains except for the RAVLT. In both groups, significant within group differences, indicating decreased performance at T1, were found for the RAVLT and CFT delayed recall between T0 and T1. The C+ group also showed significant within group differences for the WAIS-III Digit Span, WAIS-III Digit Symbol and TMT letter-number sequencing. Univariate analyses of variance, adjusted for age and IQ, did not reveal any significant differences between the C+ and C-group in case of individual cognitive domains at T1 (Table 5).

Table 4. Mean PROM scores of all patients, C+ patients and C- patients at T0 and T1

	All patients		**C+ group**		**C- group**		***C+ vs. C- ****
	T0 Mean (SD)	**T1 Mean (SD)**	**T0 Mean (SD)**	**T1 Mean (SD)**	**T0 Mean (SD)**	**T1 Mean (SD)**	***p*-value between groups at T1**
Distress Thermometer score	4.4 (2.4)	3.6 (2.5)	4.7 (2.5)	2.9 (2.3)	4.1 (2.2)	4.3 (2.5)	**<0.01**
p-value within group	**<0.01**		**<0.001**		0.666		
HADS	9.7 (6.9)	8.5 (6.8)	10.4 (7.6)	7.8 (6.1)	9.0 (6.1)	9.2 (7.4)	0.381
p-value within group	**<0.01**		**<0.001**		0.838		
FACIT Fatigue Scale	38.7 (9.5)	39.0 (8.8)	38.4 (10.6)	38.3 (8.7)	38.9 (8.4)	39.7 (9.0)	0.349
p-value within group	0.651		0.768		0.295		
CFQ	28.5 (12.8)	28.6 (15.2)	27.7 (11.8)	27.2 (12.8)	29.3 (13.7)	29.9 (17.3)	0.573
p-value within group	1.000		0.711		0.704		

Abbreviations: SD: standard deviations, HADS: hospital Anxiety and Depression Scale, FACIT: Functional Assessment of Chronic Illness Therapy, CFQ: Cognitive Failure Questionnaire

Table 5. Mean raw scores of all patients, C+ patients and C- patients at T0 and T1

	All patients		**C+ group**		**C- group**		***C+ vs. C-*** *****
	T0 Mean (SD)	**T1 Mean (SD)**	**T0 Mean (SD)**	**T1 Mean (SD)**	**T0 Mean (SD)**	**T1 Mean (SD)**	***p*-value between groups at T1**
COWA semantic word fluency	22.6 (6.8)	23.0 (7.0)	21.6 (5.6)	22.9 (6.3)	23.5 (7.8)	23.1 (7.8)	0.738
p-value within group	0.408		0.075		0.610		
COWA phonetic word fluency	10.4 (4.9)	10.8 (4.8)	10.6 (5.0)	10.5 (4.8)	10.3 (4.7)	11.1 (4.8)	0.413
p-value within group	0.306		0.827		0.069		
WAIS-III Digit Span	10.6 (3.2)	10.9 (3.3)	10.4 (3.3)	11.1 (3.2)	10.7 (3.0)	10.8 (3.4)	0.452
p-value within group	0.116		**<0.05**		0.878		
WAIS-III Digit Symbol	66.8 (19.5)	68.3 (19.6)	66.9 (18.9)	69.4 (18.6)	66.6 (20.2)	67.3 (20.6)	0.860
p-value within group	**<0.05**		**<0.05**		0.547		
RAVLT delayed recall	10.9 (3.5)	10.0 (3.7)	10.7 (3.1)	9.8 (3.4)	11.2 (3.8)	10.2 (4.0)	0.403
p-value within group	**<0.001**		**<0.05**		**<0.01**		
CFT delayed recall	20.2 (4.8)	22.5 (5.4)	20.4 (4.7)	22.2 (5.2)	19.9 (4.9)	22.9 (5.7)	0.396
p-value within group	**<0.001**		**<0.01**		**<0.001**		
TMT number sequencing	39.8 (18.2)	38.6 (18.9)	38.0 (15.7)	36.7 (17.0)	41.6 (20.4)	40.4 (20.6)	0.548
p-value within group	0.294		0.432		0.492		
TMT number-letter sequencing	93.7 (47.7)	87.9 (43.0)	94.3 (45.1)	84.3 (38.8)	93.2 (50.5)	91.5 (46.8)	0.599
p-value within group	0.094		**<0.05**		0.777		

*cognitive domains adjusted for age and IQ. Abbreviations: SD: standard deviations, COWA: Controlled Oral Word Association, WAIS: Wechsler Adult Intelligence Scale, RAVLT: Rey's Auditory Verbal Learning Test, CFT: Complex Figure Test, TMT: Trail Making Test

CONCLUSION

We aimed at 1) validating the widely used DT as a screening tool to predict CRCI in a group of general cancer patients scheduled for curative treatment, 2) evaluating objective CRCI versus subjective cognitive complaints, 3) analysing cognitive changes over time and 4) comparing assessment results of C+ and C- patients. Our data showed that the DT failed to predict CRCI at T1. On the contrary, baseline PROMs including the DT and FACIT-fatigue scale were able to predict subjective cognitive complaints at T1. We found a lower verbal memory performance in all patients over time. Further, we did not detect differences on neuropsychological test scores at T1 between C+ and C-patients.

To our knowledge, this is the first study that looked into in the feasibility of the DT as a screening tool to predict CRCI six months post-treatment initiation. In our sample, respectively 25.5% and 28.3% of patients presented with a CRCI at T0 and T1. We stated that we would only accept the DT as a screening tool if we would find an AUC of at least 0.70. Unexpectedly, we found a trend for an inverse relationship between the degree of distress and the risk on CRCI with an AUC<0.5 indicating that patients with a CRCI indicate a lower distress level. A possible explanation for this finding may be that cognitively impaired patients do not acknowledge the impact of their diagnosis and upcoming treatment and that they would therefore indicate a lower degree of distress.

Our data indicate that IQ, no surgery and gender may also influence CRCI at T1. We previously reported that IQ predicts baseline CRCI in cancer subjects [367]. It has also been reported that IQ influences neuropsychological test scores [356]. Surprisingly, patients not receiving surgery are more at risk of developing CRCI at T1. A possible explanation may be that those patients had a (non-significant) lower premorbid IQ than patients who did receive surgery (data not shown). Further, female gender also increased CRCI risk. In our sample, this may be a result of including a high number of female individuals (69.8%) with the majority of those being diagnosed with breast cancer (68.9%). Gender differences have been observed previously by Lezak et al. (2012) in non-cancer subjects [378]. On the contrary, Visovatti et al. (2016) could not confirm these findings in a group of colorectal cancer patients [144]. A difference should be made between having a CRCI at T1 and the development of CRCI from baseline to T1. In our sample, 12 patients had no CRCI at baseline and developed CRCI by the time assessment six-months post treatment initiation. While 12 patients are a rather small group for statistical analysis, data showed no difference in terms of treatment, but did indicate a mean increase of in fatigue level in these patients (data not shown). Another interesting question is why breast cancer patients seem to be more prone to have cognitive troubles after their treatment has ended. One explanation may be that the breast cancer patients included in our trials, of which the majority only received radiotherapy followed by hormonal treatment, experience more distress as a results of less close follow up compared to the C+ group where the period between the end of the treatment and the second assessment was much shorter (data not shown). However, more research is necessary to look into these hypotheses.

When comparing objective test scores with subjective cognitive complaints, results did not fully match. This is in line with Hutchinson et al. (2012) who stated that objective and perceived impairment could be unrelated because subjective complaints may be an indicator of distress, rather than of CRCI [379]. Interestingly, ROC-curve analysis indicated that the DT and certainly the FACIT-fatigue scale at T0 could be used to predict cognitive complaints in cancer patients

six months post treatment initiation. Although it has been reported that distress and fatigue influences self-reported cognition [380], we are – to our knowledge – the first to report upon the possibility predicting cognitive complaints by use of the DT and FACIT-fatigue scale. It is known that stress may induce cognitive changes [137]. Nonetheless, these findings further highlights the importance of the early detection of psychosocial problems so that appropriate care can be implemented. A prospective trial, however, should be set up to confirm these findings.

We compared test scores at T0 and T1 of the individual cognitive domains. Most scores improved over time which can be attributed to the practice effect [133]. The RAVLT delayed recall showed decreased performance at T1. Similar results were found when comparing the C+ and C- group. Worse RAVLT performance over time has not always been found in other studies. Deprez et al. (2012) for example found worse performance in C+ patients, but increased scores in C- patients and healthy controls [381]. In our trial, the RAVLT was the last test to be assessed in the test battery and was further the only test for which an alternative form was used. Therefore, we are left to speculate that lower results could be influenced by these factors.

Further, we compared C+ and C- patients of all cancer types. Between group analyses did not detect any differences between test scores at T1. Although, it has been suggested that chemotherapeutic regimens may result in lower cognitive performance, researchers have not reached a consensus on the exact pathophysiology [382]. Further, others have previously suggested that the influence of chemotherapy in the etiology of CRCI may be smaller than initially thought [383]. A reason why no difference was found could be the result of the different types of regimens included in the trial. Patients were allowed to participate in this trial regardless their type of chemotherapy. Further, it has been reported that the effects of cytotoxic drugs on cognition can recover over time [384]. The type of cytotoxic drug probably did not affect neuropsychological test score, as all were considered neurotoxic in some level (data not shown). As some patients only received a short chemotherapy schedule, cognitive decline may have been present shortly after treatment had ended. Another reason could be attributed to the dose of the chemotherapy patients received as it has been stated that high-dose chemotherapy appears to impair cognitive functioning more than standard-dose chemotherapy [385]. Data is not available regarding this matter and can therefore not be assessed.

The strengths of this study include multiple aspects. First, we are the first to examine the feasibility of the DT to predict CRCI in a group of general cancer patients. Although we obtained a negative result, we found that the DT might be able to predict subjective cognitive complaints. We also found that fatigue seems to have a high impact on patient-perceived impairment and that it may be possible to predict cognitive complaints with the FACIT-fatigue scale. These findings emphasize that it is crucial to address psychosocial issues and that it is essential to identify those at the beginning of the treatment. By using questionnaires, which are already used in routine practice, such as the DT, screening for cognitive complaints could be easily implemented. Second, this trial included a variety of cancer types. Other research mainly focused on breast cancer patients. Nevertheless, other cancer patients also experience cognitive disturbances. Third, we have included an equal amount of patients who did and who did not receive chemotherapy. Therefore, we were able to compare assessment results of both groups. An interesting finding was that we did not detect any differences in any of the assessed cognitive domains at T1 between the C+ and C- group. Although imaging studies have shown that white matter integrity may be altered as a result of chemotherapy [131, 381], our data suggest that processes other than the chemotherapeutic regimen may induce CRCI. This confirms that the term ‘chemobrain’ may have been an unfortunate choice.

The results of this trial also need to be interpreted with caution. We did not include a healthy control group. We were however able to compare assessment results of cancer patients with and without a chemotherapeutic treatment. As a result, we were able to compare cognitive outcomes of C+ and C- patients. On the other hand, when comparing the number of impaired patients to the binomial probability distribution [355, 367], we found significantly more impaired patients in our sample at both time points (data not shown). This suggests that other factors may also play a role in the existence of CRCI. One of those factors that was not assessed within this trial is coping. It has been mentioned that effective coping strategies could act as a protective factor for individuals who have a high risk for CRCI. Nonetheless, the way a patient deals with cancer influences distress and it could therefore be stated that coping and distress are correlated [386, 387]. The same could be said for depression [388]. Nonetheless, it has to be mentioned that distress is a multifactorial variable that includes a variety of emotions such as coping, but also anxiety and worry. Therefore, when assessing distress, these factors are indirectly taken into account. On the other hand, lower levels of distress and thus lower levels of subjective cognitive complaints, could have been the results of closer psychological support between the baseline assessment and T1. Though this was not monitored, it should be mentioned that psychological support is offered to all patients at the beginning of their cancer treatment trajectory. Further, we did not obtain a balanced distribution of cancer types and included a high number of breast cancer patients. As initial research focuses on breast cancer patients, being able to include 'having a breast cancer diagnosis' as a confounding factor in the regression analyses was interesting. Especially since this variable did not predict CRCI.

In conclusion, we can state that the DT cannot be used to predict CRCI, but that it can be used as a screening tool to predict subjective cognitive complaints six months after treatment initiation. This trial further indicates that psychosocial factors have an important role in self-reported cognitive complaints and that PROMs may be used to predict those impairments. Addressing these issues is crucial to understanding self-reported cognitive dysfunctions. Last, our findings suggest that variables other than chemotherapy may influence objective cognitive impairments in cancer patients and that more research is warranted to overtake the exact pathophysiology of CRCI in order to select proper treatments.

CHAPTER 5

The use uHear™ as a screening tool for hearing loss in a geriatric oncology population

PART I

Evaluation of uHear™ - an iOS-based application to screen for hearing loss - in older cancer patients undergoing a comprehensive geriatric assessment

Based on

Implementation of uHear™ - an iOS-based application to screen for hearing loss - in older cancer patients undergoing a comprehensive geriatric assessment

Lycke M et al. *Journal of Geriatric Oncology*. 2016

Abstract

OBJECTIVE

Validation of uHear™ as a screening tool to detect hearing loss in older cancer patients as part of a Comprehensive Geriatric Assessment (CGA).

METHODS

Patients (≥70 years) with a histologically confirmed diagnosis of cancer, were enrolled at the time of CGA screening. Patients were evaluated by uHear™, which was compared to conventional audiometry as gold standard. We defined a pure-tone average (PTA) of ≥ 40 dB HL as the pass or fail screening cut-off. Validation of uHear™ was defined in terms of diagnostic accuracy through Receiver Operating Characteristics (ROC)-analysis. To accept uHear™, we estimated that the Area Under the ROC-curve (AUC) had to differ significantly from 0.50 with an AUC of at least 0.70. The Whispered Voice Test and Hearing Handicap Inventory for the Elderly were also administered.

RESULTS

Thirty-three patients consented for participation. In one patient, the results of one ear were excluded from the analysis as the patient was documented with a known hearing disorder in that ear. Significant hearing loss, defined by a PTA of ≥ 40 dB HL calculated from the air conduction thresholds at 0.5, 1.0 and 2.0 kHz, was found in 15.4% of tested ears. uHear™ showed excellent diagnostic accuracy with an AUC±SE of 0.98±0.14. It provided maximum sensitivity (100.0%) but poor specificity (36.4%) at our predefined cut-off score of ≥ 40 dB HL.

CONCLUSION

Based on the AUC, uHear™ could be implemented as a screening tool to detect hearing loss in older cancer patients within a CGA. However, as it showed a low specificity, optimization of the cut-off score is necessary.

INTRODUCTION

The cancer incidence is 11-fold higher in patients aged 65 or more than in their younger counterparts [2]. Some older patients may tolerate treatment as well as younger patients, although others might suffer from severe toxicity and may require treatment modifications. For this reason, it is crucial to identify those patients who have an increased risk of developing toxicities [389]. Selecting proper treatments solely based on the information the physician retrieved during the appointment, is a very difficult task. Therefore, a comprehensive geriatric assessment (CGA) has been the key to individualized care in older cancer patients [12, 390]. A CGA is a multidisciplinary evaluation assessing medical, psychosocial and functional capabilities and limitations in older cancer patients. It aims at predicting the functional age of patients including the risk on morbidity and mortality through assessing a wide range of domains such as functional status, cognition, nutrition, emotional status, polypharmacy, comorbidities and sensory dysfunctions including vision and hearing [37, 131, 366, 391].

Presbyacusis is a common problem among older people, affecting 90% of the people aged 80 and older [392]. It is estimated that at least 40% of people aged 65 years and older present with a hearing loss important enough to impair communication [156]. Acoustic deterioration can lead to social isolation [236], seriously affecting patients' ability to function properly whilst difficulties with communication can lead to a significant reduction in quality of life. In addition, poor hearing reflects whether the patient is able to hear instructions regarding potential adverse events, supportive care medications and indications of when to seek medical care [7, 393]. A formal audiogram has been proposed as the gold standard to define patients' hearing status [394]. However, such assessment is time-consuming and requires additional appointments, which may be cumbersome for cancer patients who already need to spend a lot of time in the hospital. Further, many physicians have little or no time to screen for hearing loss, which urges the necessity of a quick and simple screening tool [395].

The content of a CGA is mainly based on the NCCN Guidelines in Older Adult Oncology [131]. As mentioned, NCCN recommends assessing not solely functional domains, but they state that it is also important to take sensory dysfunctions such as vision and hearing, into account. To screen for hearing loss, NCCN advises a whispered voice test in which patients need to occlude an ear while the investigator whispers following sentence: "What is your name?". The patient passes if he hears the sentence and is able to answer it. He fails when he does not succeed in this task. The test is repeated for the contralateral ear [131]. In this paper, we will use the validated Whispered Voice Test (WVT) as the screening tool recommended by NCCN. This WVT has been validated in several studies in non-cancer subjects, and thus not in our target population, but it has shown a good sensitivity, specificity and Area Under the receiver operating characteristics (ROC) - Curve (AUC) [235]. However, various outcomes have been reported especially due to the inter-rater reliability, possibly caused by differences in loudness of the whispering, and thus decreasing the usability of the WVT in clinical practice [236].

The last decade, the use of multimedia applications has increased dramatically. More than six billion cell phones have been sold globally. This consumer-driven demand has led to changes in the society where almost everyone can afford a hand-held computer and communication device. With this growing technology, there are many cultural and infrastructural reasons to adopt cell phones as a vehicle to improve health care [396]. uHear™ was designed by Don Hayes and runs on iOS devices such as iPod, iPad and iPhone. It is easily accessible, free and fast to assess. uHear™ is an ear-level pure-tone hearing test designed to determine air conduction thresholds in each ear independently. The app has been validated for use in a general population and has

shown good performance scores in ruling out moderate hearing loss [257, 397]. In this trial, we aimed at validating uHear™ as a screening tool for hearing loss specifically in older cancer patients as part of a CGA.

METHODS

Patient selection

The registered UHEAR-trial was conducted in older cancer patients at the radiotherapy and oncology departments of the General Hospital Groeninge (Kortrijk, Belgium) from December 2014 till June 2015 (UHEAR-trial; clinicaltrials.gov identifier: NCT02381782). An ethics committee approval was obtained from the ethics committee of the General Hospital Groeninge. Patients were recruited upon presentation at the geriatric oncology clinic, where we try to evaluate all newly diagnosed cancer patients, when they received a CGA as part of routine clinical practice [24, 391, 398]. Eligible patients were at least 70 years old at the time of enrolment and needed to have a histologically confirmed diagnosis of a solid cancer or haematologic malignancy. Any type of treatment and any type of stage were allowed. Patients had to be cognitively able to perform assessments. Ears of patients with a known hearing loss, fitted with hearing aids, clinically diagnosed with Meniere's disease, retrocochlear hearing loss, autoimmune inner ear disease, fluctuating hearing loss or a history of sudden sensorineural hearing loss were excluded from analyses.

Measures

Comprehensive Geriatric Assessment

Hearing tests were assessed as part of a CGA. In routine practice, patients are screened with the Geriatric-8 questionnaire (G8). A cut-off of ≤14 was applied [399]. Patients who screen negative are deemed fit and are not assessed with a full CGA. However, for uniformity purposes, we aimed at assessing all negative screening patients with a complete assessment in this trial.

The CGA comprises following standardized measures asides to specific questions regarding social status: functional status (Activities of Daily Living, Instrumental Activities of Daily Living [48, 49]), physical status (number of falls), nutrition (Mini Nutritional Assessment - Short Form [322]), emotional status (Geriatric Depression Scale – 15 [60]), cognition (MMSE or Freund CDT [51, 330, 366]), polypharmacy (number of drugs) and comorbidities (Charlson Comorbidity Index [324]). Patients were deemed vulnerable if they presented with impairments in two or more domains within the CGA [6, 24, 313].

Audiological evaluation

A trained and certified audiologist performed all audiological measures.

Immitance measurement and pure tone audiometry

A 226 Hz tympanometry was performed with an 85 dB SPL probe tone (Zodiac 901 Middle-ear Analyzer, Madsen Electronics). Pure tone audiometry was conducted in a sound booth by use of a recently calibrated Interacoustics AC3 audiometer. The Hughson-Westlake technique was applied. Air conduction thresholds were established for conventional octave frequencies ranging from 0.25 kHz to 8.0 kHz.

uHear™

uHear™ (version 2.0, Unitron, Victoria, BC, Canada) was performed by use of an iPod touch (iOS version 8.1.2, Apple Inc., Cupertino, California, USA). Standard iPod touch ear buds were used. Testing took place in a quiet hospital room or physician's office. The application contains three modules. In this trial, we used the sensitivity test to determine air conduction thresholds at 0.5, 1.0, 2.0, 4.0 and 6.0 kHz, measured in each ear separately. uHear™ uses a 267ms pulse duration and employs a simple 10 dB down and 5 dB up approach. The lowest threshold with two responses out of three excursions is recorded as the hearing sensitivity [257].

Whispered Voice Test

The WVT was performed by the audiologist when standing behind the patient in a quiet hospital room or physician's office. While not documented, background noise in both types of rooms are comparable as they are all located in moderately busy hospital corridors. The patient had to repeat a set of three different numbers at four decreasing levels of loudness per ear with an angle of 180° azimuth: conversational voice at six inches and at two feet from the ear, and whispered voice at six inches and at two feet from the ear while the patient occluded the external auditory canal of his non-tested ear. The investigator exhaled completely prior to testing in order to ensure an equal intensity level in all assessments. A pass was given if the patient could repeat all three numbers correctly at each level of loudness or if he achieved greater than 50% success over three successive triplet sets. Failure to pass at each level of voice testing is considered indicative for hearing impairment [235].

Hearing Handicap Inventory for the Elderly

The Hearing Handicap Inventory for the Elderly (HHIE) has been developed as a self-assessment tool to assess the impact of hearing loss on the emotional and social adjustment of older patients. It consists of a 13-item subscale based on emotional side effects and a 12-item subscale exploring social and situational consequences. The HHIE scores ranges from 0 to 100 with a cut-off score of ≥43 indicating a significant perceived handicap. Scores ranging from 17 to 42 indicate a mild to moderate perceived handicap [244, 400].

Statistical Analyses

Statistical analyses were conducted by use of SPPS software (version 22; IBM SPPS Statistics, Chicago, IL) and Prism® software (GraphPad Prism 5, Inc., La Jolla, CA). Descriptive statistics were performed to present patient and tumour characteristics. Descriptive statistics were further conducted to present assessment results of both CGA and hearing tests. The Pure-Tone Average (PTA) was calculated as the average air conduction threshold found at 0.5 kHz, 1.0 kHz and 2.0 kHz. We defined a PTA of ≥40 dB HL as the pass or fail screening cut-off as this was proposed by Ventry and Weinstein for individuals aged 65 years or older [246]. Since data did not meet the criteria of normality, Wilcoxon matched-pairs signed-ranks test was used to compare uHear™ and conventional audiometry thresholds. A priori sample size calculations were based on literature review and following assumptions [156, 392]. We assumed that conventional audiometry was the gold standard against which uHear™ was compared. A diagnostic test with an AUC of 0.50 has no diagnostic value (comparable to tossing a coin). We would therefore only accept uHear™ if the AUC significantly differed from 0.50 at the 5% significance level. We aimed to include 63 eligible ears. A sample of 25 from the positive group and 38 from the negative group would achieve 80% power to detect a difference of 0.20 between the AUC under the null hypothesis of 0.50 and an AUC under the alternative hypothesis of 0.70 using a two-sided z-test at a significance level of 0.05. The data are discrete

(rating scale) responses. The AUC is computed between false positive rates of 0.00 and 1.00. The ratio of the standard deviation of the responses in the negative group to the standard deviation of the responses in the positive group is 1.00. Sensitivity and specificity with 95% confidence intervals (95%CI) were calculated at our predefined cut-off score. Positive and negative predictive values were also determined (PPV and NPV, respectively).

RESULTS

Patient Characteristics

In total, 34 patients consented for participation. One patient withdrew during the testing phase due to deterioration of the overall condition. Of the remaining 33 patients or 66 ears, the results of one ear were excluded from the analyses as the patient presented with a known hearing disorder in that ear.

Patients had an average age of 76.4 years (range: 70-85). The majority of patients were males (69.7%). Patients presented with a cancer diagnosis of following sites: haematologic malignancy (33.3%), genitourinary (27.3%), gastro-intestinal (15.1%), breast (9.1%), head and neck (9.1%), gynaecologic (3.0%) and thoracic sites (3.0%). Most patients received systemic treatment (51.5%) and were treated with palliative intent (57.6%) (Table 1).

Patients presented with a mean G8 score of 14.2 (range: 7.0-17.0). The majority of patients (57.5%) screened negative on the G8 and were considered ‘fit’. In all but two patients, cognition was assessed through either MMSE of Freund CDT. All of those (100%) were considered as cognitively adequate. One patient participated in a trial by our group in which a full neuropsychological evaluation is performed. He showed good cognitive functioning (data not shown). One patient did not undergo any form of cognitive screening as he screened negative on the G8 and no full CGA data were obtained.

Table 1. Patient characteristics

Characteristics (n = 33)	**Mean (range)**
Age (years)	76.4 (70-85)
	n (%)
Sex	
Male	23 (69.7)
Female	10 (30.3)
Cancer site	
Haematologic malignancy	11 (33.3)
Genitourinary	9 (27.3)
Digestive	5 (15.1)
Breast	3 (9.1)
Head and neck	3 (9.1)
Gynaecologic	1 (3.0)
Thorax	1 (3.0)
Treatment type	
Systemic	17 (51.5)
Radiotherapy	6 (18.2)
Targeted therapy	6 (18.2)
Combination	3 (9.1)
Other	1 (3.0)
Treatment intent	
Curative	14 (42.4)
Palliative	19 (57.6)

Conventional audiometry vs. uHear™

Tympanometry results were not obtained in five ears since occlusion of the ear canal failed. Most patients presented with normal tympanograms (Table 2). Mean pure-tone air conduction thresholds per frequency as measured by conventional audiometry and uHear™ are presented in Figure 1. Figure 1 further shows the average difference between both tests at 0.5, 1.0, 2.0 and 4.0 kHz. Wilcoxon matched-pairs signed-ranks test indicated a statistical significant difference between thresholds found at 0.5, 1.0 and 2.0 kHz (p<0.001). No difference was found between uHear™ and conventional audiometry thresholds at 4.0 kHz (p=0.327).

Table 2. Tympanometry results

Type (n=60)	**n (%)**
A	48 (80.0%)
Ad	7 (11.7%)
As	2 (3.3%)
B	2 (3.3%)
C	1 (1.7%)

Conventional audiometry indicated 15.4% of tested ears as having a clinically significant hearing loss with a PTA ≥40 dB HL (or 10 in the positive group). uHear™ found a PTA of 40 dB HL or more in 69.2% of cases. As mentioned above, power analysis was based on a ROC-curve in which uHear™ is compared to conventional audiometry, the gold standard. ROC-curve analysis showed an excellent AUC±SE of 0.98±0.14 (Figure 2). It provided high S of

100.0% (95%CI [65.5-100.0]), but poor Sp of 36.4% (95% CI [24.1-50.5]). The PPV and NPV were 22.2% (95%CI [11.7–37.5]) and 100.0% (95%CI [80.0–100.0]), respectively (Table 3). When excluding all ears without a tympanogram, or those with a type B or type C tympanogram, uHear™ showed similar results in terms of S (100.0% (95%CI [65.5-100.0])) and Sp (38.3% ((95%CI [24.9-53.6])), indicating its value in detecting sensorineural hearing loss.

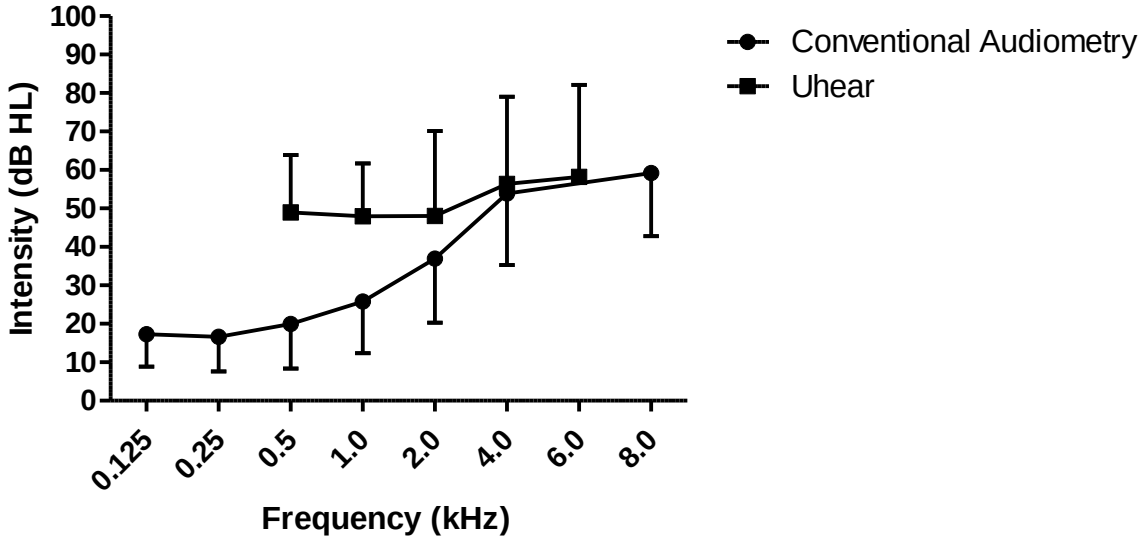

Figure 1. Mean air conduction thresholds and range measured by conventional audiometry and uHear™. Error bars indicate minima (conventional audiometry) and maxima (uHear); HL: hearing level

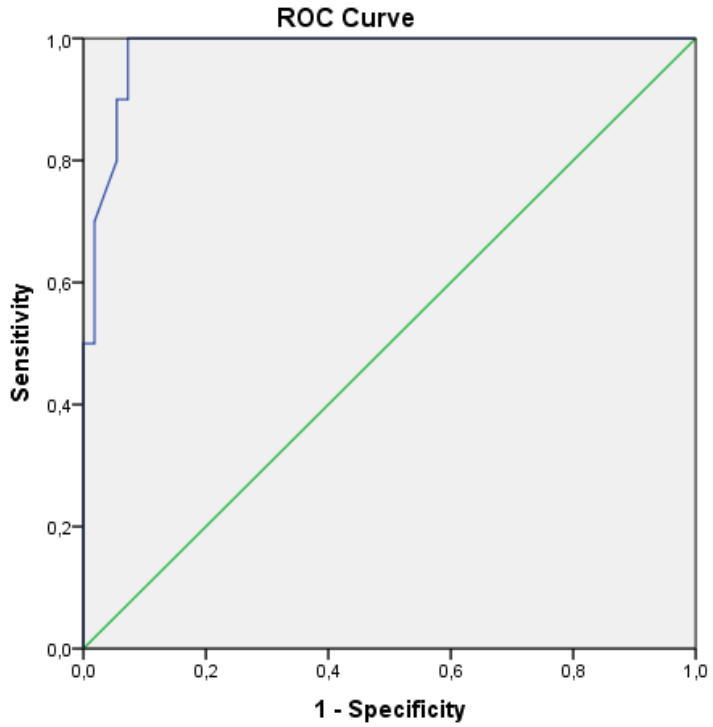

Figure 2. Receiver operating characteristics (ROC) curve of uHear™ compared with conventional audiometry as gold standard.

Since the cut-off of ≥40 dB HL resulted in a poor Sp of uHear™, exploratory analyses were performed in order to look at other cut-off scores. Results indicated that a cut-off of ≥55 dB HL would be more optimal to detect a PTA of ≥40 dB HL with conventional audiometry in this population (Figure 3.). Although 4.0 kHz had the highest correlation between both hearing tests, including this frequency in the PTA calculation did not improve the diagnostic accuracy (data not shown).

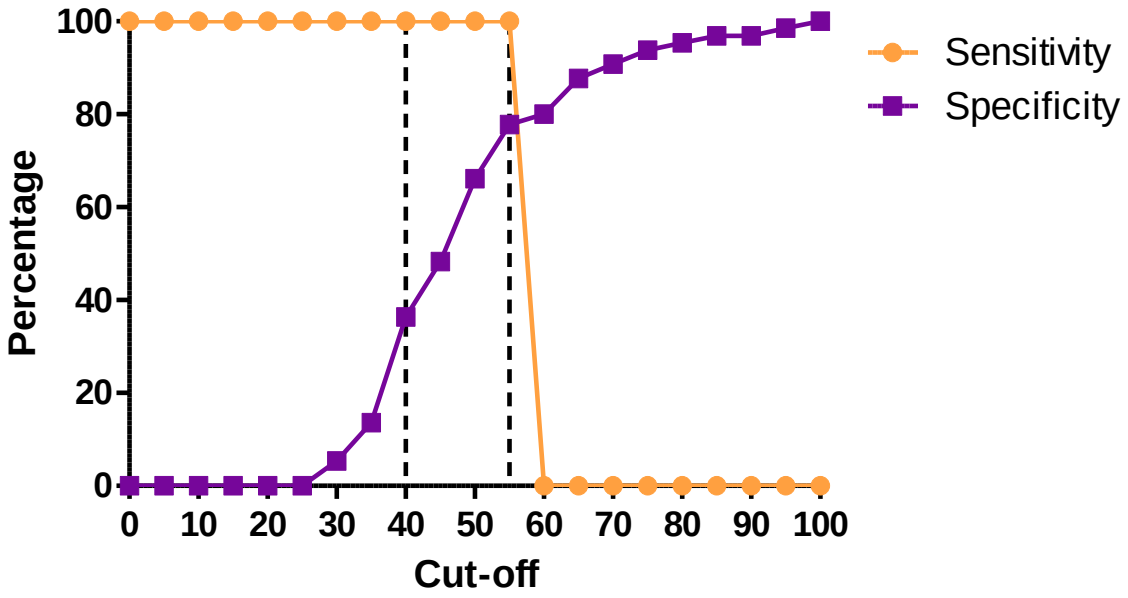

Figure 3. Sensitivity and specificity of uHear™ according to different cut-off scores based on the pure tone average

Whispered Voice Test

The WVT showed a positive test result in 4.6% of tested ears. S of the WVT was calculated as 30.0% (95%CI[8.1-64.6]). Its Sp was 100.0% (95%CI[91.9-100.0]) (Table 3).

Hearing Handicap Inventory for the Elderly

The HHIE was recorded per patient, and not per ear, as with other results described in this paper. Pass or fail results from both ears, obtained through PTA calculation, were put together for this analysis. A fail was given to patients who presented with a PTA of ≥40 dB HL in both ears.

The HHIE showed a mean score of 9.2 (0-32). No patient stated that they believed they had a significant hearing handicap. Seven patients (21.2%) showed scores between 17 and 42, indicating a perceived mild to moderate handicap. HHIE-results showed low S (0.0%, 95%CI[0.0-53.7]), but maximum Sp (100.0%, 95%CI[85.0-100.0]) when using the cut-off of ≥43. The HHIE indicated a high AUC±SE when compared to conventional audiometry (0.88±0.06) (Table 3).

Table 3. Audiological evaluation: performance measures and predictive values

	Conventional Audiometry (n = 65)	**uHear™** (n = 65)	**Whispered Voice Test** (n = 65)	**Hearing Handicap Inventory for the Elderly** (n = 33)
Vulnerability (%)				
PTA ≥ 40 dB	15.4	69.2	*	*
Screening failure	*	*	4.6%	0%
Performance measures				
S[95%CI]	*	100.0 [65.5-100.0]	30.0 [8.1-64.6]	0.0 [0.0-53.7]
Sp[95%CI]	*	36.4 [24.1-50.5]	100.0 [91.9-100.0]	100.0 [85.0-100.0]
AUC±SE	*	0.98±0.14	**	0.88±0.06
Predictive values				
PPV[95%CI]	*	22.2 [11.7–37.5]	100.0 [31.0-100.0]	**
NPV[95%CI]	*	100.0 [80.0–100.0]	88.7 [77.5-95.0]	84.8 [67.3-94.3]

**: not applicable, **cannot be calculated*

PTA: pure tone average, Se: sensitivity, Sp: specificity, AUC: area under the ROC-curve, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval

DISCUSSION

Hearing loss is widespread in older patients and can result in reduced communication and cognitive performance, reduced functionality and poor quality of life [401]. Therefore, NCCN Guidelines in Older Adult Oncology recommend an assessment of sensory functions such hearing, as part of a CGA. The NCCN proposes a screening tool that is similar to the WVT [131]. In previous reports, the WVT showed good diagnostic accuracy, although problems were found when accounting the inter-rater reliability [235, 236]. In our trial, we aimed to validate uHear™, an iOS-based application which is freely available in the iTunes store, to screen for hearing loss in older cancer patients within a CGA.

uHear™ was compared to conventional audiometry, which is considered to be the gold standard. We stated that we would accept uHear™ if we found an AUC of at least 0.70. Results showed an excellent AUC of 0.98, indicating that we can use uHear™ as a screening tool for hearing loss within the CGA. A good screening tool needs a high S and high NPV as it reduces the number of false negative cases. uHear™ showed perfect S and NPV scores of 100.0%. On the contrary, we found poor Sp (36.4%) and poor PPV (22.2%). Exploratory analyses suggested that a cut-off of ≥55 dB HL may be more suited to detect a hearing loss with a PTA of ≥40 dB HL with conventional audiometry in this population. The poor Sp and PPV results can be attributed to the overestimation of air conduction thresholds as measured by uHear™ when compared to conventional audiometry. Wilcoxon matched-pairs signed-ranks test detected significant statistical differences between thresholds at 0.5, 1.0 and 2.0 kHz, whereas no difference was found at 4.0 kHz. Increased uHear™ thresholds in lower frequencies have also been noted in previous studies and may be ascribed to following factors [257, 258]. First,

uHear™ was administered in a quiet room and not in a sound booth as with conventional audiometry. Although ambient noise was reduced to a minimum, it could not be excluded completely. Second, the average age of patients included in this trial was 76.4 years. Some patients were familiar with touch screens, whereas others had never worked with this type of device. Therefore, the tapping on the screen had to be learned upon assessment of uHear™. uHear™ demands an immediate tap when a sound is heard. When this does not happen, it registers the sound as 'not heard by the patient' and would therefore thus unwantedly elevate the threshold. However, if this effect would be present in some patients, there would be no difference between the results of both ears since frequencies are assessed alternatingly. Indeed, when comparing the results of the left and right ear for uHear™ at 0.5, 1.0, 2.0, 4.0 and 6.0 kHz, no significant differences were detected (p=0.968, p=0.963, p=0.522, p=0.890 and p=0.947, respectively). Third, both uHear™ and the standard iPod touch earbuds had not been calibrated. Therefore, it is impossible to ensure that the level and frequency of the auditory stimulus is exactly as it should be [258]. Nonetheless, having to calibrate the device and its earbuds would lower the easy accessibility of this screening tool. Another possible explanation may be found in the type of transducer that is used to asses pure tone audiometry and uHear™. Audiometric testing was performed by use of a supra-aural headphone, while uHear™ was conducted with standard Apple earbuds. As it has been reported that the use of insert earphones results in higher hearing thresholds – especially in the lower frequency range due to the loss of vibration on the ear and cranium, this could be in part have attributed to the overestimation of the lower frequencies by uHear™ [402].

When comparing uHear™ to the WVT, the screening tool proposed by the NCCN, it showed worse sensitivity results (30.0%). It did show excellent Sp (100.0%). Changing the pass or fail criteria, such as failing two out of four conditions, did not improve diagnostic accuracy as S improved (100.0%) but Sp decreased (49.1%). This was also the case when using solely the most difficult condition (whisper at 2 feet; S: 100.0% and Sp: 40.0%). However, we would still advise the use of uHear™ above the WVT. To start, the PTA in older patients can be slightly elevated due to poor attention, delayed response, interference from tinnitus and other neurophysiologic problems [403]. Therefore, patients' speech reception could better than their PTA results indicate. On the other hand, it also possible that a pure tone audiometry is less cognitively demanding compared to the processing of speech. When hearing threshold are elevated and hearing becomes more difficulties, patients have to put more effort into understanding what has been said [270]. Consequently, results on the WVT could be overestimated, thus limiting the use of this tool. Further, it is know that the WVT has a low test-retest reliability. One investigator may have a louder whisper of another, and thus leading to other results [235].

The HHIE also did not outstand uHear™ with a lower AUC of 0.88. No patient declared that they believed to have a significant hearing handicap, which resulted in a S of 0.0%. This is in line with previous reports in which was stated that patients want to postpone the acquisition of hearing aids as long as possible [404]. The HHIE did reach a high Sp 100.0%, although its clinical value is rather redundant for screening purposes. As the HHIE is filled in based on the patient's perspective on his/her hearing for both ears, the results of the audiometry had to be combined. For the comparison, it was defined that patients failed pure tone audiometry when they had a PTA greater than 40 dB HL in both ears. Nevertheless, the patient's worse ear may influence the result on the HHIE as this ear defines the patient's handicap. When looking at the diagnostic properties of the HHIE compared to a PTA of ≥40 dB HL in the better ear, the S and Sp test remained the same (0% and 100.0%, respectively).

We have already covered in part the limitations in this study. We can summarize them as follow. First, uHear™ overestimated air conduction thresholds resulting in a poor Sp. The lower the frequency, the higher the difference compared to conventional audiometry. Explanations may be found in the ambient noise level that was present in the testing room and the age of the population under study resulting in an unfamiliarity with touch screen devices. Exploratory analyses further indicated that a cut-off score of ≥55 dB HL could be more suited in this population. However, this needs to be confirmed through further research, which we are planning in the future. Second, we found a rather low proportion of patients presenting with a significant hearing loss since we did not include patients with a known hearing loss. This resulted in poorer performance scores of uHear™, WVT and HHIE. Third, since patients were recruited on one site of the hospital, we did not find a normal distribution of cancer sites. However, we feel that this did not influence results. Fourth, both uHear™ and the WVT assessed hearing monaurally. Binaural testing, however, would give more valuable information about the patient's hearing functionality. While binaural testing is not feasible for uHear™, it could be easily conducted in case of the WVT. Combining the results of both ears for uHear™ could be more beneficial. Further, 6.0 kHz was not included in the pure-tone audiometry and could therefore not be compared to the results of uHear™. Nonetheless, evaluating 6.0 kHz does not have any benefit regarding the calculation of the PTA. Last, the time needed to assess uHear™ and conventional audiometry did not significantly differ. Although recommended by the NCCN, screening for hearing loss is not always incorporated in a CGA as it increases total assessment time. Nevertheless, looking at the patient's hearing status is a crucial element of the CGA as it provides useful information for health care providers.

Although uHear™ has some limitations, it also brings many advantages. Firstly, in the population under study, despite not being documented, we feel that the assessment time of uHear™ and conventional audiometry did not differ significantly since most patients were not familiar with touch screens and training was necessary. However, uHear™ does lead to profit in time since patients do not have to be transferred to the audiology department. Further, in future, training will be redundant since more patients will be familiar with touch screens. Secondly, having an idea of the patient's hearing is crucial to health care providers. Certainly for those who have to explain the risk and benefits of the treatment and have to ensure that patients know what to do in case of adverse events. A patient with an unknown hearing disorder could feel uncomfortable to ask to repeat sentences over and over again. When these health care providers would know that the patient has a hearing problem, adequate measures can be taken such as improvement in signal to noise ratio, written instructions, etc.

We want to emphasize that in cancer patients, it is not the main goal to diagnose patients with a hearing loss, but we rather want to be able to give physicians a complete view of the patients' capabilities so that tailored care can be implemented. Based on the results of this trial, we can conclude that uHear™ is usable as a screening tool for older cancer patients within a CGA and that it is more favourable to use when compared to the NCCN proposed WVT or to the HHIE.

ACKNOWLEDGEMENTS

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CHAPTER 5

The use uHear™ as a screening tool for hearing loss in a geriatric oncology population

PART II

The use of uHear™ - by use of a new scoring method based on hearing grades - in older cancer patients undergoing a comprehensive geriatric assessment

Based on

The use of uHear™ to screen for hearing loss in older cancer patients as part of a comprehensive geriatric assessment

Lycke M et al. *Acta Clinica Belgica*. 2017

Abstract

OBJECTIVE

Validation of uHear™ as a screening tool to detect hearing loss in older cancer patients without a known hearing loss, as part of a Comprehensive Geriatric Assessment (CGA).

METHODS

Patients, aged ≥70 years, were evaluated by uHear™ and conventional audiometry, which is considered the gold standard, as part of a CGA. The pass or fail screening cut-off for uHear™ was defined as having ≥2 consecutive hearing grades starting from the moderate-severe threshold zone ranging from 0.5 – 2.0 kHz. To accept uHear™ as screening tool, it was predefined that the combined sensitivity (S) and specificity (Sp) of the test (S+Sp/2) had to be at least 80% and that an actual combined (S+Sp)/2 of 90% would be found.

RESULTS

Ninety ears were tested. Of those, 24.4% of tested ears presented with a pure tone average of 40 dB HL or higher as measured by conventional audiometry, whereas a positive result was obtained in 26.7% of tested ears by uHear™. The combined (S+Sp)/2 was calculated as 77.5%.

CONCLUSION

uHear™ is a feasible tool for use within the CGA and shows promising results. However, further research is warranted in order to obtain the most optimal cut-off method for routinely use within geriatric oncology.

INTRODUCTION

Presbyacusis is one of the most prevalent conditions affecting older adults [405]. Finding a person aged 70 years or older without a known hearing disorder or whose hearing sensitivity has not declined from youthful levels is rare [156]. The prevalence of hearing loss increases with age, and as a result of higher life expectancies the number of individuals presenting with hearing impairment is expected to increase in upcoming years [406]. It is known that impaired communication, e.g. by hearing loss, is associated with decreased cognitive, emotional, physical and social functioning and that it can contribute to the development of delirium and dementia [407]. Consequently, hearing loss can lead to a reduced quality of life [405]. Further, sensory deficits also affect the ability to give adequate informed consent in oncology [408]. Therefore, the NCCN Guidelines in Older Adult Oncology recommend an assessment of the sensory functions such as vision and hearing, as part of a Comprehensive Geriatric Assessment (CGA) [102].

A CGA has been the cornerstone in the management of older cancer patients for many years [12]. It has found its way into oncology as there is an emerging need to develop a means to characterize the functional age of older patients with cancer, rather than their chronological age [22]. A CGA can be described as a multidisciplinary assessment of the older patient in which problems in multiple health domains are uncovered, described and explained, if possible. This assessment further aims at predicting morbidity and mortality [409, 410]. Its benefits have been widely described and include the prevention of geriatric syndromes, recognition of cognitive disorders, improved health status and detection of unsuspected conditions that may interfere with cancer treatment [410]. In cancer patients, it may also predict chemotherapy toxicity and quality of life [7, 24].

Although the NCCN Guidelines in Older Adults Oncology recommend a screening for hearing loss, it is not always incorporated into a routine geriatric assessment. Hearing loss can be easily detected through pure-tone audiometry. However, such assessment requires a transfer to the audiology department of the hospital, is time-consuming and not feasible to schedule in a busy geriatric oncology clinic with hundreds of geriatric oncology patients annually. Further, it can be considered as cumbersome for the patient who is already scheduled for a large number of diagnostic and therapeutic interventions. The NCCN therefore recommends an initial screening by use of a whispered voice test in which the patient is asked to repeat a sentence or sequence of numbers that is presented by the examiner by use of a whispered voice when standing behind the patient [102]. However, problems arise when accounting the inter-rater reliability, caused by differences in loudness of the whisper [411]. Recent work conducted by our group looked into the possibility of using uHear™, an iOS-based application that runs on iOS devices such as iPod, iPhone and iPad as a screening tool to detect hearing loss in older cancer patients as part of a CGA. Data showed promising results as uHear™ reached a high area under the ROC curve (AUC) and maximum sensitivity. However, it showed poor specificity, hampering the use of uHear™ in clinical practice [412].

Another limitation of uHear™ is its scoring system. Figure 1 gives an example of results given by the screening tool. In our previous trial, the pass or fail screening cut-off was defined as having a pure-tone average of at least 40 dB HL, calculated from the air conduction thresholds obtained at 0.5, 1.0 and 2.0 kHz [412]. Calculation of this numerical cut-off showed some difficulties as the thresholds of uHear™ are reported as a hearing grade per frequency rather than in sound intensity. Thus, for scoring purposes, a scoring sheet had to be drafted and every result obtained with uHear™ had to be compared to the scoring sheet in order to obtain

numerical thresholds. Another recent trial, conducted by Handzel et al. (2013), in patients with a sudden sensorineural hearing loss, also investigated the use of uHear™ and used the presence of two or more consecutive hearing grades as a cut-off score to define impaired hearing [413]. Therefore, in this trial, we will aim at validating uHear™ with a pass or fail screening cut-off defined as having two or more consecutive hearing grades starting from the moderate-severe threshold zone ranging from 0.5 – 2.0 kHz (Modified Handzel-uHear™ screening).

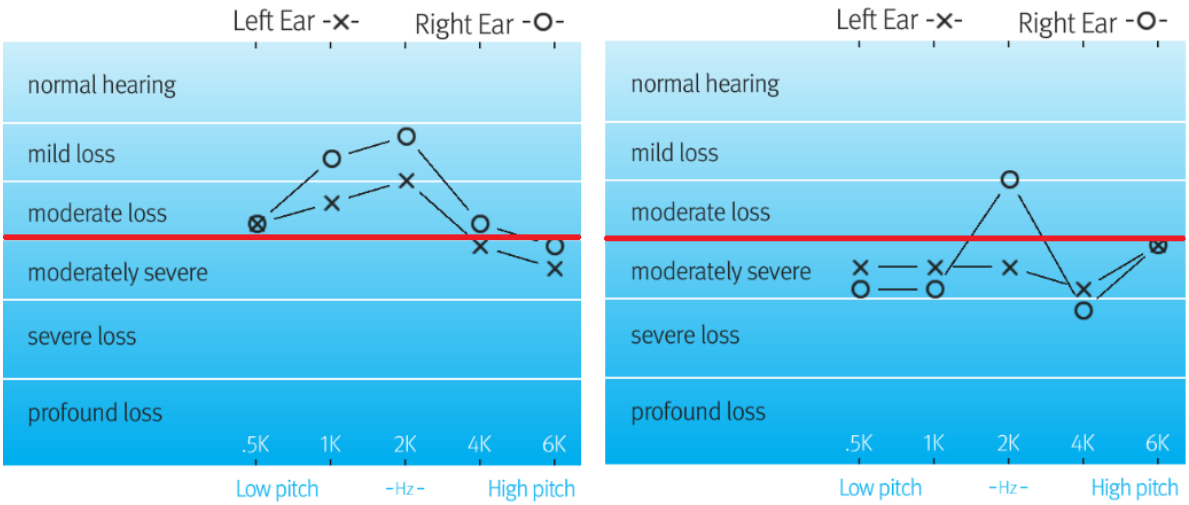

Figure 1. Examples of results given by uHear™. Red line indicates pass or fail screening cut-off. In the left figure, both ears have hearing tresholds above the red line (cut-off line) at 0.5, 1.0 and 2.0 kHz and pass the test. In the right figure, the left ear fails the test as all three frequencies are below the red line. The right ear also fails the test as 0.5 and 1.0 kHz are (consecutively) below the moderately severe (red) line.

METHODS

Patient selection

All patients of the UHEAR-BIS-trial (clinicaltrials.gov identifier: NCT02662998) were recruited at the radiotherapy and oncology departments of the General Hospital Groeninge (Kortrijk, Belgium) between January 2016 and August 2016. Eligible patients needed to be 70 years or older at time of enrolment and had to have a histologically confirmed diagnosis of a solid cancer or haematologic malignancy. Any type of treatment and any type of stage were allowed. Patients had to be cognitively able to perform the assessments. Ears with a known hearing loss, hearing aids, clinically diagnosed Ménière's disease, retrocochlear hearing loss, autoimmune inner ear disease, fluctuating hearing loss or a history of sudden sensory neural hearing loss were excluded from participation. The ethical committee of the General Hospital Groeninge, Kortrijk Belgium, approved the trial. All patients gave written informed consent upon participation in the trial.

Measures

Comprehensive Geriatric Assessment

The audiological evaluation was conducted as part of a CGA, which is proposed as the key treatment approach for older cancer patients [86]. The CGA comprises following standardized measures: functional status (Activities of Daily Living, Instrumental Activities of Daily Living [48,

[49]), physical status (number of falls), nutrition (Mini Nutritional Assessment - Short Form [322]), emotional status (Geriatric Depression scale – 15 [60]), cognition (Mini Mental State Examination (MMSE) and/or Freund Clock Drawing Test (CDT) [51, 330, 366]), polypharmacy (number of drugs) and comorbidities (Charlson Comorbidity Index [324]). Patients were deemed vulnerable if they presented with impairments in two or more domains within the CGA [6, 24, 313].

Audiological evaluation

All hearing assessments were performed by a certified and accredited – by the Belgian government - audiologist.

Immitance measurement and pure tone audiometry

A 226 Hz tympanometry was performed with an 85 dB SPL probe tone (Zodiac 901 Middle-ear Analyzer, Madsen Electronics, United States). Pure tone audiometry was conducted in a sound booth by use of a recently calibrated Interacoustics AC3 audiometer, applying the Hughson-Westlake technique. Air conduction thresholds were established for conventional octave frequencies ranging from 0.25 kHz to 8.0 kHz, including 6.0 kHz in order to compare all frequencies to those assessed by uHear™. The Pure-Tone Average (PTA) was calculated as the average of the air conduction thresholds found at 0.5 kHz, 1.0 kHz and 2.0 kHz. We defined a PTA of ≥ 40 dB HL as the pass or fail screening cut-off as this was proposed by Ventry and Weinstein for individuals aged 65 years or older [246].

uHear™

Hearing loss was screened by an iOS-based application, named uHear™ (version 2.0, Unitron, Victoria, BC, Canada) using an iPod touch (iOS version 9.2.1, Apple Inc., Cupertino, CA, USA). Standard iPod touch earbuds were used. The test was performed in either a quiet hospital room or physician's office. For this trial, we used the sensitivity test, which determines the quietest air conducted sound the subject can hear at 0.5, 1.0, 2.0, 4.0 and 6.0 kHz, measured in both ears separately. uHear™ uses a 267 ms pulse duration and employs a simple 10 dB down and 5 dB up approach. The lowest threshold with two responses of three excursions is recorded as the hearing sensitivity [257]. A modified Handzel-uHear™ screening method was defined with a pass or fail screening cut-off as having two or more consecutive hearing grades starting from the moderate-severe threshold zone ranging from 0.5 – 2.0 kHz (Figure 1). Hearing grades were converted from hearing thresholds as advised by Unitron (personal communications) according to standard ASHA regulations [225] (Table 1).

Table 1. Conversion of hearing thresholds to hearing grades

Threshold (dB HL)	Hearing grade
-10 to 25	Normal hearing
26 to 40	Mild loss
41 to 55	Moderate loss
56 to 70	Moderately severe
71 to 90	Severe loss
>90	Profound loss

Abbreviations: dB HL: decibel Hearing Level

Statistical Analyses

Statistical analyses were conducted by use of SPPS software (version 23; IBM SPPS Statistics, Chicago, IL) and Prism® software (GraphPad Prism 5, Inc., La Jolla, CA). Descriptive statistics were performed to present patient and tumour characteristics. Descriptive statistics were further conducted to present assessment results of both CGA and hearing tests. Wilcoxon matched-pairs signed-ranks test was used to compare uHear™ and conventional audiometry thresholds. Sample size calculations are based on previous research [412] and are defined as following assumptions. We accept conventional audiometry as the gold standard against which uHear™ is compared. Sample size calculations are based on the assumption that the combined sensitivity (S) and specificity (Sp) of the test (S+Sp)/2 has to be at least 80% and that we will find an actual combined (S+Sp)/2 of 90%. S and Sp with 95% confidence intervals (95%CI) were calculated with the predefined pass or fail screening cut-off. Positive and negative predictive values were also determined (PPV and NPV, respectively).

RESULTS

Patient Characteristics

Forty-five patients, with an average age of 76.4 years (range 70.0-91.0), consented for participation. Of those, a slight majority (53.3%) included female individuals. Patients presented with cancer of following sites: haematologic malignancy (44.4%), genitourinary sites (15.7%), gynaecologic sites (13.3%), digestive sites (6.7%), head and neck (8.9%), unknown primary tumour (4.4%), musculoskeletal sites (2.2%), skin (2.2%), and lung (2.2%). All patients but one received a systemic treatment. The majority of patients were treated with palliative intent (62.2%) (Table 2).

According to the definition of vulnerability based on the CGA, 40.0 % of patients were deemed vulnerable as they presented with two or more deteriorated domains. Although all patients were deemed cognitively capable of performing the audiological assessment, two patients (4.4%) scored below the cut-off score on the MMSE. The cognitive test was not assessed in another two patients due to an incomplete CGA assessment.

Table 2. Patient Characteristics

Characteristics (n = 45)	Mean (range)	n (%)
Age (years)	76.4 (70.0-91.0)	
Sex		
Female		24 (53.3)
Male		21 (46.4)
Cancer site		
Haematologic malignancy		20 (44.4)
Genitourinary		7 (15.7)
Gynaecological		6 (13.3)
Head and neck		4 (8.9)
Digestive		3 (6.7)
Unknown primary		2 (4.4)
Skin		1 (2.2)
Musculoskeletal		1 (2.2)
Lung		1 (2.2)
Treatment type		
Systemic (chemotherapy, biotherapy, targeted therapy)		44 (97.8)
Supportive care		1 (2.2)
Treatment intent		
Palliative		28 (62.2)
Curative		17 (37.8)

Audiological assessment results

In two ears, tympanometry results could not be obtained, as optimal probe tips were not provided. The majority of patients presented with a type A tympanogram (87.8%) (Table 3). Based on conventional audiometry, 24.4% of tested ears presented with a PTA of 40 dB HL or higher. Figure 2 shows mean air conduction thresholds for both conventional audiometry and uHear™ at 0.5, 1.0, 2.0, 4.0 and 6.0 kHz. Wilcoxon matched-pairs signed-ranks test detected significant statistical differences (p<0.001) for all frequencies except for 4.0 kHz. uHear™ tends to overestimate air conduction thresholds in the lower frequencies, whereas it underestimates them at 6.0 kHz (Table 4).

Table 3. Tympanometry results

Type (n=88)	n (%)
A	79 (89.7)
As	7 (8.0%)
Ad	1 (1.1%)
B	1 (1.1%)

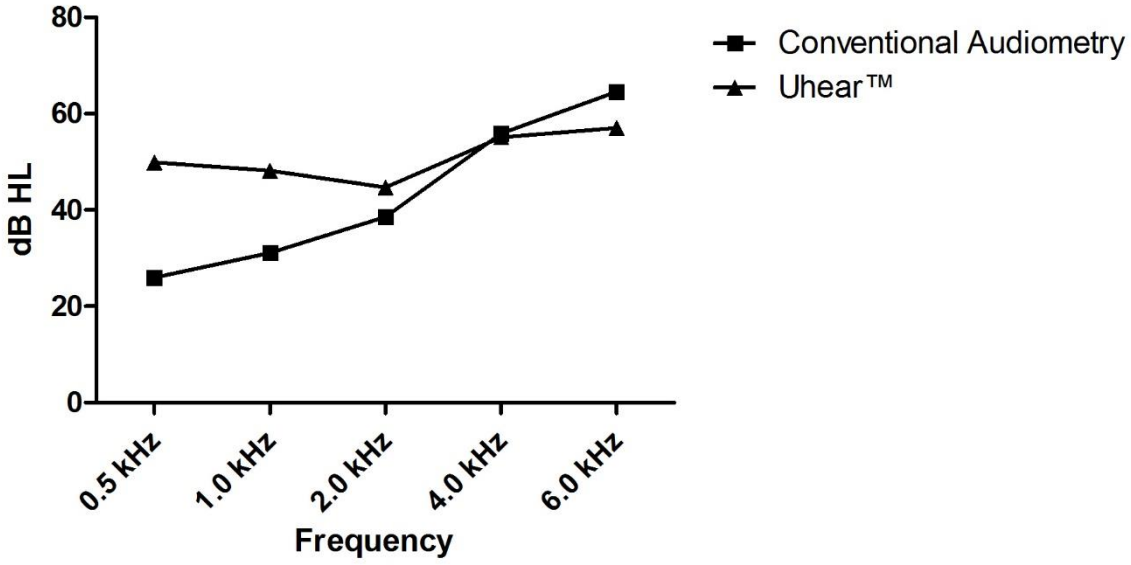

Figure 2. Mean air conduction thresholds measured by conventional audiometry and uHear™. Abbreviation: dB HL: decibel Hearing Level

Table 4. Mean air conduction thresholds for conventional audiometry and uHear™

Frequencies (kHz)	Conventional audiometry Mean threshold (dB HL) Mean (SD)	uHear™ Mean threshold (dB HL) Mean (SD)	Mean difference Mean (SD)	*p*-value
0.5	25.9 (11.8)	49.9 (15.1)	23.9 (14.2)	<0.001*
1.0	31.1 (12.7)	48.2 (13.5)	17.1 (11.9)	<0.001*
2.0	38.6 (15.1)	44.7 (15.5)	6.1 (9.1)	<0.001*
4.0	55.9 (16.7)	55.1 (18.2)	-0.8 (9.5)	0.346
6.0	64.6 (18.7)	57.1 (19.6)	-7.5 (12.1)	<0.001*

Abbreviations: dB: decibel, HL: hearing level, SD: standard deviation

According to uHear™, 26.7% of the tested ears failed the screening criteria. When looking at the diagnostic properties of the test, when using the modified Handzel method, uHear™ showed a sensitivity of 68.2% (95% CI [45.1-86.1]) and specificity of 86.8% (95% CI [76.4-93.8]). It was calculated that uHear™ would only be accepted as a screening tool for hearing loss within the CGA if the combined S and Sp of the test (S+Sp/2) was at least 80% and that an actual combined (S+Sp)/2 of 90% would be found. In this case, a combined result of 77.5% was obtained. The PPV and NPV of the test was calculated as 62.5% (95%CI[40.6-81.2]) and 89.4% ((95%CI[79.4-95.6]), respectively.

DISCUSSION

Older cancer patients are extremely sensitive to functional decline as a result of their cancer diagnosis and its treatment. Therefore, the NCCN Guidelines in Older Adult Oncology advise to assess patients with a CGA in order to select or adapt an individualised treatment. The CGA assesses vulnerability in several domains and states that an evaluation of the patient's hearing is crucial to identify those patients who may not adequately hear the given information

concerning their cancer diagnosis and the cancer treatment [86]. Since the proposed screening tool by the NCCN Guidelines is based on a whispered voice and many problems can arise with that type of test, with this trial we aimed at validating uHear™, an easily available iOS-based application, to screen for hearing loss in older cancer patients as part of the CGA [412].

To the best of our knowledge, we are the first to look into the feasibility of uHear™ as a screening tool for use within the CGA. Previous research by our group established that a pass or fail screening cut-off for uHear™, based on the PTA, is difficult to calculate and reduces the usability of the tool. Therefore, we retrospectively determined a new pass or fail screening cut-off that is defined as having two or more consecutive hearing grades starting from the moderate-severe threshold zone ranging from 0.5 – 2.0 kHz. In our sample and based on this cut-off, uHear™ identified 26.7% of tested ears of having a significant hearing loss with a PTA of ≥40 dB or more as measured with conventional pure-tone audiometry. The latter identified 24.4% of tested ears as having an actual PTA of 40 dB HL or higher. It was predefined that we would only accept uHear™ as a screening tool for use within the CGA if we would find an average combined S and Sp of at least 80.0% and that we would find an actual combined result of 90.0%. In this sample, a combined (S+Sp)/2 of 77.5% was found, therefore rejecting uHear™ as a screening tool within the CGA.

A good screening tool needs a high sensitivity and high NPV in order to reduce the number of false negative cases. Table 5 shows diagnostic accuracy of data obtained in this cohort when using different scoring methods. When using a cut-off score based on the PTA ≥40, as was used in our previous trial, an S of 100.0%, but Sp of 38.2% was detected which would result in a large number of patients with a referral to the otolaryngologist while no significant hearing loss is present. When using the modified Handzel method, S and NPV dropped to 68.2% (95% CI [45.1-86.1]) and 62.5% (95% CI [40.6-81.2]), respectively. On the contrary, the Sp of the test increased to 86.8% (95% CI [76.4-93.8]) and the PPV was calculated as 89.4% ((95% CI [79.4-95.6]). Although this modified Handzel method would miss a few of the ears with an actual significant hearing loss as measured by conventional audiometry, it does have a much better combined diagnostic property compared to using a cut-off score based on a PTA of 40 dB HL or more. Further, as the new cut-off was based on retrospective findings, which accounted for uHear™'s limitations, the higher diagnostic accuracy in this paper can be attributed to the newly defined cut-off and is not just the result of using a new set of subjects.

The limitations of uHear™ have been listed previously. In summary, it is known that uHear™ overestimates the lower frequencies. Some reasons can explain this difference. First, uHear™ demands an immediate tap when a sound is played. When this does not happen, it registers the sound as 'not heard by the patient' resulting in an elevated threshold. In this population, most patients are not familiar with a touch screen device. Therefore, to reduce this effect, the patient was given detailed instructions on how to tap the screen followed by a brief moment of exercise. When the audiologist detected difficulties, the patient was asked to raise the hand when he/she heard the sound and the audiologist would then immediately tap the screen. Second, although ambient noise was reduced to a minimum, it could not be reduced completely. Third, non-calibrated standard earbuds were used. As a result, it is not possible to guarantee that the intensity level and frequency of the auditory stimulus is exactly as it should be [258]. Further, it has been reported that higher hearing thresholds in lower frequencies can be attributed to the use of insert earbuds. When compared to supra-aural headphones, insert headphones show similar or sometimes even slightly better hearing thresholds in higher frequencies [402]. In order to reduce the latter these limitations, a new screening cut-off was calculated in which the overestimation of the lower and mid-frequencies was taken into

account. Fourth, patients with a known hearing loss were excluded from the trial. Therefore, only a limited number of patients with a significant hearing loss were found. Although testing patients with a known hearing loss would not give any new information and can thus be considered redundant, excluding those patients may alter the diagnostic properties of the screening tool. Free field-testing could be of use in patients who are fitted with hearing aids as amplification may be insufficient for proper speech understanding. Fifth, as in routine audiology screening, outcome results were calculated per ear and not per patient. Nevertheless, in normal practice routine, a screening failure in one ear would result in a referral to the audiologist of otolaryngologist regardless of the results of the other ear. However, when combining results of the two ears, the screening tool shows a comparable S of 68.8% and Sp of 82.2% (data not shown). Last, we did not find a normal distribution of cancer types. This is the result of recruiting patients in only one oncology day care centre. However, this should not have influence hearing results.

There is a need to further optimize this screening tool as it shows potential for use within the CGA. First, for all health care providers who need to give information to older cancer patients, it is crucial to know if the patient hears their messages. Older patients are very proud of their independence and in many cases, hearing and vision loss are one of the first functional declines they have to face. Although wearing glasses is well accepted by both young and older people, hearing aids are by many persons not that well accepted. As a result, older patients may try to hide their hearing loss which, in this specific population, may lead to missing crucial information about the cancer diagnosis, its treatment and its treatment-related side effects [414]. Second, uHear™ was well accepted by the patients according to the audiologist's judgement. Third, uHear™ is a fast and straightforward screening tool, it decreases the number of unnecessary appointments with the audiologist or otolaryngologist and with this new pass or fail screening cut-off, it is very easy to score.

A possible way to increase the diagnostic properties of the screening tool may be to use a pass or fail screening cut-off stating that the patient fails the screening if two or more non-consecutive hearing grades in the 0.5-4.0 kHz region are detected in at least one ear, starting from the moderate-severe hearing grade. An exploratory post-hoc analysis, using this criteria, was applied to the current cohort and was compared to a PTA of 40 dB HL or greater in at least one ear measured by conventional audiometry (Table 5). This showed a better S and a comparable Sp compared to the use of the modified Handzel-uHear™. Next, we applied this future-uHear™ screening to the data of previous cohort, which can be considered as blinded and independent from the current cohort. We obtained a higher S, but a slightly lower Sp, compared to the use of the modified Handzel-uHear™ in the current cohort.

In conclusion, we can state that uHear™ is not ready to be used within the CGA. However, as the tool shows promising results, further research is warranted in order to obtain the most optimal cut-off method before it can be used as a surrogate for audiometry within an oncogeriatric population.

Table 5. Overview of the results obtained in the current and previous cohort using the different scoring systems

	Current population (N=45)			Previous population (N=33) [412]		
	A	**B**	**C**	**D**	**E**	**F**
	Modified Handzel-uHear™ screening*	**Original uHear™ screening [412]**	**Proposed uHear™ screening optimisation**	**Modified Handzel-uHear™ screening**	**Original uHear™ screening* [412]**	**Proposed uHear™ screening optimisation**
S (%) **95% CI**	68.2 [45.1-86.1]	100 [81.5-100.0]	73.9 [51.3-88.9]	100 [65.5-100.0]	100 [65.5-100.0]	78.6 [48.8-94.3]
Sp (%) **95% CI**	86.8 [76.4-93.8]	38.2 [27.0-50.9]	86.4 [64.0-96.4]	89.1 [77.1-95.5]	36.4 [24.1-50.5]	78.9 [53.9-93.0]
PPV (%) **95% CI**	62.5 [40.6-81.2]	34.4 [23.2-47.4]	85.0 [61.1-96.0]	62.5 [35.9-83.7]	22.2 [11.7-37.5]	73.3 [44.8-91.1]
NPV (%) **95% CI**	89.4 [79.4-95.6]	100 [84.0-100.0]	76.0 [54.5-89.8]	100 [90.9-100.0]	100 [80.0-100.0]	83.3 [57.7-95.6]
(S+Sp)/2 (%)	77.5	69.1	80.2	94.6	68.2	78.8
AUC (±SE)	NA	0.881 ± 0.036	NA	NA	0.980 ± 0.14	NA

Abbreviations: S: sensitivity, Sp: specitivity, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, SE: standard error; NA: not applicable.

* validation cohorts

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CHAPTER 6
Conclusion

PART I
Main findings

The aim of this doctoral thesis was to explore screening measures to detect cognitive dysfunctions and hearing loss as part of a CGA in older cancer patients as well as cognitive dysfunctions in cancer patients of all ages receiving curative cancer treatment. Figure 1 give an overview of the included population within this thesis. Figure 2 shows a schematic overview of the main research questions that were addressed.

Chapter 3 gives an overview of the added value of the use of the Freund Clock Drawing Test (CDT) to screen for cognitive losses as part of the CGA. The Freund CDT was compared to the well-known and frequently used Folstein Mini Mental State Examination (MMSE). After establishing a retrospectively determined cut-off score of ≤4, the Freund CDT was prospectively validated as a screening tool to detect cognitive dysfunctions in older cancer patients.

Chapter 4 focusses on cancer-related cognitive impairments (CRCI) in both young and older cancer patients. Whereas it was first thought that CRCI were a result of a chemotherapeutic treatment, these last few years it has been suggested that psychological variables may also influence CRCI. In Part I, an overview is given on predictors of baseline CRCI. Results indicated that the IQ of a patient predicts the cognitive performance at baseline. Further, fatigue also influenced neuropsychological assessment results. In Part II, the distress thermometer (DT) was evaluated as a screening tool to predict CRCI six months after treatment initiation. Although the tool failed to predict objective CRCI, it did seem to predict subjective cognitive complaints.

Chapter 5 explores the use of uHear™, an iOS-based application to screen for hearing loss, as part of the CGA. In a first trial, uHear™ was evaluated in its current form using a cut-off based on the Pure Tone Average, which is calculated as the average air-conduction threshold measured at 0.5, 1.0 and 2.0 kHz. As the tool showed a good sensitivity, but poor specificity, a new pass or fail screening cut-off was defined as having two or more consecutive hearing grades within the 0.5-2.0 kHz zone. Using this cut-off score increased the diagnostic properties of the test, but failed to validate the screening tool for use within the CGA in routine practice.

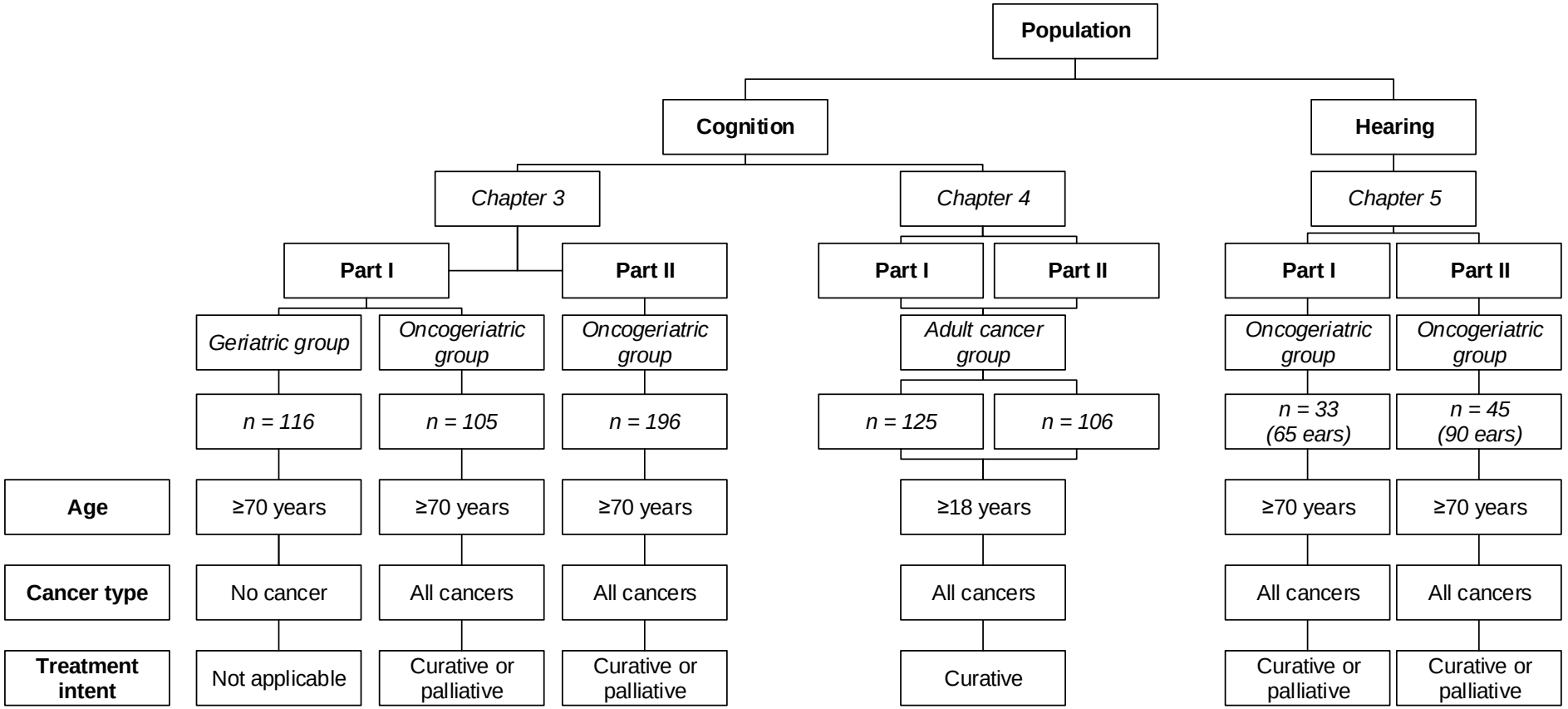

Figure 1. Overview of the included population per Chapter

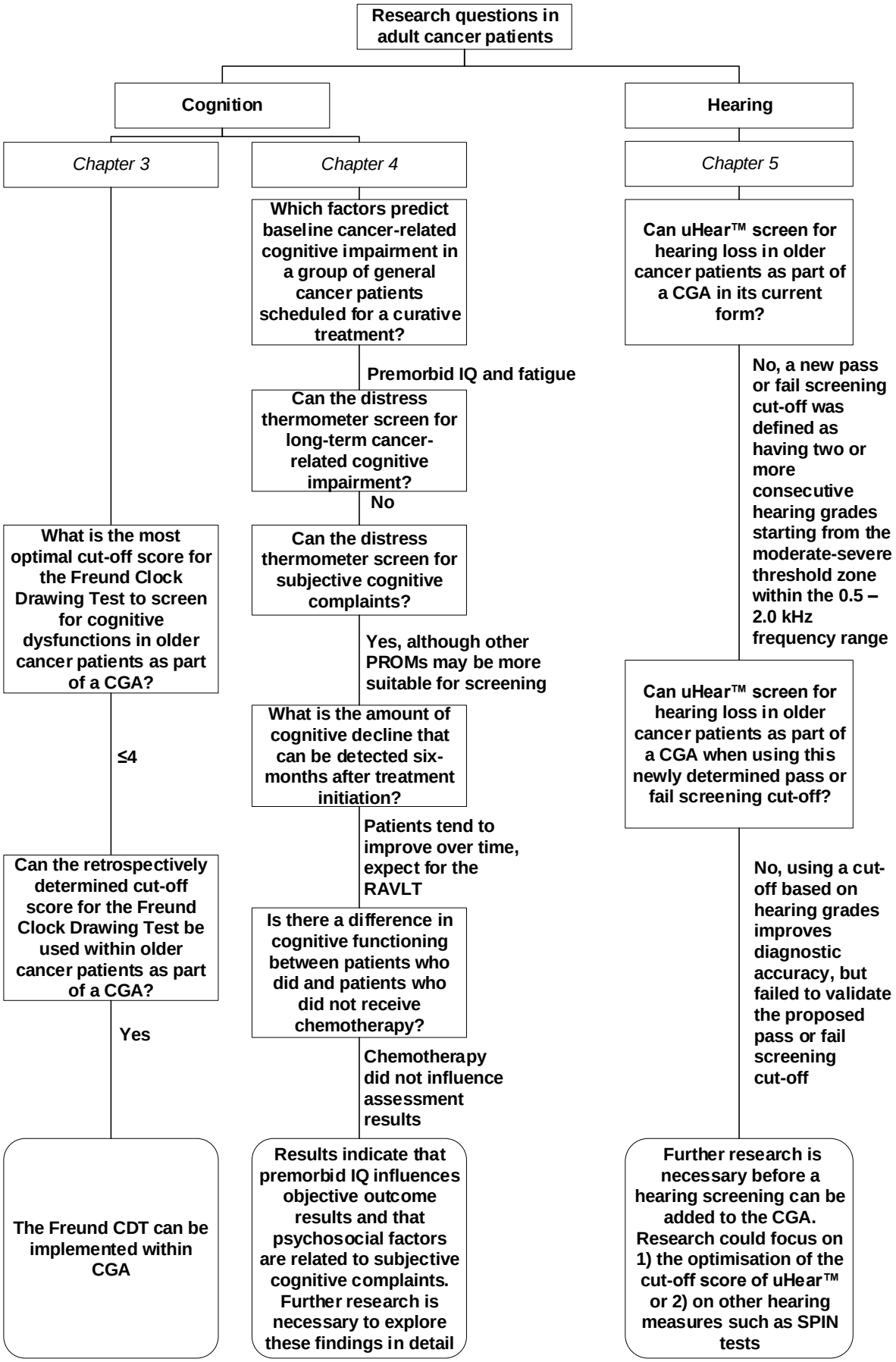

Figure 2. Flowchart representing research questions

CHAPTER 6

Conclusion

PART II

Screening for cognitive dysfunctions in older cancer patients

For any oncology health care provider, it is crucial to know if the patient is able to understand the presented information. Therefore, the NCCN Guidelines in Older Adult Oncology recommend evaluating the patient's cognitive capabilities when performing a CGA. In most cases, the cognitive functioning is assessed through the well-known and widely validated MMSE as it is very often used to screen for dementia in various patient populations. However, the MMSE can be time-consuming when added to an already extensive list of questionnaires and it may be interpreted as cumbersome for the cancer patient, who has – in most cases – a normal cognition [29, 415].

When looking at other available screening tools for cognition to use within the CGA, the CDT was chosen above other screening methods such as the MOCA, as it is an easy and fast to administer bedside screening tool while still providing sufficient valuable information [416, 417]. Scoring the CDT, on the other hand, is rather difficult as many scoring methods are described [418]. Further, not a single scoring method provided a cut-off score for use within an oncogeriatric population. Another method of screening the older cancer patient's cognitive function is to use the Mini-Cog, which consists out of a clock drawing test combined with the 3-word delayed recall (3-WDR) test that is used within the MMSE. The latter test would increase the diagnostic properties of the tool and is further advised by the NCCN Guidelines in Older Adult Oncology [415].

In Chapter 3, Part I, a cut-off score for the Freund Clock Drawing Test to screen for cognitive dysfunctions in older cancer patients as part of a CGA was established. The Freund scoring system was selected as it is easy to assess and uses a straightforward scoring method. Part I comprised a general geriatric population as well as an oncogeriatric population. As for this thesis, only the latter patient population is of our interest, following conclusion will apply only to this patient group.

In total, 105 older patients with cancer were included. Patients were assessed by a full CGA, including the MMSE and CDT. Afterwards, the Mini-Cog was calculated. A potential cognitive deficit was found in 29.5% of patients when using a cut-off score of 23 or less on the MMSE. Median CDT and MMSE scores were 5 and 25, respectively, with a median score of 2 on the 3-WDR test. The diagnostic properties of both the Freund CDT and Mini-Cog were presented with the AUC of the test, the S and Sp. Results indicated an optimal cut-off score of ≤4 on a scale ranging from 0 to 7 for the Freund CDT. When using this cut-off score, 37.1% of patients had a potential cognitive deficit. When comparing the results of the CDT to the MMSE, the AUC (SE) of the Freund CDT was 0.88±0.03. The S was calculated as 80.7% (95% CI [61.9–91.9]) and Sp as 81.1% (95% CI [70.0–88.9]). When comparing the Mini-Cog to the MMSE, the test showed an S and Sp of 80.7% (95% CI [61.9–91.9]) and 83.8% (95% CI [73.0–91.0]), respectively. From these latter results, it can be concluded that the added value of the 3-WDR is rather limited when accounting the extra assessment time. Further, in Part I, the interrater-reliability of the Freund scoring method was evaluated. The Kappa score, evaluating CDT interrater-reliability, was 0.84 indicating a high agreement between the two raters, in classifying patients as cognitively normal or potentially cognitively impaired. Therefore, when accounting the good diagnostic properties of the test and the high interrater-reliability, the Freund CDT with a cut-off score of ≤4 seemed to be the most optimal test to use within an oncogeriatric population.

Part II focused on the prospective validation of this retrospectively determined cut-off score. In the PROACTIVE-trial, the Freund CDT was compared to the Folstein MMSE when using the

retrospectively determined cut-off score of ≤4. As the Mini-Cog did not significantly outstand the Freund CDT, it was no longer included in the evaluation.

One-hundred ninety-six patients were included in the analyses. Patients were evaluated by a full CGA, including the CDT and MMSE. Potential cognitive deficits were identified in 27.0% of patients according to the MMSE. According to the CDT, 34.7% had a potential cognitive impairment. Median MMSE and CDT scores were 27 and 5, respectively. Spearman's correlation coefficient showed a significant negative correlation between MMSE and age (p<0.01; r_s = -0.23) and a significant positive association between MMSE scores and education age (p<0.01; r_s = 0.24). Results did not detect a significant association between age, education age, and CDT test results (p=0.07; r_s = -0.13 and p=0.07; r_s = 0.13, respectively).

It was stated that the Freund CDT would only be accepted as a screening tool for cognitive dysfunction within an oncogeriatric population when using a cut-off score of ≤4, if the AUC of at least 0.85. At the predefined cut-off score, the AUC± SE of the CDT showed excellent diagnostic accuracy (0.95 ± 0.17). Further, it provided an S of 94.3% (95% CI [83.4-98.5]) and Sp of 87.4% (95% CI [80.6–92.2]). This demonstrates that the Freund CDT can be used to screen cognitive functioning in older patients with cancer as part of a CGA. The AUC of the CDT in Part II was higher than in the first study (0.95 vs. 0.88), indicating that the retrospectively defined cut-off score of ≤4 is optimal within this population.

Limitations of Chapter 3

Limitations of Chapter 3 should be mentioned with respect to the study population and study measurements. In case of the study population, it should be noted that in Chapter 3, patients were included upon representation at the geriatric oncology clinic. As not all oncogeriatric patients were referred for a CGA, the distribution of cancer types was not as could be expected from known incidence figures. For example, in Chapter 3, Part I, the largest patient group comprised head and neck cancer patients while head and neck cancer is not that common [419]. However, although the distribution of cancer diagnoses in Part I differed from those in Part II, results of the first part were confirmed in the second study. As the proposed cut-off was selected in the original manuscript of Dr. Freund, it is possible to extrapolate the results to the whole geriatric oncology population. Another limitation is the lack of a healthy control group. Though considered more vulnerable than the oncogeriatric group, a cut-off score of ≤4 was also preferred in the group consisting of general geriatric subjects without cancer. Further, as the CDT was prospectively validated in a new cohort with almost 200 patients, it can be stated that a comparison with a healthy control group would be more cumbersome than the actual added value. Next, only a minority of patients were deemed fit on the CGA as the majority of the included patients were evaluated by a full CGA because they had screened positive on the G8-questionnaire. In routine practice, patients are initially evaluated with the G8-questionnaire. Solely when the patient screens positive, a full CGA is performed. In Chapter 3, the group of fit patients had been assessed with a complete CGA because their treating physician demanded it. The achieved cut-off score may thus not be representative for patients who screened negative on the G8-questionnaire or patients who are evaluated with other screeners. However, the G8-questionnaire contains seven items from the Mini Nutritional Assessment and age. One of the items included in the G8-questionnaire concerns cognition and depression. This item has previously shown to correlate with MMSE test scores [420, 421].

The following limitations apply to the used measurements. First, in Chapter 3, the MMSE is considered the gold standard within the CGA in most hospitals in Belgium. Therefore, the CDT was compared to the MMSE and not to other measures such as the MoCA. Despite the MMSE

to be widely used to screen for dementia, the MMSE has to be considered as a screening tool and not as a diagnostic test. When a patient would screen positive on the CDT, it is important to understand that the detected cognitive dysfunction may slightly differ from the alterations that would be found by the MMSE. In order to properly assess a patient, the CDT had to be compared to a full neuropsychological assessment. However, within the CGA, it is not the intention of diagnosing patients, but merely to detect those domains in which the older patient with cancer shows vulnerabilities. If a patient would screen positive on the CDT, it is advised to first assess the patient with the MMSE before a referral to the neurologist or neuropsychologist is made. Especially since recent findings regarding geriatric interventions based on CGA results, indicated that only a limited number of patients with a referral to the memory clinic were actually seen by a neurologist or neuropsychologist (personal communications with Dr. C. Kenis). Therefore, no data is available on in-depth neuropsychological assessments of patients who were deemed cognitive vulnerable by the CDT or MMSE. Second, in Chapter 3, Part I, the Mini-Cog was also compared to the MMSE. As both the CDT and the 3-WDR of the MMSE were assessed, the Mini-Cog was calculated retrospectively and not assessed in real time. Further, unlike in other versions of the Mini-Cog, a pre-drawn circle for conduction of the CDT was used. A pre-drawn circle prevents participants from possibly drawing a circle not large enough to contain the numbers and hands, or from not being symmetrical, which may affect the spatial arrangement of the numbers [422]. However, the CDT was assessed as it was described by Dr. Freund [272]. Immediate sequential assessment of both the CDT and the Mini-Cog separately would lead to strong recall bias. Next, in Part I, the education level of the patient was not asked and could therefore not be included in the analysis, which led to the hypotheses that the CDT might be too easy for patients with a higher education. However, it had been reported that education did not affect the result when using the Freund scoring method [292]. Nonetheless, in Part II, the educational level of the patient had been assessed and was included in the analysis. Results indicated that education age did not influence CDT results and can therefore be used to assess all older patients with cancer regardless their education level. Another shortcoming of chapter 3 is that the CGA did not include an objective hearing assessment, because it is not yet included in routine practice. Therefore, lower outcomes on the CDT or MMSE can be due to a loss of hearing. Nonetheless, no correlation was found between the degree of hearing loss and the result on the CDT or MMSE in chapter 5 (data not shown).

Strengths of Chapter 3

In Chapter 3, the CDT was validated as a screening tool to detect cognitive dysfunctions in older cancer patients as part of the CGA. The strengths of this tool are various. For example, the CDT was reported as a quick screener for cognition, especially when compared to the MMSE or MoCA [417]. However, it did not provide an optimal cut-off score for use within a geriatric oncology population. Further, as many scoring methods have been published, selecting an easy and straightforward system was necessary [423]. The scoring method, that was selected in Chapter 3, had been published by Dr. Barbara Freund [272] and uses a 7-item scoring scale. Scoring the Freund CDT is easy as the scoring rules are clear and direct, as indicated by its high interrater-reliability. Further, the retrospective determined cut-off score of ≤4 has been validated in Part II in a large and heterogeneous sample of older cancer patients and can be implemented directly within the CGA.

When comparing the MMSE to the CDT, the CDT brings many advantages. First, the CGA is performed in the early trajectory of the cancer diagnosis or cancer treatment at a time where

many patients still have to cope with the idea of having cancer and the thought of having to receive a cancer treatment. Since many cancer patients present with a good cognition, it has been reported that the assessment of MMSE can be experienced as annoying by (cancer) patients [29, 326]. The CDT on the other hand is far less confronting and is therefore more suitable to use within this specific population. Further, the CDT can be administered in less time than the MMSE, which reduces the total assessment time of the CGA. Further, the CDT is more sensitive than the MMSE. While this could lead to a certain number of false positives, it does not outweigh the reduced assessment time when choosing the CDT instead of the MMSE. Fourth, it has been previously reported that the MMSE can be influenced by the education age of the patient, whereas the CDT is not when the patient is given a pre-drawn circle [292, 308].

Implications for routine practice

The data in Chapter 3 indicated that the Freund CDT can be used as an initial screener for cognitive function as part of the CGA. Proper screening is necessary and the results should be reported and made available in the patient's file. In this way, all health care professionals can access this information and are made aware of the patient's cognitive functioning. As the diagnostic properties of the test were even higher in the second set of patients (Part II), it can be stated that the CDT is ready to be implemented in routine practice. Since the MMSE is also a screening tool, it should be noted that a positive test result on the CDT should be followed by an assessment with the MMSE before a referral to another health care professional is made. Ideally, a referral should be made to the neurologist or (neuro) psychologist for a comprehensive cognitive workup. A referral to the geriatric day clinic where the patient can be evaluated by the geriatric nurse, geriatric psychologist, occupational therapist and geriatrician is another possibility. Though in case this is not possible, for example, when the patient is too ill, health care professionals can take the cognitive dysfunction into account and for example give written instructions. The data in Chapter 3 indicated that in case of a general geriatric population, the Mini-Cog – including the Freund CDT - should be assessed. However, a prospective validation trial should be performed as the results for the Mini-Cog were calculated retrospectively. It should also be noted that there is a thin line between general geriatric patients and oncogeriatric patients as geriatric patients have a high risk of developing cancer. Therefore, the geriatric and the geriatric oncology team should meet regularly to discuss when the geriatric oncology team steps in to assess a CGA. Obviously, both teams need to work closely together to avoid unnecessary evaluations.

CHAPTER 6

Conclusion

PART III

Screening for cancer-related cognitive impairment in cancer patients receiving curative treatment

These last few years researchers have started to pay more attention to the psychosocial problems that cancer patients have to deal with when facing a cancer diagnosis and cancer treatment. Cancer-related cognitive impairments, or CRCI, are one of those psychosocial aspects that have been studied frequently during the last decade as many cancer patients may experience concentration problems, distractibility, forgetfulness, difficulties in remembering names or numbers and a lack of mental sharpness [124, 424].

Initial research tended to focus on breast cancer patients since this patient population was amongst the first to report cognitive changes following a chemotherapeutic treatment. As a result, cognitive malfunctioning after a cancer treatment was called 'chemobrain' [425, 426]. Researchers have tried to find an explanation why these problems may arise. Some have looked into structural and functional changes in the brain using imaging studies, others have tried to identify other factors that may cause chemobrain [121, 131, 369]. However, it was interesting to find that a number of patients experienced cognitive difficulties prior to any adjuvant treatment [365]. Only few researchers have looked into baseline CRCI and those few focused on breast cancer patients alone. Therefore, no consensus has been reached on those factors that can explain the number of patients with CRCI at that time [145, 365].

In Chapter 4, Part I, research focuses on identifying risk factors for CRCI prior to the cancer treatment. Identifying possible risk factors for baseline CRCI may lead to new screening methods in the early detection of CRCI. In total, 125 patients consented for participation. Patients were assessed with a neuropsychological assessment and patient-reported outcome measures (PROMs) prior to the cancer treatment. An overall CRCI, based on the definition of the International Cognition and Cancer Task Force (ICCTF), was detected in 29.6% of patients before treatment [148]. Binary logistic regression analysis indicated that overall CRCI, according to the definition of the ICCTF, was predicted by a lower premorbid IQ ($\beta = -0.084$, $p<0.01$) and a higher level of fatigue ($\beta = -0.054$, $p<0.05$). No differences were found between impaired and non-impaired patients for age, gender, education age, distress, anxiety, depression, fatigue, subjective cognitive complaints, days between surgery and baseline assessment, active treatment with anxiolytics/antidepressants/antihypnotics, having a prior or current diagnosis of depression or anxiety, stage (early vs late stage), or cancer type (breast cancer vs other cancer type). A significant difference was found for premorbid IQ ($p<0.01$) as measured by the Dutch Adult Reading Test. Non-impaired patients presented with a mean premorbid IQ of 107.0 (range: 79.0-124.0), whereas the mean premorbid IQ of impaired patients was calculated as 101.5 (range: 82.0-116.0).

When looking at individual cognitive domains, multiple regression analyses revealed that all cognitive domains can be predicted by premorbid IQ, which indicates that a higher IQ results in a better test score. Visual and verbal episodic memory, information processing speed, semantic word fluency, and flexibility were also influenced by age, favouring younger patients. Verbal episodic memory was further predicted by gender. Processing speed was also in part predicted by an active treatment for hypertension. Similar findings regarding these risk factors have been found in other trials [145, 362, 363]. However, when screening for CRCI, identifying risk factors for overall CRCI is more interesting and more valuable for routine practice.

One of the most interesting findings in Chapter 4, Part I, is that premorbid IQ seems to play an important role when trying to identify those patients who are more prone to present with CRCI at baseline. Although it has not previously been reported in a group of general cancer patients and in terms of overall CRCI, it is known that neuropsychological test scores are influenced by the IQ of the cancer patient. Ahles et al. (2008), for example, reported that pre-treatment cognitive reserve was related to post-treatment cognitive decline in a group of breast cancer

patients exposed to chemotherapy [365]. Schilder et al. (2010) also reported that IQ influenced cognitive outcome results in postmenopausal breast cancer patients [115].

In addition to premorbid IQ, the level of fatigue of the patient also influenced overall CRCI. It is no surprise that cancer patients can experience a high level of fatigue at baseline when accounting the number of doctor appointments and exploratory or diagnostic interventions that they are faced with [427]. Only limited data is available to support this finding. Booth-Jones et al. (2005) examined the cognitive function of patients undergoing a bone marrow transplantation and reported that the level of fatigue influences cognitive impairment [360]. Another trial stated that symptoms of fatigue were related to observed impairments in breast cancer patients when compared with healthy controls, prior to adjuvant treatment [143].

Chapter 4, Part II, continues the search for variables predicting CRCI, but when compared to Part I, this chapter aims at evaluating whether the DT can be used to predict objective cognitive impairments six months after treatment initiation (T1). As previously mentioned, researchers have tried to identify several causes of CRCI. Distress has been suggested as a potential risk factor, but it had not been investigated objectively. It was also investigated whether the DT could be used to predict subjective cognitive complaints at T1. In Part II, we also looked into the degree of cognitive decline between the baseline assessment (T0) and T1. Last, as the initial term for CRCI was ascribed as chemobrain, the role of chemotherapy was examined.

Chapter 4, Part II, includes the same patient population of Part I. Six months after patients had started their treatment, they were invited to participate in the second assessment of the CONCEPT-trial. A dropout of 15.2% was noted. Of the initial 125 patients, five patients withdrew from the trial without giving a specific reason, five patients felt too ill, four patients did not want to make the extra travel to the hospital, three patients had died as a consequence of their disease or treatment and two patients declared to have no time. The remaining 106 patients were assessed with the same neuropsychological test battery as in Part I including PROMs.

At T0, 60.4% of patients showed a DT score of ≥4, whereas 50% met these criteria at T1. According to the definition of the ICCTF, 25.5% and 28.3% of patients presented with a CRCI at T0 and T1, respectively. In order to accept the DT as a screening tool to predict CRCI, it was calculated that the AUC under the null hypothesis was 0.50 and that an AUC under the alternative hypothesis of 0.70 would be found. ROC-curve analysis showed an AUC <0.5, therefore rejecting the alternative hypothesis. With an AUC below 0.5, it can be stated the screening tool has less value than tossing a coin and has no value for use within routine practice. Binary logistic regression analysis found that fewer distress at T0 (B=-0.267, p<0.05), having a lower premorbid IQ (B=-0.066, p<0.05), female gender (B=1.861, p<0.05) and no surgery (B=-1.745, p<0.05) predicted CRCI at T1. Chemotherapy did not influence the risk on CRCI (B=0.186, p=0.666).

As premorbid IQ seems to influence assessment results at both T0 and T1, there should be no doubt about the role of this variable. Results of Chapter 4, Part II, also indicated that in this selected patient group, chemotherapy did not seem to influence assessment results since no differences in neuropsychological test scores could be detected when comparing patients with and without chemotherapy at T1. This supports why researchers have started to use the term ‘CRCI’ instead of chemobrain or chemofog [383].

Interestingly, female individuals tend to have more CRCI at T1 than males. In the selected sample, a high number of females were included (69.8%) with the majority of those being diagnosed with breast cancer (68.9%). Gender differences have been observed previously in non-cancer subjects [378], but have not been confirmed in cancer subjects [144]. An interesting

question is why breast cancer patients seem to be more prone to have cognitive difficulties six months after treatment initiation. An explanation may be that the breast cancer patients included in our trials, of which the majority only received radiotherapy followed by hormonal treatment, experience more distress as a results of less close follow up compared to the cancer patients who received chemotherapy where the time period between the end of the treatment and the second assessment was much shorter (data not shown). Another interesting finding was that only few patients actually developed CRCI from T0 to T1 whereas in other subjects the CRCI, detected at baseline, was no longer present at T1. Patient groups seemed similar in terms of gender, diagnosis and treatment. The first group, however, showed more signs of fatigue at T1 while fatigue in the second group decreased. This also supports the theory that psychosocial problems may attribute to CRCI.

In case of subjective cognitive complaints, as measured by the Cognitive Failure Questionnaire (CFQ), ROC-curve analyses showed an AUC±SE of respectively 0.642±0.067 for the DT. Although this still not meets the hypothesis criteria of 0.70, it does indicate the role between the level of distress and the patients' perception of their own cognitive functioning. When looking into the FACIT-Fatigue Scale to screen for cognitive complaints at T1, the AUC±SE was calculated as 0.794±0.057. The latter two AUC's, when using PROMs, clearly indicate that psychosocial factors influence how patients perceive their memory and concentration.

When looking into changes over time, in most cognitive domains, patients tended to perform better at T1 when compared to the baseline assessment. Only in case of verbal memory, measured by the Rey's Auditory Verbal Learning Test (RAVLT), a decline in performance was observed. Although this has been previously found in another trial [132], in this test battery, the RAVLT was the last test to be assessed. This finding could thus merely be the result of the patient's level of mental fatigue at that point.

Limitations of Chapter 4

In Chapter 4, limitations to the study population, study design and used normative data to convert raw neuropsychological test scores can be noted. Part I and II are based on findings of the CONCEPT-trial. The CONCEPT-trial included a group of general cancer patients. Whilst the inclusion of a heterogeneous group of patients has the advantage of obtaining information on CRCI in all cancer types, a distribution of the different cancer diagnoses as would be expected from prevalence figures was not found. In the trial, a high number of breast cancer patients were included. As a result, some results may have been influenced by the high number of female individuals with breast cancer that participated in the trial. For example, in Part II, it was found that the female gender predicted the CRCI outcome. As the majority of the included female subjects were diagnosed with breast cancer, this highly suggests that not females in general, but solely breast cancer patients are more prone to present with CRCI. When looking at previous research, this finding is not that surprising, as initial trials investigating CRCI have been focussing on this patient group. It remains interesting, however, as previously mentioned, why breast cancer patient are more vulnerable to cognitive deficits. Regarding the study population, it should be mentioned that patients with a current depression or anxiety disorder were allowed to participate in the trial, though it is known that these emotional disorders could affect cognitive performance. As it has been reported that depressive patients show less motivation to complete a task, we hypothesized that patients, were willing to participate, were intrinsically motivated to perform well on the neuropsychological assessment. Ultimately however, no patient with a depressive or anxiety disorder was included. Results could also have been biased if patient's received psychological support between the baseline assessment

and the assessment at T1. Though the number of patients receiving support was not documented, all patients were offered psychological guidance by either an oncologist nurse or oncopsychologist. Consequently, if this would have altered their test results, this effect between patients should be limited.

Another limitation of the data presented in Chapter 4 concerns the study design. The CONCEPT-trial was set up as a prospective, observational study including a group of general cancer patients scheduled to receive a curative cancer treatment. In order to fully attribute the obtained results to the cancer process, a healthy control group should have been included. Nonetheless, it would have been difficult to find a proper control group as these subjects would have had to be healthy, but at the same time would have had to suffer from a sufficient degree of distress, fatigue, etc. To reduce this limitation, a few methods were selected. First, the number of patients that presented with a CRCI was compared to the binomial probability distribution by use of a binomial test. When using such test, the number of patients that would be expected to present with a CRCI based on the number of neuropsychological test that are included in the test battery, has to be calculated. When including eight independent tests, approximately 17% of patients would perform 2 SDs below the normative mean on a single test. This number was then compared to the actual number of cancer patients that scored at least -2 SDs below the normative mean on one test. In both Part I and II, a significant difference between the expected and the actual number of patients meeting those criteria was found, indicating that normal variance alone could not explain why that many patients score -2 SDs below the normative mean on a single test. When looking into the effect of chemotherapy at T1, patients without chemotherapy were used as a control group, as an equal number of patients were included with and without chemotherapy.

Regarding the used normative data for converting raw scores into standardized z-scores, it has to be mentioned that some neuropsychological tests, such as the RAVLT and Complex Figure Test (CFT), did not provide optimal z-scores for older patients. Z-scores can only be calculated in three age categories (>30, 30-50, and <50 years), which may result in higher number of impaired older patients. On the other hand, when performing the linear regression analyses in Chapter 4, Part I, raw test scores were used instead of z-scores. Raw scores were selected to be able to compare our results with findings of other researchers. Therefore, the age and IQ effect may be more present in these results. Nonetheless, when using the standardized z-scores, IQ effects remain present in all domains. The influence of age remains present in the RAVLT and both conditions of the Trail Making Test (TMT). For the RAVLT, this may be due to the suboptimal normative data. In case of the TMT, the age effect should have been ruled out when converting into z-scores. Nonetheless, it has been reported that age may influence processing speed and executive functioning in cancer patients [145].

Changes were not evaluated by use of the RCI. The main reason is that, as mentioned in the introduction, patients with a lower baseline score would need a greater percentage of decline in order to be meaningful by the RCI. As it has been reported that baseline cognition can be affected in cancer patients, an RCI would not detect some changes as clinically relevant while they do influence the patients' subjective feeling about their cognition.

The trials in Chapter 4 also did not include any questionnaires regarding rumination. Rumination can be described as the repetitive and recursive rehearsal of cognitive content. Rumination could be of interest when looking into predictors of CRCI as research has reported an association between rumination and impaired problem solving and concentration [428]. In cancer patients, rumination has been found to correlate with the level of depression and anxiety

[429]. Further, higher levels of rumination were also related with increased psychological distress [430]. Therefore, it could be stated that rumination was indirectly assessed in this chapter. Nonetheless, while rumination itself was not directly assessed, the EORTC quality of life questionnaire was assessed at baseline and six-months post treatment initiation. One of the questions included in this questionnaire asks the patients if they worried during the last week. While not examining rumination itself, it was found that the score on the DT and the score on the question of the EORTC QoL scale were correlated (r_s=0.555; p<0.001). Therefore, it could be stated that it was indirectly assessed. Nonetheless, binary logistic regression analysis revealed that this question could not predict baseline CRCI nor could it predict objective CRCI at T1 (data not shown). However, future research should implement rumination questionnaires in order to evaluate its influence on CRCI.

Strengths of Chapter 4

CRCI in general is considered as a hot topic within the field of psycho-oncology. Many patients experience cognitive troubles and very little is known about its etiology. Screening for CRCI is important as to day, there is a growing group of cancer survivors who want to return to work and pick up their social activities after treatment. Having to deal with memory and concentration problems delays this process, seriously affecting their quality of life. A lot of research has been performed these last years in order to learn more about CRCI. Whereas some cancer treatments may induce neurotoxicity, most systemic treatments cannot cross the blood-brain barrier. In both Part I and II, a large number of hypotheses were tested. New insights were found and new hypotheses have become apparent.

One of the difficulties researchers are faced with when studying CRCI, is to find a good definition. In order to compare results of CRCI with others, the ICCTF published following definition: patients will be marked as having a cognitive impairment if they either present with two or more test scores at or below -1.5 SDs from the normative mean or if they present with one test score at or below -2.0 SDs [148]. In Chapter 4, this definition was used. The ICCTF also published guidelines concerning the minimal neuropsychological data set that a researcher should implement when conducting trials into CRCI. As advised, the used neuropsychological test battery was based on their suggestions. Implementing the definition and the proposed assessment is essential if researchers want to compare their trial results.

In Chapter 4, a general group of cancer patients was included. Whereas other researchers tend to focus on one cancer type, mainly breast cancer, it is important to include patients with cancer diagnoses other than breast cancer as they may also experience cognitive dysfunctions. Further, as a large group of breast cancer patients was included, it was possible to compare the results of those patients with the results of other cancer patients. In Part I, for example, it was found that breast cancer patients - although not statistically significant - experienced more subjective cognitive complaints when compared to other cancer patients. On the contrary, a fewer percentage of breast cancer patients was found to have CRCI compared to other cancers. One explanation may be that the breast cancer patients included in our trials, of which the majority only received radiotherapy followed by hormonal treatment, experience more distress as a results of less close follow up compared to the C+ group where the period between the end of the treatment and the second assessment was much shorter (data not shown). Further, in Part II, by including an equal number of patients with and without chemotherapy, the effect of chemotherapy on CRCI at T1 could be compared between both groups. An important finding was that in this selected patient group, chemotherapy did not

seem to influence CRCI. This may suggest that the impact of chemotherapy is smaller than suggested by others.

Implication for routine practice

As it was found that CRCI are influenced by the patient's IQ, researchers should implement some form of IQ test when conducting research into CRCI so neuropsychological assessment results can be adjusted for this variable. Further, psychosocial variables such as distress and fatigue seem to play an important role in the etiology of cognitive complaints. While for a researcher, it is interesting to know the exact number of patients with an objective CRCI, subjective cognitive complaints tend to influence the patients' life far more when they want to return to their former lives. An interesting trial could also examine the reciprocal effect of coping, rumination and distress on cognitive complaints in cancer patients.

To date, there are no rehabilitation programs available to cope with cognitive complaints. Next, as distress and fatigue influence these problems, reversing distress and fatigue, next to coping mechanisms for cognitive difficulties, may be more interesting. Further, it should be noted that the results, found in Chapter 4, Part II, might provide a first step towards a proper screening method. When screening for subjective cognitive complaints, both the DT as well as the FACIT-Fatigue Scale could potentially be used. However, as this was not the focus of the CONCEPT-trial, a prospective study validating these measurements should be set up.

CHAPTER 6
Conclusion

PART IV
Screening for hearing loss in older cancer patients

When conducting a CGA, the NCCN Guidelines in Older Adult Oncology recommend to evaluate sensory (dys)functions including the patient's vision and hearing [102]. Whereas difficulties with vision can be easily detected as most patients with vision loss wear eye glasses, hearing loss often stays undetected [213]. As a logical consequence, the NCCN recommends to screen for hearing loss by a screening tool that is comparable to the Whispered Voice Test (WVT) [102]. Nonetheless, in a busy clinical practice, an evaluation of the patient's hearing status is often not included in the CGA.

Chapter 5 of this thesis focused on a screening tool to assess hearing loss in older cancer patients as part of the CGA. Since the WVT did not seem to be the most optimal test for use, especially when one accounts the problems regarding the poor interrater-reliability, it was decided to use an existing mobile health application that can be used on a cell phone or tablet. uHear™ was selected as the screening tool against which conventional pure tone audiometry would be compared. There are several reasons why this particular tool was selected. First, uHear™ was freely available to all persons who have a device running on iOS software. Second, the interface was user-friendly and straightforward in use. Third, there was no data available for any of the other existing hearing applications in which older cancer patients were selected. Further, older patients were often not included in trials looking at the diagnostic properties of these apps, whereas one trial evaluated uHear™ in older subjects. Further, uHear™ showed a good S and Sp in several settings, including an evaluation in a clinical setting outside a sound booth. Since the latter was comparable to the setting in which we wanted to use the application, uHear™ was favourable when compared to the other existing screening tools [431].

The first research question that was investigated evaluated whether uHear™ could be used as a screening tool to detect hearing loss in older cancer patients as part of the CGA, when using the application in its current form (Chapter 5, Part I). In Part II, a new scoring method was evaluated. Following table (Table 1) gives an overview of the diagnostic properties of uHear™ in each cohort. When using the original method, uHear™ was compared to conventional pure-tone audiometry both using a pass or fail screening cut-off based on a PTA of ≥40 dB HL. In the validation cohort, uHear™ found a PTA of 40 dB HL or more in 69.2% of tested ears. It showed an excellent S of 100.0%, but poor Sp of 36.4%. This method showed similar results in terms of diagnostic accuracy when calculated in the second cohort. While in Chapter 5, Part I, uHear™ - scored with the original method - had an excellent AUC of 0.98, it is not suitable as a scoring method as too many patients would be referred to the audiologist, even though they would not show a significant hearing loss when assessed by conventional audiometry. This highly reduces the usability of the tool in clinical practice. Several explanations may be found for this poor Sp results. uHear™ overestimated the actual hearing level in the lower frequency region. Although ambient noise was reduced to a minimum, it could not be excluded completely. Further, this specific patient population was not familiar with the touch screen device. As uHear™ demands an immediate tap when a stimulus is presented to the patient's ear, a delayed tap caused by the unfamiliarity of using a touch screen, may have led to higher hearing thresholds.

Retrospectively, new scoring cut-offs and scoring methods were tested. This led to two new possible ways for scoring uHear™. The first improved scoring method was also based on the PTA. Instead of using a PTA of 40 dB HL or more as the cut-off score, the cut-off for uHear™ was increased to ≥55 dB HL. When comparing this to conventional audiometry hearing results with a PTA of ≥40 dB HL, S remained 100.0%, but Sp of the test improved significantly to

78.0%. Although this highly improves the diagnostic properties of the test, scoring uHear™ by calculating the PTA is not practical as a scoring sheet has to be used since uHear™ results are not presented in numerical data, but in hearing grades. Therefore, a new method based on these hearing grades may be easier for use in routine practice. Scoring uHear™ by using this type of scoring system had previously been tested by Handzel et al. (2013) [413].

By using the data of Chapter 5, part I, a new pass or fail screening cut-off was defined as having two or more consecutive hearing grades starting from the moderate-severe threshold zone ranging from 0.5 – 2.0 kHz. When evaluated in the first cohort, uHear™ showed a sensitivity of 100% and specificity of 89.1% (Table 1). As this new method showed promising results, it was validated in a second set of subjects as discussed in Chapter 5, Part II. Data showed a sensitivity of 68.2% and specificity of 86.8%. It was stated that – in order to validate the tool - the combined S and Sp of uHear™ (S+Sp/2) in this second cohort, had to be at least 80% and that an actual combined (S+Sp)/2 of 90% would be found. As the combined (S+Sp)/2 of the test was calculated as 77.5%, it has to be concluded that the tool cannot be implemented within the CGA.

When comparing the diagnostic properties of uHear™ from Part I and Part II, solely looking at the validation cohorts, following conclusion can be noted. First, the S dropped from 100.0% to 68.2%. On the contrary, the Sp improved from 36.4% to 86.8%. When comparing the combined diagnostic property ((S+Sp)/2), results improved from 68.2% up to 77.5%. Although this new cut-off score would miss a few of the ears with an actual significant hearing loss as measured by conventional audiometry, it does have a much better combined diagnostic property compared to using a cut-off score based on a PTA of 40 dB or more. Second, when looking at the S and Sp of uHear™ when using a cut-off based on a PTA of 55 dB or more in Part II, results did not excel the S and Sp of the test with the pass or fail screening cut-off based on hearing grades (data not shown). Third, using a scoring method based on hearing grades highly improves the usability of the tool as the result can be read directly from the screen, whereas a scoring sheet has to be used when using a cut-off based on the PTA.

An option to increase the S and Sp of the screening tool may be to use a pass or fail screening cut-off stating that the patient fails the screening if two or more non-consecutive hearing grades are detected in at least one ear within the 0.5-4.0 kHz frequency region starting from the moderate-severe threshold. When comparing this criterion to a PTA of at least 40 dB HL in one ear as measured by conventional audiometry, the obtained data in Chapter 5, Part II, show an S of 73.9% and a Sp of 86.4% (Table 1).

In Chapter 5, Part I, the WVT was also compared to conventional audiometry as this was the screening tool that was proposed by the NCCN Guidelines. The tool showed a low S (30.0% (95%CI[8.1–64.6])), but excellent Sp (100.0% (95%CI[91.9–100.0])). However, a good screening tool needs a high S as it reduces the number of false negative cases. While changing the pass or fail cut-off for the WVT (for example fail when 2 out of 4 conditions are missed) showed a better diagnostic accuracy, using another scoring method for the uHear™ remains favourable as results indicate a better combined diagnostic accuracy than any type of pass or fail cut-offs of the WVT. In this paper, the diagnostic properties of the Hearing Handicap Inventory for the Elderly (HHIE) were also investigated. Since most patients had difficulties admitting they had a hearing problem, this tool was unable to screen for objective hearing loss as measured by conventional audiometry.

Table 1. Overview of the diagnostic properties of uHear™ per cohort and per scoring method

	First cohort (n=33) *Population of Chapter 5, Part I*			**Second cohort (n=45)** *Population of Chapter 5, Part II*		
	Original method*	**New method**	**Optimised method**	**Original method**	**New method***	**Optimised method**
S (%)	100	100	78.6	100	68.2	73.9
95% CI	[65.5-100.0]	[65.5-100.0]	[48.8-94.3]	[81.5-100.0]	[45.1-86.1]	[51.3-88.9]
Sp (%)	36.4	89.1	78.9	38.2	86.8	86.4
95% CI	[24.1-50.5]	[77.1-95.5]	[53.9-93.0]	[27.0-50.9]	[76.4-93.8]	[64.0-96.4]
PPV (%)	22.2	62.5	73.3	34.4	62.5	85.0
95% CI	[11.7-37.5]	[35.9-83.7]	[44.8-91.1]	[23.2-47.4]	[40.6-81.2]	[61.1-96.0]
NPV (%)	100	100	83.3	100	89.4	76.0
95% CI	[80.0-100.0]	[90.9-100.0]	[57.7-95.6]	[84.0-100.0]	[79.4-95.6]	[54.5-89.8]
(S+Sp)/2 (%)	68.2	94.6	78.8	69.1	77.5	80.2
AUC (±SE)	0.980 ± 0.14	NA	NA	0.881 ± 0.036	NA	NA

Abbreviations: S: sensitivity, Sp: specitivity, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, SE: standard error; CI: conficence interval; NA: not applicable.

Original method: pass or fail cut-off defnided by a PTA of 40 dB or greater

New method: pass or fail cut-off defined as having two two or more consecutive hearing grades starting from the moderate-severe threshold zone ranging from 0.5 – 2.0 kHz

Optimised method: pass or fail screening cut-off stating that the patient fails the screening if two or more non-consecutive hearing grades are detected in at least one ear within the 0.5-4.0 kHz frequency region, starting from the moderate-severe hearing grade

* validation cohorts

Limitations of Chapter 5

Limitations of Chapter 5 relate to the study design, study population and used measurements. With respect to the study design, in both the UHEAR and UHEAR-Bis trial, the PTA was calculated as the mean of the threshold levels at 0.5, 1.0 and 2.0 kHz. A limitation to the use of these three frequencies in older patients is that it eliminates those frequencies that are most affected in case of ARHL. Further, stating that the patient has a significant hearing loss if the PTA is 40 dB HL or greater when using these frequencies, is very strict and communication may be already seriously affected at that point. Turner at el. (1990) reported that a loss exceeding 30 to 40 dB on speech frequencies (ranging from 300 to 3000 Hz) is unacceptable for proper communication [432]. Adding 4.0 kHz into the equation may in part compensate for this limitation and provide more information on the hearing capability for speech frequencies. In Chapter 5, Part I, the use of these three frequencies was chosen, as these are the frequencies that are provided by the ASHA to calculate the PTA. In Part II, three frequencies instead of four were used to calculate the PTA as adding 4.0 kHz did not substantially improve diagnostic accuracy (data not shown). Nonetheless, a speech-in-noise (SPIN) screening test may be more useful in these cases. There are some Dutch SPIN-tests that could be of value in this particular population, such as the Digit Triplet Test, developed by Jansen et al. (2013) [433]. Though freely available on the internet, administration is rather time-consuming which prolongs the already intensive CGA assessment. Further, those tests requires a computer or laptop and is therefore less practical for use in a busy geriatric oncology clinic where many patients are seen in patient rooms. There are some SPIN-tests available for use on iOS and Android devices such as the SPIN-test included in uHear™, however, those screening measures are not available not in Dutch, which limits the use of SPIN-tests in the setting and population of interest.

Another limitation regarding the study design is that both the UHEAR and UHEAR-Bis trial excluded patients with a known hearing loss, which was defined as either having a documented diagnosis that is available in the patient record or having hearing aids. Consequently, only a limited number of patients with a significant hearing loss were included in the trial. This may have altered the diagnostic properties of the WVT, HHIE and uHear™ as in a validation study, all patients - with or without hearing loss – typically would have been included. If the patient has a known hearing disorder, a screening test is redundant as health care providers can already approach the patient appropriately. In case of hearing aids however, it could be possible that they do not offer optimal amplification as it has been noted that even with sufficient elevation of the sound to an audible level, speech intelligibility can remain poor [434]. Therefore, in these cases, free-field (FF) testing would be more suitable though it would be difficult to perform a FF-test based on pure tones in a hospital room of physician's office where background noise cannot be excluded. Further, while mentioning FF testing, another shortcoming of uHear™ is that it does not combine the results of both ears, while in normal listening situations, the information received by both ears is processed together through central processes. As a result, missed information by one ear can be heard by the other and vice versa which could improve hearing sensitivity. When conducting uHear™, it is not possible to mask the other ear. Thus, in case of a large discrepancy of the hearing thresholds between both ears, the non-tested ear may influence the patient's response and could therefore lead to an underestimation of the actual threshold. Another reason to implement FF tests includes the type of transducer used in these trials. Audiometric testing was performed by use of a supra-aural headphone, while uHear™ was conducted with standard Apple earbuds. As it has been reported that the use of insert earphones result in higher hearing thresholds – especially in the

lower frequency range due to the loss of vibration on the ear and cranium, this could be in part have attributed to the overestimation of the lower frequencies by uHear™ [402].

Regarding the study population, the distribution of cancer types was not according to the expected incidence. This was a result of including on solely one site of the hospital. However, this should not have altered results, as there was no cancer type that was more prominent than another.

In respect of the used measurements, some limitations for uHear™ were reported. First, uHear™ tends to overestimate lower frequency. This may be due to the ambient noise that is present in the room during testing. Further, higher hearing thresholds per frequency may have been detected as a result of the unfamiliarity of the patient with a touch screen device. uHear™ demands that the subjects taps the screen immediately when a sound is heard. However, older patients are not that familiar with touch screen devices and difficulties with the tapping were observed in some cases. When using the screening tool, standard non-calibrated Apple earbuds were used accompanied by an iPod Touch of the examiner. Therefore, one cannot be 100 percent sure that the sound level of the stimulus presented by the device is exactly the sound level it should be. However, the usability of the tool is significantly reduced as in routine practice, recalibration of earbuds would interfere with an easy implementation of the screening tool. These shortcomings in uHear™ have led to a low Sp of the test, resulting in a large number of patients needlessly being referred to the audiologist or otolaryngologist. In order to tackle these limitations, a new screening method – accounting for these effects – was retrospectively determined and evaluated in part II. This resulted in an improved Sp and another step forward in the search of the best cut-off score for uHear™ to screen for hearing loss within the CGA.

In Chapter 5, both hearing and cognition were assessed. While not within the scope of the research conducted and not predefined as an endpoint of the trials, looking at the relationship between these variables could be interesting as it has been reported that impaired hearing is associated with a greater risk of dementia [435]. Retrospective analyses looking into the correlation of the PTA and the result on the MMSE or CDT, did not reveal any interaction nor in the first nor in the second cohort (data not shown). This could be the results of following reasons. Firstly, it was predefined that patients with diagnosed dementia or a poor cognition, according to the investigator's judgement, could not participate in the trial. Second, patients with a known hearing disorder or known hearing loss were also excluded from participation. Therefore, the exact link between hearing and cognition in this population could not be properly assessed.

Strengths of Chapter 5

In Chapter 5, a new screening method to detect hearing loss in older patients with cancer was evaluated. uHear™ was selected since it had shown a good S and Sp in previous research [257]. The tool is very easy to use and the administration time was set at approximately five minutes. Further, uHear™ can be used on any device that runs on iOS software, such as an iPod, iPad of iPhone and could therefore be easily implemented if results would have been excellent. When evaluating uHear™, it was found that the assessment time of the screening tool and conventional audiometry did not differ significantly as most patients were not familiar with touch screens and training was necessary. However, uHear™ does lead to profit in time since patients do not have to be transferred to the audiology department of the hospital. Further, in the future, training may become redundant since it can be expected that more

patients will be familiar with touch screens. uHear™ was also well accepted by patients according to the judgement of the audiologist.

Implications for routine practice

At present, most geriatric oncology teams do not implement a hearing screening when assessing the CGA. The hearing assessment as part of the CGA should not be included to define the patient's total vulnerability. It should be used as an important informative assessment as knowing if the patient has a decreased hearing is crucial for cancer patients who need to hear and understand a lot of information on their diagnosis, its treatment and possible treatment-related side effects. Older patients are very proud of their independence and in many cases, sensory dysfunctions including vision and hearing loss are one of the first functional declines they have to deal with. Although wearing glasses is well accepted by both young and older people, hearing aids are not that well accepted by many persons. As a result, older patients tend to hide a hearing loss which, in an oncogeriatric population, may lead to missing essential information about the cancer diagnosis, its treatment and/or its treatment-related adverse events [414]. If health care providers know that the patient has trouble hearing, they can easily adapt their speech and improve the signal to noise ratio, make sure they have a good pronunciation, give written instructions, make sure the patient has heard the information, etc. Providing a hearing screening as part of the CGA is the first step toward addressing hearing loss in the older cancer patient in an objective manner. Further, it should be noted that addressing the patient's hearing will probably not lead to an increased use of hearing aids in this population. Though uHear™ was well accepted by patients, even by those with a significant hearing, patients were not eager to go see a hearing aid professional.

It can be disputed whether uHear™ is the best screening tool to implement within the CGA. It has without doubt some benefits such as its accessibility, its user-friendly interface, its administration time and its diagnostic accuracy but it cannot be ignored that there is still a need for improvement as it shows a large discrepancy between threshold levels measured by the tool and standard pure tone audiometry. The use of uHear™ to monitor ototoxicity, however, should be evaluated as results in the higher frequency region correspond with those of conventional audiometry.

Further, as shortly mentioned above, a SPIN-test would be more suited to implement within the CGA as it provides information the patient's functional status. As there are no Dutch SPIN-tests available for use on mobile phones, future research could focus on developing a short Dutch and French SPIN-test, equivalent to for example uHear™' speech-in-noise test, that can be used within the CGA. Preferably, this new screening tool offers binaural testing.

CHAPTER 6
Conclusion

PART V
Future perspectives

In future, it will remain essential to further explore screening measures to detect cognitive and auditory dysfunctions in cancer patients of all ages. For any health care provider and in any clinical setting, it is crucial to know whether a patient can hear and understand the given information.

Older patients with cancer are extremely vulnerable to deteriorate as a consequence of their cancer diagnosis and cancer therapy. Therefore, a CGA remains the key pre-treatment approach in order to establish the patient's ability to tolerate the proposed therapy as CGA-based interventions can increase both life expectancy and quality of life. When screening for cognitive dysfunctions within the CGA, based on the results of this thesis, it can be concluded that the Freund CDT can be implemented within the CGA. A positive result on the CDT should always be followed by an assessment with the MMSE before a referral to a neuropsychologist, neurologist or geriatric day clinic is made, as our results indicated a number of false positives on the CDT. Consecutive assessment by the MoCA instead of the MMSE, since this test is more sensitive to detect mild cognitive impairments and assesses more cognitive domains, can also be considered. However, it should be noted that this thesis does not provide data on the subsequent assessment of the MoCA after a positive CDT result. Cognitive assessment results should be reported in the patient's medical record. In case the CGA assessment reveals impaired cognition and an in-depth neuropsychological assessment is not possible, health care professional should be made aware of the patient's cognitive functioning through a notification when the patient's medical record is opened. Further, it is advised to confirm CGA findings with a patient proxy in case of declined cognition as answers on e.g. ADL and IADL may be different from reality.

While the CGA aims at identifying pre-existing cognitive impairment, older cancer patients may experience cognitive decline due to their cancer, cancer treatment or cancer-related psychosocial factors. Further, these problems may be present in both old and younger cancer patients. Future research on CRCI is essential as many patients experience cognitive complaints and still only little is known about its existence, especially since CRCI negatively influences patients' QoL and return to work process [436]. Further, it is necessary to broaden the landscape of CRCI and to investigate the influence of a cancer diagnosis and treatment in all cancer types and not solely in breast cancer patients. It was surprising that already at baseline, many cancer patients presented with cognitive difficulties. Though one could attribute this cognitive loss to a pre-existing deficit, this theory does not explain these cancer-related cognitive impairments, or CRCI, in younger subjects. As it was found that premorbid IQ is a confounding factor for CRCI at baseline, researchers conducting future clinical trials on CRCI are strongly advised to implement a short IQ test.

This thesis also highlights the importance of psychosocial screening in cancer patients as it may influence both objective and subjective cognitive dysfunctions at baseline and six months after treatment initiation. Future research should focus on the use of psychosocial screening measures such as a rumination scale, the DT and FACIT-Fatigue scale to screen for subjective cognitive complaints. Since distress is a multifactorial emotion, the individual role of different variables such as coping, depression, worry and anxiety should be examined. Further, in expectation of the exact pathophysiology, clinical trials should be set up to reduce the cognitive side-effects that cancer patients experience before, during and after cancer treatment such as the EMOTICON trial which examines the use of emotional freedom techniques, which is a brief and easy to learn self-help tool that involves tapping specific acupressure points on the top of the head, the face, collarbone and under the arm while pronouncing specific problems of

physical or emotional nature, to reduce cognitive complaints (clinicaltrials.gov identifier: NCT02771028) [437]. The EMOTICON-trial is based on the hypothesis that stress reduction leads to a reduction of cognitive complaints.

It may be difficult to distinguish pre-existing cognitive deficits from CRCI. Therefore, research should focus on the detailed investigation of the difference between pathological cognitive ageing and induced cognitive decline due to the cancer diagnosis, cancer treatment or related psychosocial variables. In most CRCI cases, it is expected that the cognition will return to baseline levels after cancer treatment has ended. Nonetheless, awaiting a clear understanding of these mechanisms, it is advised to schedule follow-up assessments once the cancer treatment has ended in order to re-evaluate the patient's cognition and prescribe proper interventions. Future trials should also focus on the development of a minimal neuropsychological dataset that can be used to assess ongoing CRCI in cancer patients/survivors.

The latter domain investigated within this thesis regards screening for hearing loss as part of a CGA in older cancer patients. At this point, it is not possible to include uHear™ within the CGA as it is not ready to be used in routine practice. Future trials should focus on either optimising the screening tool and exploring its value in case of ototoxicity monitoring or on the development of an eHealth tool providing a new pure-tone based screening method or short SPIN-test. Preferably, this SPIN test should be kept short as listening effort is often increased in older subjects and assessment of such test could enhance fatigue, which is already present in many cancer patients. Nonetheless, this type of test gives an adequate overview of listening in daily situations. It should further be evaluated whether this new screening could be conducted binaurally or in free field. Next, as the whispered voice test, the tool proposed in the NCCN guidelines, also failed to show excellent diagnostic properties, we advise against the use of this tool. We do strongly advise to incorporate a subjective assessment of the patient's hearing. If the person conducting the CGA feels the patient has a hearing loss, this should be mentioned in the CGA report. Ideally, a pop-up regarding this matter should appear when any health care provider opens the patient's medical record. It is not advised to ask the patient about his or her beliefs of their hearing as our results indicated a large discrepancy between patient reported hearing loss and objective audiometry results. Further, as there is an obvious interaction between hearing and cognition, future research is needed to examine this relationship in cancer patients as decline may be accelerated due to the cancer treatment.

In conclusion, it can be stated that there is a need to screen for both cognitive dysfunctions and hearing loss in cancer patients. While the Clock Drawing Test is ready to be implemented within the CGA for use in older patients with cancer, further research is necessary to select adequate screening tools for CRCI and hearing loss.

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CURRICULUM VITAE

Personalia

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Education

2013 – 2017	**PhD** Thesis: Screening measures to detect cognitive and auditory dysfunctions in (older) cancer patients Ghent University
2014 – 2016	**Teacher Education** IVO Brugge
2007 – 2011	**Master of Science in Logopaedic and Audiological Sciences - main subject Audiology** Thesis: The use of OAE as a screening measure. Magna Cum Laude Ghent University
2001 – 2007	**Latin - Sciences** Onze-Lieve-Vrouwecollege Assebroek

Additional Training

- Permanent Training Programme 'Hearing Aid Technician' (2010-2011)
- Online Course: Counselling for Cochlear Implantation: covering all the facts? (March 2011)
- Internal course Medical French (collaboration az groeninge, KULAK - BLCC, 2012)
- Certificate Good Clinical Practice for Clinical Trial Sites (Renewed Sep 2013)
- Certificate in Introductory Statistics. Basics of Statistical Interference (Doctoral School, Nov-Dec 2013)
- Certificate in Analysis of Variance (Doctoral schools, Jan-Feb 2014)
- Effective Slide Design (Doctoral Schools, May 2014)
- Speed Reading (Doctoral Schools, May-June 2014)
- Authentic Networking (Doctoral Schools, March 2015)

Teaching Assignments

- 'Routine Geriatric Oncology' (AZ Groeninge Kortrijk, January 2013)
- 'Basics of Geriatric Oncology' in the context of a postgraduate training for oncology nurses (HIVV KATHO-VIVES Kortrijk, February 2012, May 2013, June 2014, January 2016)

Publications

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