Unravelling heterogeneity in elderly cancer patients

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Design cover: Huub Maas & Inno van den Heuvel, Almedeon bv
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Printed by Almedeon bv, Oisterwijk

ISBN 978-90-9026372-4

Publication of this thesis was financially supported by Integraal Kanker Centrum Zuid (IKZ), Eindhoven and TweeSteden ziekenhuis, Tilburg/Waalwijk.

integraal
kankercentrum
Zuid

Unravelling heterogeneity in elderly cancer patients

Ongelijksoortigheid van ouderen met kanker ontrafeld

Proefschrift

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam

op gezag van de

rector magnificus

prof. dr. H.G. Schmidt

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op

donderdag 10 november 2011 om 13.30 uur

door

Hubert Alfons Anna Maria Maas

geboren te Terneuzen

ERASMUS UNIVERSITEIT ROTTERDAM

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Chapter 1

Context of this thesis

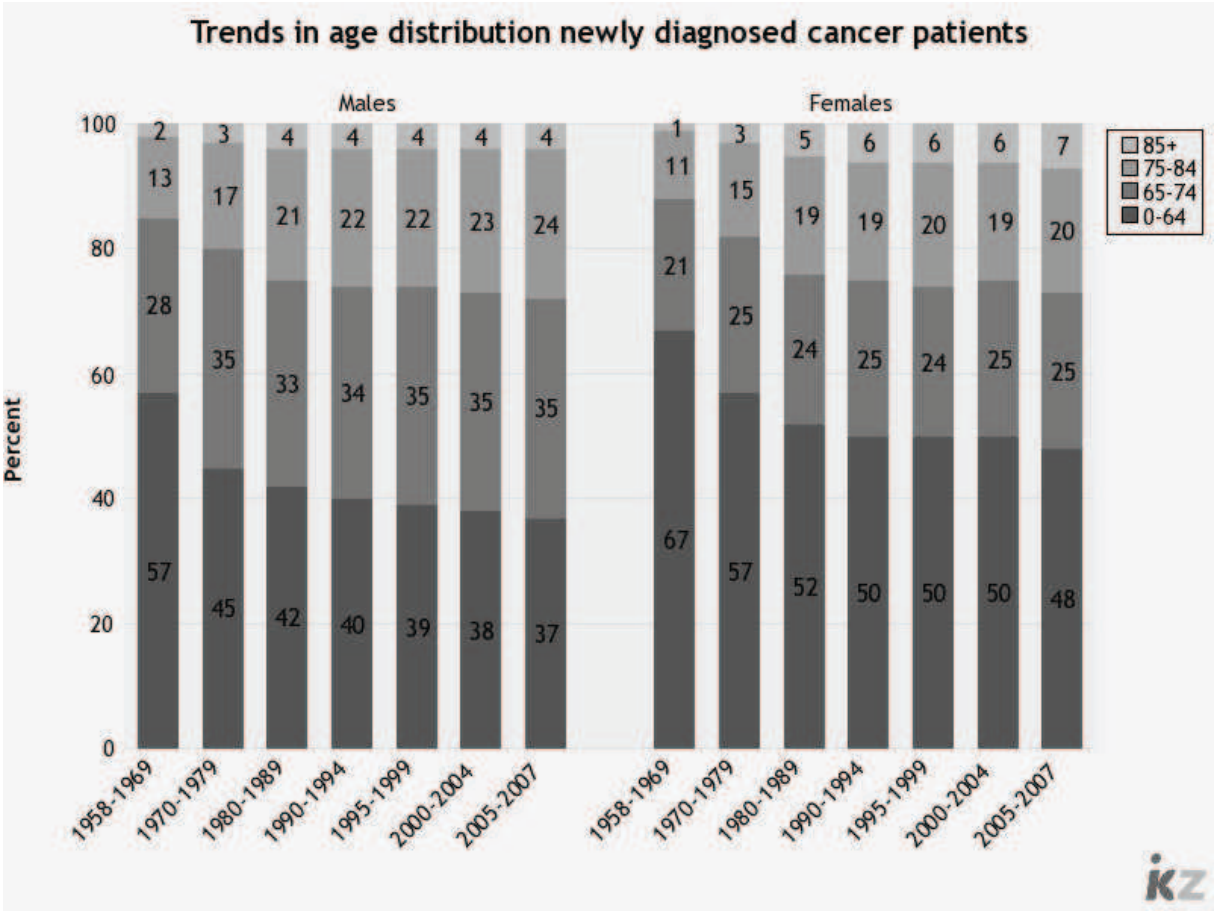
Introduction

Ageing societies are facing the impact of demographic changes in the next decades. By the year 2040 14% of the world population will be aged 65 and over, and 3.3% will be aged 80 years and over.[1] In the Netherlands in particular the population over 65 years is expected to increase from 14% in 2005 to 27% in 2040 and the proportion of octogenerians will more than double from 3.5% to 8.7%. In response to this, ageing is often portrayed as a financial-economical burden rather than social advance or challenge.[2] Effects on the health care system are numerous: more people will call on health care facilities, with an increasing frequency of combined acute and chronic diseases; limited functional capacities will be more present among elderly; and demographic and health care changes induce the need for more health care workers: in the Netherlands a `depletion state´ on health care professionals is predicted.[3] In community and clinical care, health care workers have to deal with groups of elderly patients that are very heterogeneous with respect to their underlying health status.[6] In this chapter key-elements are outlined that may be relevant to the delivery and outcome of cancer care in the heterogeneous group of elderly cancer patients.

Cancer care in ageing societies

With the ageing of the population the incidence rates for many tumour types will increase.[4] Figure 1 shows the trends on age distribution in newly diagnosed cancer patients in the Southern Netherlands (data from Eindhoven Cancer Registry). The percentage of male patients above 65 years of age rose from 43% in the 1960s up to 63% in 2005-2009. In the same period women showed a comparable trend from 33% to 52%. A shift towards the oldest old was also recognized (nowadays almost 30% of all newly diagnosed cancer patients is 75 years or older). Although the number of trials that include elderly is increasing, there are still discrepancies between trial populations and populations seen in clinical practice with respect to the age of included patients and other casemix-variables.[5-7] Since elderly patients (especially those with serious comorbidity) are often excluded from clinical trials, it is not clear whether treatment guidelines based upon these clinical trials are generalizable to the older cancer patients in everyday practice.[8, 9,10] Clinical trial data for patients over 80 years old are scarce.[11] Therefore, besides clinical trials other sources of information are needed to evaluate cancer care in elderly populations. Population-based data as collected by cancer registries give important information on treatment and outcomes in everyday practice.

Figure 1



Older patients, different patients, different needs?

Multimorbidity

Apart from functional limitations and dependency, multimorbidity is common in elderly patients. In Dutch general practitioners´ practices about two thirds of people aged 75 and over have one or more chronic conditions and more than 40% has two or more chronic conditions.[12] In newly diagnosed cancer patients serious concomitant conditions were present in 12% of adult patients below 45 years of age, 28% of those aged 45-59 years, 53% of those aged 60-74 years, and 63% of patients over 75 years of age. Males exhibited a 10% higher prevalence of comorbid conditions than females with similar tumours.[13] Especially the proportion of patients with 2 or more comorbid conditions increased from 17% in patients aged 50-64 years to 45% in patients above 80 years. In a more recent population-based study of our group, prevalence of any comorbid condition was highest for patients with lung (74%), kidney (69%), esophagus (72%), bladder (70%), and pancreas cancer (67%).[14] High prevalence rates of diabetes were observed for cancer of the cervix and corpus uteri, kidney and pancreas (respectively 31%, 25%, 21% and 24%). One should keep in mind that in these studies a

selection of comorbid diseases has been made (often related to comorbidity indices, i.e. Charlson's comorbidity index). As a consequence, i.e. arthrosis and diseases leading to visual or hearing impairment were not included.

In a review on studies on co-morbidity Heijmans concluded that the aim of most studies on comorbidity was to investigate its relation with treatment choices, mortality or complications.[15] In case of concomitant disease(s) treatment for an index-disease according to guidelines was attempted significantly less frequently. Incidence of complications showed no uniform trend, although especially diabetes mellitus was related to a higher rate of complications in course and treatment of an index-disease.[15,16] Also mortality, functional status, healthcare utilization and quality of life have been shown to be related to comorbidity.[17] Diseases that affect systems that are essential for maintaining physiological homeostasis (cardiopulmonary and renal system) were affecting mortality. Concomitant mental disorders were associated with decreased dependency and quality of life. As the prevalence of co-morbid conditions among elderly patient groups is regularly high, this emphasizes the need to obtain data concerning the course of (index)diseases and the benefits and complications of treatment regimens in this group with multimorbidity.

As a consequence of morbidity, and especially multimorbidity, polypharmacy may be present. Prevalence of polypharmacy is independently associated with the number of somatic complaints, chronic disease and increasing age.[18] Drug-interactions are of particular importance in oncology owing to the narrow therapeutic index and the inherent toxicity of anticancer agents.[19, 20] Although most drug interactions are manageable (monitoring, dose-adaptation, dose-timing), problematic polypharmacy and preventable medication-related hospital admissions are especially determined by impaired cognition, multi-morbidity (4 or more), dependent living situation, non-adherence to medication regimens and impaired renal function.[20 21] All of these are factors that are highly prevalent in elderly patient groups.

Functional status

In elderly, functional status is an important indicator of overall health condition. It reflects the need for health care services and, amongst others, it determines mortality risk.[22-25] Identification of prognostic factors is relevant for a correct choice of cancer treatment or a well-considered use of additional non-oncologic interventions. Patients disabilities in Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) predict mortality.[27] Information on these disabilities is additional to the assessment of treatment risks with the Eastern Cooperative Oncology Group (ECOG) performance status.[26, 27] Nevertheless, in oncology the prognostic effects of pre-treatment IADL and

ADL are not without controversies.[28]

Objective measures of physical performance (gait and balance tests, handgrip strength) are correlated with disability, age and severity of main disease and were of value to stratify risks on mortality, disability, length of hospital stay and institutionalization.[29,30,31,32] Performance scores predicted length of hospital stay, even independent from level of comorbidity or ADL-functioning. Recently Biesma reported the association between Timed-up-and-go scores (a performance score) and survival in patients who received chemotherapy for non-small-cell lung cancer.[33] In patients with malignant lymphoma physical performance scores differentiated among patients, especially in patients who were viewed functionally independent according to a routine-oncological assessment technique.[34] Medical diagnosis alone seems to have limited capacity to distinguish elderly patient groups with high or low mortality risk, functional decline and prolonged hospital stay.[35] Assessment of functional status or physical performance scores are likely to be additional tools in elderly patient groups to reveal heterogeneity in health status and its potential consequences.

Illness presentation

In elderly patients illness presentation is often viewed as "atypical", referring to absence of a straightforward one-to-one relationship between a group of symptoms and signs and a specific disease. As people are increasingly qualified as "frail", a greater part of them shows atypical illness presentation: a Canadian, single centre study reported that vital elderly presented with an atypical presentation in 25% of the cases.[36] In contrast, 59% of elderly with functional limitations and dependency showed an atypical illness presentation. Single symptom states such as acute confusion and falls appeared to be key-symptoms and, correlated with atypical presentation.[36]

Furthermore, complexity is increased because alternative explanations can be given for a specific complaint or symptom i.e. a new complaint can be attributed to an already known disease, or a complaint is the resultant of a set of interacting disease processes.[37, 38] As a consequence of this complexity, diagnostic procedures may be hampered, therapeutic interventions may be delayed and toxicities reported less spontaneously.[39, 40, 77, 81] To what extent an altered illness presentation explains delay or under-investigation remains unclear. Other explanations can not be ruled out i.e. an ageïstic point of view by health care workers or an increased patient-delay compared to younger patients. Indeed in the UK, older patients, men and patients with lower social-economic status (SES) also showed lower awareness on cancer warning signs. Especially in patients with low SES masking of cancer symptoms may be relevant.[78, 79]

Vitality versus vulnerability

Many physiological and cognitive functions tend to decline over the life span.[42-45] Adaptation strategies to age-related losses are common and highly individual.[46] A progressive path to disability becomes more and more frequent, a process primarily characterized by changes in body composition, sarcopenia and impairments in gait and balance.[47] Eventually this process leads to a condition of frailty, a condition primarily determined by its consequences in patients: (a) high risk of negative health outcomes, i.e. functional decline, institutionalization, death; (b) experience of wide and potentially dangerous fluctuations in health status when a minor, acute medical condition occurs; (c) tendency to develop side effects, toxicity and complications when medical or surgical interventions are employed that are potentially harmful.[48]

During past decades numerous authors have argued on the concept of `frailty´ and proposed operational definitions of the `frailty syndrome´.[49-60] The latter to make frailty a measurable entity and, by this, subject of studies on health and health care in the elderly. Operational definitions can be divided in those including only physical and/or functional parameters. [50, 57-60] and those including psychological and social parameters next to physical and functional parameters.[49, 51-56, 61] Data on prevalence of frailty depend largely on the concept of frailty used.[62] Frailty defined by physical and functional parameters leads to prevalence of 7% (USA) and 11 % (the Netherlands) in community dwelling elderly aged 65 and over.[50, 60] A broader concept of frailty (including also psychological and social parameters) leads to higher prevalence rates:i.e.in the Netherlands from 17 to 32 % in community dwelling elderly above 65 years, 40 to 46 % above 70 years and 47 % elderly aged 75 years and over.[49, 54, 63, 64]

Frailty is distinct but overlapping with multimorbidity and disability. In addition, both frailty and multimorbidity predict disability, adjusting for each other.[65] 27 % of the frail population had neither multimorbidity nor any limitation on ADL.[65] In the Longitudinal Aging Study Amsterdam (community dwelling elderly ≥ 65 yr), only 2 % was frail and had neither disabilities nor multimorbidity.[64] [62] Thus, to study vulnerability/frailty both disabilities and multimorbidity seem highly relevant.

Data on prevalence of frailty in populations with cancer become increasingly available across the industrialized countries. [66, 67] Although knowledge on prevalence of frailty in cancer patients is still fragmentary, one third up to half of the cancer patients older than 70 years is qualified as frail by using frailty-indices that operationalize a broad concept of frailty. [68, 69, 70]

It is advocated that assessment of underlying vulnerability and frailty should be implemented in clinical trials on cancer patients; these trials should not only be directed at improving survival but also at maintaining function and quality of life.[66]

In general medicine Comprehensive Geriatric Assessment (CGA) is viewed as an appropriate tool to

analyze and develop a coordinated and individualized treatment plan in elderly patients.[71] Benefits of CGA on functional decline, institutionalization and mental function seem consistent, benefits on mortality are inconclusive.[72-7] Both selection of frail patients and control on interventions are suggested to improve efficient implementation of CGA.

Aims of this thesis

The health status of patients with cancer is usually described in terms of dissemination and histo-pathological data. In groups of elderly patients many other parameters (i.e. multimorbidity, dependency on functional status and `frailty`) also determine their health status. As a consequence heterogeneity in health status will increase in elderly patient groups with a given disease (compared to younger patients). These patient characteristics or age per se may also determine cancer care utilization and outcomes of cancer care (survival, complications).

Clinical trials often use eligibility criteria that do not take into account the patient characteristics as seen in everyday practice. Population-based studies can bridge the gap of knowledge between clinical trials in selected patients and usual care. Cancer registries are known to have reliable data-management on diagnosis of cancer, received treatment(s), a number of patient characteristics and outcomes.[80] Their system of datamanagement works on the interface of a prospective and retrospective study-design. Therefore, population-based studies can give a unique “real life” insight into heterogeneity in treatment choices, complications and outcomes in patients who usually do not take part in trials or clinical studies. Apart from these, they also give the opportunity to reveal time trends and (especially in regional setting) to give feedback to physicians and oncology teams. Data analyzed in chapters 2.1, 2.2 and 2.6 of this thesis are derived from the Comprehensive Cancer Center South. Since 1993, this registry offers one of the world most well known sources of population-based data on comorbidity in cancer patients. In chapter 2.3, 2.4 and 2.5 also data from six other Dutch regional Cancer Registries (North-East, East, West, Rotterdam, Limburg and Central) are analyzed.

The aim of this thesis is to describe and quantify heterogeneity in elderly cancer patients, primarily by analyzing age, gender and concomitant disease(s). Secondly, the impact of these factors on heterogeneity is determined on cancer treatment strategies and their outcomes. Thirdly, the role of geriatric assessment in oncology is evaluated as a working method to unravel heterogeneity in elderly cancer patients and its potential as a triage-instrument to deliver appropriate care in elderly cancer patients. **Chapter 2** descibes population-based studies on the effects of multi-morbidity,

gender and age at time of cancer diagnosis in relation to treatment choice, complications/toxicities and survival in elderly patients with colorectal, (small-cell and non-small-cell) lung, breast and ovarian cancer. **Chapter 2.1** gives insight into the prognostic role of increasing age and concomitant conditions on resection rates and course of disease in patients with stage I-III colorectal, stage I-II non-small-cell lung cancer and stage I-III breast cancer. In **chapter 2.2**, the impact of age, gender and comorbidity is investigated on the use of adjuvant, pre-operative (5x5 Gy) radiotherapy and subsequent effects on survival in patients with mobile rectal cancer. Additionally, **chapter 2.3** focuses on the clinical dilemmas in patients over 75 years old with rectal cancer (pT2-pT3) who are either treated with short course, pre-operative radiotherapy or just with surgery alone. Dilemmas are, wherever possible, related to patient characteristics present at time of diagnosis of cancer. In **chapter 2.4** motives for adherence to treatment guidelines, completion of chemotherapy and toxicity are described in patients with small-cell lung cancer aged ≥ 75 years. The question whether chemotherapy remains a prognostic factor in the very elderly with small-cell lung cancer is answered in **chapter 2.5**.

Chapter 3.1 and **3.2** deal with the potential role of geriatric assessment in cancer care. **Chapter 3.1** reviews the impact of comprehensive geriatric assessment (CGA) in oncology and compares the results with (CGA) in general medicine. In **chapter 3.2** a prospective pilot study is described. Aim of this study is to compare the predictive value of usual clinical judgment, performance status and geriatric assessments towards feasibility of chemotherapy in patients older than 70 years old.

Chapter 4 summarizes the main findings of this thesis and discusses these findings in relation to recent literature and clinical practice in geriatric oncology.

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Chapter 2

Population-based studies on heterogeneity in elderly cancer patients, influence of patient characteristics at time of diagnosis

Chapter 2.1

Comorbidity in older surgical cancer patients: influence on patient care and outcome

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Published, European Journal of Cancer. 2007;43:2179-2193

Abstract

Evidence is scarce about the influence of comorbidity on outcome of surgery, whereas this information is highly relevant for estimating the surgical risk of cancer patients, and for optimising pre-, peri- and postoperative care. In this paper the prognostic role of increasing age and comorbid conditions in patients diagnosed with stage I-III colorectal, stage I-II NSCLC or stage I-III breast cancer between 1995 and 2004 in the southern part of the Netherlands is summarized.

Almost all patients with stage I-III colon cancer or rectal cancer underwent surgery regardless of age or comorbidity. In contrast, the resection rate among elderly patients with stage I-II NSCLC was clearly lower than among younger patients and was significantly lower when COPD, cardiovascular diseases or diabetes were present. Among patients with stage I-III breast cancer, those aged 80 or older underwent less surgery, and the resection rate appeared to be lower when cardiovascular diseases or diabetes were present.

Among patients with resected colorectal cancer postoperative morbidity and mortality was higher among those undergoing emergency surgery, but also among those with reduced pulmonary function, cardiovascular disease or neurological comorbidity. Among those with resected NSCLC postoperative morbidity and mortality was related to reduced pulmonary function or cardiovascular disease. Since surgery for breast cancer is low risk and elective surgery, morbidity and mortality was not higher for elderly or those with comorbidity.

Among patients with colorectal or breast cancer, comorbidity in general, cardiovascular diseases, COPD, diabetes (only colon and breast cancer) and venous thromboembolism had a negative effect on overall survival, whereas the effect of comorbidity on survival of stage I-

II NSCLC was less clear.

Elderly and those with comorbidity (especially cardiovascular diseases and COPD) among colorectal cancer and NSCLC patients had more postoperative morbidity and mortality. Prospective randomized studies are needed for refining selection criteria for surgery in elderly cancer patients and for anticipation and prevention of complications.

Introduction

Due to ageing of the population and rising incidence rates of most cancers with age, the mean age of patients diagnosed with cancer is increasing in western countries. This implies that patients increasingly suffer from one or more other serious (chronic) diseases, especially cardiovascular diseases, COPD, hypertension or diabetes [1]. Besides affecting life expectancy, comorbid conditions may complicate major surgery in cancer patients, especially when they are frail [2-6]. Surgery is the only curative treatment option for patients with colorectal cancer, stage I-II non-small cell lung cancer (NSCLC) or breast cancer. Until now, evidence is lacking about the influence of specific comorbid conditions on outcome of surgery as these elderly patients are often excluded from clinical trials. This information, however, is highly relevant for estimating the surgical risk of cancer patients, and for optimising pre-, peri- and postoperative care. Choice for surgery is clearly different among the different tumour groups. Generally spoken, surgery for colorectal cancer is often preferable because of bleeding or obstruction and the intention to perform a curative procedure (although in a non-curative setting alternative procedures are present). Surgery among lung cancer patients is high risk surgery, and radiotherapy is an alternative. Therefore, there is a strict selection of surgery among lung cancer patients. Surgery for

breast cancer is low risk, but among older patients hormonal treatment is an alternative, which means that there is a more 'elective' selection.

In this paper we summarize our findings with respect to the prognostic role of increasing age and comorbid conditions in patients diagnosed with stage I-III colorectal, stage I-II NSCLC or stage I-III breast cancer in the registration area of the population-based Eindhoven Cancer Registry, and discuss them against the background of the literature.

Patients and methods

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants and only general hospitals. Since 1993 serious comorbidity with prognostic impact has been recorded for all patients. The Charlson comorbidity index is most widely used for recording comorbidity and was validated in various studies [7]. We used a slightly modified version of this index for recording comorbidity. Comorbidity was defined as life-shortening diseases that were present at the time of cancer diagnosis (previous cancer, cardiovascular diseases, COPD, diabetes, hypertension, autoimmune diseases, rheumatoid arthritis (only severe), kidney diseases (glomerulonephritis, pyelonephritis), gastrointestinal (stomach ulcer & resection, colitis), liver diseases (cirrhosis, hepatitis), dementia and chronic infections.

Trained registry personnel extract all data from the medical records between 6 and 12 months after diagnosis. The medical record is generally regarded as the most complete source of information on the patient's past and current health status [8].

Patients aged 50 or older with cancer of the colon or rectum (stage I-III), NSCLC (stage I-II) or breast (stage I-III), newly diagnosed between 1995 and 2004, were included for this

overview. Patients for whom no information on comorbidity was found in the medical records were excluded (9.9%). Eventually, 4911 colon, 2674 rectal, 2385 NSCLC and 8501 breast cancer patients were left for analyses.

Surgery did not include diagnostic operations. Surgery comprised appendectomy, hemicolectomy, sigmoid resection, rectosigmoid resection, low anterior resection, subtotal colectomy, total colectomy and rectum amputation for colorectal cancer, wedge excision, segment resection, bisegment resection, lobectomy, bilobectomy, pneumonectomy, sleeve resection and carina resection for NSCLC, and breast conserving surgery and mastectomy for breast cancer.

Postoperative complications were studied in a random sample of resected patients (colon stage I-III N=223, rectum stage I-III N=108, NSCLC stage I-II N=176, breast stage III N=490). Complications within 3 months of diagnosis were gathered from the medical records. Complications registered were minor infections (e.g. wound infections, wound dehiscence, urinary tract infections), major infections (e.g. abscess, peritonitis, anastomotic leakage), pulmonary complications (e.g. pneumonia), haemorrhage (requiring blood transfusion or reoperation), thrombo-embolic events, cardiac failure (e.g. cardiac insufficiency), kidney failure, stoma problems (e.g. stomal necrosis, only for colorectal cancer) and other complications. Also death due to complications was recorded, judged from the information in the medical record whether the patient's death could be directly linked to a preceding complication.

Follow-up was completed up to 1 January 2006. In addition to passive follow-up via the hospitals, this information was also obtained from the municipality administration database that collects data on all deceased and emigrated persons via the civil municipal registries.

Differences in the proportion of patients undergoing surgery according to age and

comorbidity were tested by means of a two-sided Chisquare test.

For resected patients, the association between comorbidity and postoperative complications was evaluated in a logistic regression model. First, a model including age, gender, stage, histology (only for NSCLC) and presence of comorbidity (yes versus no) was built. The models for colon and rectal cancer also included preoperative haemoglobin level and timing of surgery (elective or emergency), and the model for NSCLC also included type of surgery (pneumonectomy versus other surgery). Then the model was run again with presence of comorbidity replaced by presence of each separate comorbid condition (no comorbidity as a reference).

Survival time was defined as the time from diagnosis to death (all causes) or the end of the study. The independent prognostic effect of the number of comorbid conditions was estimated with a multivariable Cox regression model. The hazard rates for death were adjusted for age, gender, histology (only for NSCLC) and stage. With respect to comorbidity, also the prognostic effects of the specific diseases were evaluated. For the latter, a separate model was built for each of the most common concomitant diseases (cardiovascular diseases, COPD, diabetes and hypertension). The SAS computer package (version 8.2) was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina, USA, 1999).

Results

Surgery

Table 1 shows the general characteristics and resection rates of the patients. Almost all patients with stage I-III colon cancer and stage I-III rectal cancer underwent surgery regardless of age or comorbidity (figures 1a and b). The proportion of patients with stage I-II

NSCLC who underwent surgery was only 15% of those aged 80 or older versus 88% of age group 50-64 and 67% of those aged 65-79 (P<0.01) (figure 1c). Among patients up to 80 years, the resection rate was significantly lower when COPD, cardiovascular diseases or diabetes were present or in case of 2 or more comorbid conditions. Among patients with stage I-III breast cancer younger than 80 years 99% underwent surgery, compared with only 81% of those aged 80 or older (P<0.01, figure 1d). Among those undergoing surgery, the application of breast conserving surgery decreased from 60% of those aged 50-64 years to 23% of those aged 80 or older (P<0.01). For those aged 65 years or older, the resection rate appeared to be lower when comorbidity was present, especially cardiovascular diseases or diabetes. Axilliary dissection for those undergoing breast conserving surgery also decreased in the presence of comorbidity, as did adjuvant radiotherapy (results not shown).

Table 1 *General characteristics and resection rate of patients*

	Stage I-III colon		Stage I-III rectum		Stage I-II NSCLC		Stage I-III breast	
Age								
50-64	1243	*(99)*	943	*(99)*	832	*(88)*	4265	*(100)*
65-79	2766	*(99)*	1382	*(96)*	1377	*(67)*	3299	*(97)*
80+	891	*(98)*	349	*(92)*	176	*(15)*	937	*(81)*
Gender								
Male	2456	*(99)*	1564	*(96)*	1912	*(69)*		
Female	2455	*(99)*	1110	*(96)*	473	*(76)*	8501	*(97)*
Squamous cell					1104	*(69)*		
Adenocarcino					499	*(85)*		
Large cell					278	*(51)*		
I	956	*(100)*	1112	*(99)*			3766	*(98)*
II	2378	*(98)*	944	*(93)*			3894	*(97)*
III	1577	*(99)*	782	*(98)*			841	*(90)*
None	1737	*(99)*	1112	*(97)*	579	*(82)*	4433	*(99)*
One condition:	1600	*(99)*	855	*(97)*	859	*(69)*	2501	*(96)*
Cardiovascular	386	*(99)*	183	*(95)*	213	*(73)*	356	*(92)*
COPD	171	*(99)*	117	*(97)*	319	*(62)*	199	*(98)*
Diabetes	130	*(99)*	70	*(99)*	46	*(63)*	248	*(97)*
Hypertension	420	*(98)*	241	*(98)*	78	*(86)*	1022	*(98)*
2 or more	1574	*(99)*	707	*(95)*	947	*(64)*	1567	*(91)*

Postoperative morbidity and mortality

Thirty-five percent of resected stage I-III colon cancer patients and 44% of resected stage I-III rectal cancer patients suffered from any complication within 3 months of diagnosis (figures 2a and b). The most frequent complications were minor infections (11% for colon and 13% for rectum), major infections (10% for colon and 11% for rectum) and cardiac failure (9% for colon and 4% for rectum). Among colon cancer patients elderly suffered more often from

pulmonary complications than younger patients (p=0.07), whereas among rectal cancer patients postoperative death occurred more often among elderly than younger patients (p=0.06). The risk of developing a postoperative complication was significantly higher for patients with emergency surgery compared to elective surgery (72% versus 34% for colon cancer, P<0.01). Colon cancer patients undergoing emergency surgery suffered more often from pulmonary, cardiac, kidney and stoma complications, and postoperative death. Cardiac complications occurred more often among colon cancer patients with COPD or cardiovascular disease compared to those without comorbidity (14%). In logistic regression analysis including age, comorbidity, emergency surgery and haemoglobin level, the risk of developing any postoperative complication among colon cancer patients was significantly higher for those undergoing emergency surgery (OR=3.63, 95%-CI 1.36-9.71). Two to three percent of patients with colon or rectal cancer aged 50-64 and 13-19% of those aged 80 or older died due to complications. Nine of 21 patients who died postoperatively suffered from cardiovascular diseases and/or COPD before surgery, 6 underwent emergency surgery (6 of 15 among colon cancer), and 12 of 21 patients suffered from major infection and/or cardiac complication after surgery.

Fifty percent of patients with stage I-II NSCLC younger than 80 who underwent surgery suffered from one or more complications within 3 months of diagnosis compared to 75% (N=3!) of elderly (figure 2c). The most frequent postoperative complications were major infections (19%) and minor infections (13%). Major infections occurred more often among patients with diabetes compared to those without comorbidity (38%). In logistic regression analysis, the risk of developing any postoperative complication was not significantly related to any of the comorbid conditions, age or pneumonectomy (results not shown).

Postoperative death occurred in 25% of patients aged 80 or older (N=3) compared to 3-5% of

those younger than 80 (P<0.01). Three of nine patients who died postoperatively suffered from COPD or cardiovascular disease before surgery, 4 patients had a major infection, one patient had a pulmonary complication, one had a cardiac complication, one had a combination of a major infection and kidney failure, and one had a combination of haemorrhage, thrombo-embolic complication and cardiac complication.

The proportion of breast cancer patients with complications after surgery was 19% for age group 50-64, 21% for age group 65-79 and 16% for age group 80+ (no significant difference, figure 2d). Minor infection (10%) was the most common complication. In logistic regression analysis, however, the risk of developing any postoperative complication was not significantly related to any of the comorbid conditions and neither to age or type of surgery (results not shown).

Overall survival

In multivariable survival analysis among patients with resected tumours, the risk of death increased with increasing age, even after adjustment for gender, stage, histology and presence of comorbidity. Comorbidity also had an independent prognostic effect for patients with colon cancer, rectal cancer and breast cancer (table 2). Among patients with stage I-II NSCLC, only the presence of two or more comorbid conditions had an independent prognostic effect. When the separate comorbid conditions were evaluated in multivariable models, cardiovascular diseases, COPD and diabetes had an independent prognostic effect among patients with colon or breast cancer (see also figures 3a and 3d). Among patients with rectal cancer, cardiovascular diseases and COPD had an independent prognostic effect (see also figure 3b). Among patients with stage I-II NSCLC none of the specific diseases had a significant effect (see also figure 3c, only age group 65-79, because there were not enough patients in age group 80+).

Table 2 *Multivariable analysis of overall survival for resected patients aged 65 years or older with colon, rectal, NSCLC and breast cancer*

	Stage I-III colon		Stage I-III rectum		Stage I-II NSCLC		Stage I-III breast	
Age								
50-64*	1		1		1		1	
65-79	1.66	1.50-	1.67	1.47-	1.47	1.31-	1.69	1.54-
80+	3.39	3.02-	3.06	2.59-	2.38	1.61-	4.01	3.58-
Gender								
Male*	1		1		1			
Female	0.83	0.77-	0.86	0.77-	0.67	0.58-		
Squamous cell*					1			
Adenocarcinoma					1.06	0.94-		
Large cell undiff.					1.30	1.09-		
I*	1		1				1	
II	1.53	1.36-	1.55	1.36-			2.03	1.86-
III	2.84	2.53-	2.48	2.17-			3.27	2.90-
None*	1				1		1	
One condition:	1.42	1.29-	1.33	1.17-	1.10	0.95-	1.20	1.09-
Cardiovascular	1.55	1.35-	1.37	1.09-	1.11	0.90-	1.28	1.05-
COPD	1.51	1.24-	1.68	1.31-	0.98	0.80-	1.42	1.11-
Diabetes	1.30	1.04-	1.30	0.95-	1.20	0.79-	1.25	1.01-
Hypertension	1.09	0.94-	1.22	1.00-	0.99	0.74-	0.98	0.85-
2 or more	1.76	1.60-	1.79	1.57-	1.29	1.12-	1.89	1.71-

†Hazard ratio for death

*Reference category

Discussion

Surgery

When surgery is inevitable like in patients with colorectal cancer, higher age or the prevalence of comorbidity did not significantly affect the resection rate. Surgery is the cornerstone for cure. Its goal is also to gain immediate relief of symptoms. Treatment options that do not focus on immediate relief of symptoms were however less applied in the elderly: several previous studies have shown that elderly patients with stage III colon carcinoma received less adjuvant chemotherapy and elderly patients with rectal cancer received less preoperative radiotherapy [9-12]. The influence of age on the resection rate of breast cancer was also of less importance, probably because breast surgery is a low specific risk surgery, although elderly are less likely to undergo breast conserving surgery, axillary node dissection, postoperative radiation or chemotherapy [13-17]. Despite 'undertreatment' by conventional criteria, the rates of local recurrence and distant metastasis in resected breast cancer patients in the USA were not increased in comparison with conventionally treated elderly patients [16]. In our study, breast cancer patients also underwent less surgery when cardiovascular diseases or diabetes were present. Previous studies from the USA, the Netherlands and Switzerland have shown that comorbidity also had an independent influence on receiving postoperative radiotherapy [2, 14, 15, 17-21].
Older patients with stage I-II NSCLC (with serious comorbidity) more often received radiotherapy instead of surgery. The same was found in previous British, American, Japanese and Dutch studies [20, 22-27]. Surgical mortality for lung cancer patients increased markedly with age and was especially high for pneumonectomy [6, 28-30]. In our study, the resection

rate was also lower in case of comorbidity (especially COPD), probably because of the expected higher incidence of postoperative complications and mortality [5, 6, 25, 31, 32].

Postoperative morbidity and mortality

Table 3 gives an overview of the literature concerning influence of comorbidity on postoperative morbidity/mortality. Previous studies have shown that perioperative risk is not really different in healthy elderly and younger patients undergoing surgery for breast cancer [33, 34], suggesting that age by itself is not the key determinant of perioperative risk. The fact that elderly breast cancer patients and those with comorbidity did not have more postoperative complications than younger patients might be explained by the fact that breast surgery is low risk surgery, but also by (appropriate) selection for surgery [34]. Generally spoken, surgery is often inevitable in colorectal cancer patients. However there is some difference between rectal cancer and colon cancer patients. In colon cancer patients obstructive tumors can often be resected or successfully bypassed, thus preserving bowel continuity even in a palliative setting. In rectal cancer patients resection in advanced cancer stages is a major procedure, and especially in the palliative setting radiotherapy combined with stenting may be considered. However if unresected, rectal cancer patients often will end with a diverting stoma to alleviate the symptomps of the pelvic tumor. In our study we indeed found a higher risk of postoperative complications among those who underwent emergency surgery. Special pre-, peri- and postoperative attention for patients with deep vein thrombosis at cancer diagnosis or following cancer diagnosis is warranted, because of the significant higher postoperative complication rate and poorer survival that was found in several studies [35-38]. The number of patients with deep vein thrombosis at cancer diagnosis in our study was too small to draw conclusions. In a recent study with data from

the Memorial Sloan-Kettering Cancer Center, preoperative major comorbidity (heart, lung, liver, kidney disease and/or diabetes) was the only clinicopathologic factor associated with postoperative complications in patients with rectal cancer [41]. The presence of COPD and cardiovascular diseases have also been shown to be associated with postoperative morbidity in colorectal cancer [37, 42, 43]. In our study, postoperative mortality among colorectal cancer patients was associated with COPD or cardiovascular comorbidity, emergency surgery or major postoperative infections or postoperative cardiac morbidity. In previous studies postoperative mortality among colorectal cancer patients was related with comorbidity in general, neurological or cerebrovascular comorbidity and postoperative complications [37, 42, 43, 47-49].

Among patients with NSCLC, vascular diseases, insulin-dependent diabetes, COPD, hemiplegia and pulmonary functions were predictive for postoperative complications [6, 31, 50-53]. In our study, 3 of 9 NSCLC patients who died postoperatively suffered from COPD or cardiovascular disease before surgery. In previous studies postoperative mortality was higher among elderly, those undergoing pneumonectomy, preoperative FEV1 (Forced Expiratory Volume) <60%, % of predicted VO2max and patients with COPD and/or cardiovascular disease [6, 27, 28, 31, 32, 50-55]. Others did not find a significant effect of comorbidity on postoperative mortality [56, 57].

Table 3 Overview of literature concerning influence of comorbidity on postoperative morbidity/mortality

Tumour	Age	Year of	Reference	Influence of comorbidity on:	
				postoperative morbidity:	postoperative mortality:
Colon	40+	1995-1999	[37]	COPD: more pneumonia or haemorrhage**	comorbidity: higher risk of dying**
		1993-1995	[36]	Deep vein thrombosis: more infections, 3+ comorbidities associated with venous thromboembolism: OR=2.0*	
		1997-1999 2002	[43]	related with neurological (OR=1.6) and cardiovascular (OR=1.7) comorbidity*	related with neurological comorbidity*
	all	1991-1995	[42]	COPD, pneumonia or CVA: more 30-day morbidity (OR=1.3, 2.5, 1.4 resp.)*	CVA: more 30-day mortality (OR=1.9)*
Rectal	40+	1995-1999	[37]	COPD: more postoperative morbidity**	comorbidity: higher risk of dying**
		1993-1995	[36]	3+ comorbidities associated with venous thromboembolism: OR=2.0*	
		1997-1999 2002	[43]	related with neurological and cardiovasc comorbidity*	related with neurological comorbidity*
	70+	1995-2001	[44]	comorbidity: OR=2.3*	
	25-90	1988-2002	[41]	comorbidity: more morbidity (p=0.02)**	
NSCLC	70+	1993-1998	[32]		related with cardiac and respiratory diseases**
	61-66	1990-2004	[6]	FEV1<60%: OR=2.7*	FEV1<60%: OR=1.9*
		1990-1997	[54]		3+ cardiovasc risk factors: OR=2.4* related with cardiovasc comorbidity**
	67+	1999	[27]		COPD and/or cardiovascular comorbidity: higher 2-month mortality**
	all	1993-1994	[50]	vascular disease: OR=2.2*	vascular disease: OR=2.8*
	all	1991-1995	[51]	insulin-dependent diabetes: OR=2.8* COPD: OR=1.3*	
stage I	80+	1980-2002	[56]	hemiplegia: OR=2.6*	NS*
stage I		1994-1999	[57]		NS*
resected	all		[31]	related with % of predictive VO2max	related with % of predictive VO2max
resected	all	1992-1997	[52]	COPD: more postoperative morbidity**	COPD: higher postoperative mortality rate**
resected	all	2004-2005	[53]	cardio-respiratory morbidity related with FEV1	
Breast	40+	1995-1999	[34]	NS**	

* multivariable analysis

**univariable analysis NS=not significant

Survival

Table 4 gives an overview of the literature concerning influence of comorbidity on survival. For patients with colon, rectal or breast cancer, comorbidity had an independent prognostic effect [10, 14, 15, 21, 34, 36, 44, 58-60]. This negative influence of comorbidity on survival of cancer might be due to several mechanisms: the increased risk of death due to the comorbid condition itself, neglect of treatment of the comorbid condition, more contra-indications for anti-cancer treatment, or a higher rate of treatment-related complications. In several previous studies the adverse effects of comorbidity on survival appeared to be independent of cancer treatment, so less aggressive treatment could not (fully) account for the observed differences in survival between patients with and without comorbidity [10, 14, 15, 21, 24, 34, 36, 44, 58]. In previous studies, the number of postoperative complications was also found to be an independent prognostic factor [23, 36, 38, 40, 41, 44, 48, 61, 62].
Among patients with lung cancer in our study, only the presence of 2 or more comorbid conditions had an independent prognostic effect [24]. In other studies also one comorbid condition had a prognostic effect [27, 52, 54, 57, 59, 60, 63-65]. In some previous studies other scales for measuring comorbidity were used: the Kaplan-Feinstein Index [64] and the Cumulative Illness Rating Scale-Geriatric (CIRS-G) [69]. In one of the studies, comorbidity affected overall survival in surgically resected stage I NSCLC patients, when comorbidity was rated according to CIRS-G, but not according to the Charlson scale [63]. In another American study comorbidity count and the Charlson index were significant predictors for lung cancer survival, but only explained 2.5% and 2.0% of the survival variation, respectively [65].
Probably the influence of comorbidity on survival is of less importance in the case of a lethal

disease such as lung cancer. Possibly many of these patients die of the cancer, before they become at risk of dying from the comorbid condition. This was confirmed in two American studies, in which the prognostic effect of comorbidity was found to be smallest for tumours with a poor prognosis [59, 60]. Especially reduced pulmonary function and cardiovascular diseases seemed to have an independent effect on survival of lung cancer [27, 54, 56]. Although the proportion of postoperative morbidity and mortality was significantly higher among elderly with colorectal cancer or stage I-II NSCLC (especially those with reduced pulmonary function or cardiovascular comorbidity), current medical practice is that elderly patients undergo surgery if they are fit enough. There are three future ways to achieve better outcomes. First, selection for surgery will improve because of new and better staging techniques (e.g. MRI/PET-scanning). Preoperative selection in elderly is essential, considering the adagium “do not harm”. Secondly, preoperative selection and interventions should focus on comorbidity and general functioning of especially older patient groups. Comprehensive geriatric assessment (CGA) [66, 67] and a proper screening tool are recommended. Thirdly, an integrated care programme consisting of combined surgical and medical specialists can achieve less complications and mortality in elderly surgical patients. [70, 71].

Table 4 Overview of literature concerning influence of comorbidity on survival

Tumour				
Colon		1993-1995	[36]	postoperative venous thromboembolism: HR=1.8*
		1997-1999		
	50+	1995-2001	[10]	HR=1.2-1.4*
	55+	1992	[58]	HR=1.3-2.5*
	all	1995-2001	[59]	HR=1.4-1.7*
localized	all	1991-1995	[38]	venous thromboembolism: HR=3.2*
regional	all	1991-1995	[38]	venous thromboembolism: HR=2.2*
localized	all	1995-2001	[60]	HR=2.5*
Rectal		1993-1995	[36]	postoperative venous thromboembolism: HR=1.8*
	70+	1995-2001	[44]	comorbidity: OR=1.7*
	50+	1995-2001	[10]	HR=1.3-1.6*
	all	1995-2001	[59]	HR=1.4-1.7*
localized	all	1991-1995	[38]	venous thromboembolism: HR=3.2*
regional	all	1991-1995	[38]	venous thromboembolism: HR=2.2*
NSCLC		1990-1997	[54]	5-year survival 1.5x higher in group without cardiovasc comorbidity*
	67+	1999	[27]	COPD: HR=1.1*
stage I	80+	1980-2002	[56]	FEV<1.5L: HR=2.5*
stage I	46-83	1990-1998	[63]	CIRS-G(4): HR=3.4*
stage I+II	all	1995-1999	[24]	NS*
stage I		1994-1999	[57]	HR=1.9-2.2*
		1995-1998	[65]	HR=1.2-4.5*
	all	1995-2001	[59]	HR=1.2-1.5*
resected	all	1992-1997	[52]	COPD: poorer prognosis**
stage I+II	all	1995-2001	[60]	HR=1.8*
localized	all	1991-1995	[38]	venous thromboembolism: HR=3.1*
Breast	40+	1995-1999	[34]	high impact comorbidity: OR=2.9*
	all	1995-2001	[15]	HR=1.3-2.3*
	all	1995-2001	[59]	HR=1.8-2.0*
	70+	1992-1999	[21]	HR=1.5-2.1*
	80+	1989-1999	[14]	Acute or subacute comorbidity: poorer overall mortality
localized	all	1991-1995	[38]	venous thromboembolism: HR=6.6*
regional	all	1991-1995	[38]	venous thromboembolism: HR=2.4*
localized	all	1995-2001	[60]	HR=2.9*

* multivariable analysis

**univariable analysis

NS=not significant CIRS-G: Cumulative Illness Rating Scale

Conclusions

Our study emphasizes that comorbidity primarily has an impact on overall survival and less on postoperative complications, although high rates of postoperative complications remain. Comorbidity also leads to withholding surgical interventions if surgical therapy is commonly recognized as 'high risk' (e.g. stage I-II NSCLC) or if alternative non-surgical treatment is available (e.g. stage I-III breast cancer). Previous studies have shown that operative risk is especially high among colorectal cancer patients with reduced pulmonary function, cardiovascular diseases or neurological comorbidity or those undergoing emergency surgery, and NSCLC patients with COPD or cardiovascular diseases. Among patients with colorectal or breast cancer, comorbidity in general, cardiovascular diseases, COPD, diabetes (only colon and breast cancer) and venous thromboembolism had a negative effect on overall survival, whereas the effect of comorbidity on survival of stage I-II NSCLC was less clear. Since elderly patients with comorbidity are often excluded from clinical trials, most results were drawn from non-randomized studies, in which preoperative selection has played a major role. This indicates the need for prospective studies for refining selection criteria for surgery in elderly cancer patients in order to prevent complications where possible and to anticipate complications. Future studies should also include quality of life, because for elderly quality of life is often more important than the number of life years gained.

Take home messages:

1. Patients with comorbidity often have a poorer survival
2. Anticipate postoperative complications in case of:
    a. (Elderly) colorectal cancer patients with reduced pulmonary function, cardiovascular diseases or neurological comorbidity;

b. (Elderly) NSCLC patients with reduced pulmonary function or cardiovascular diseases.

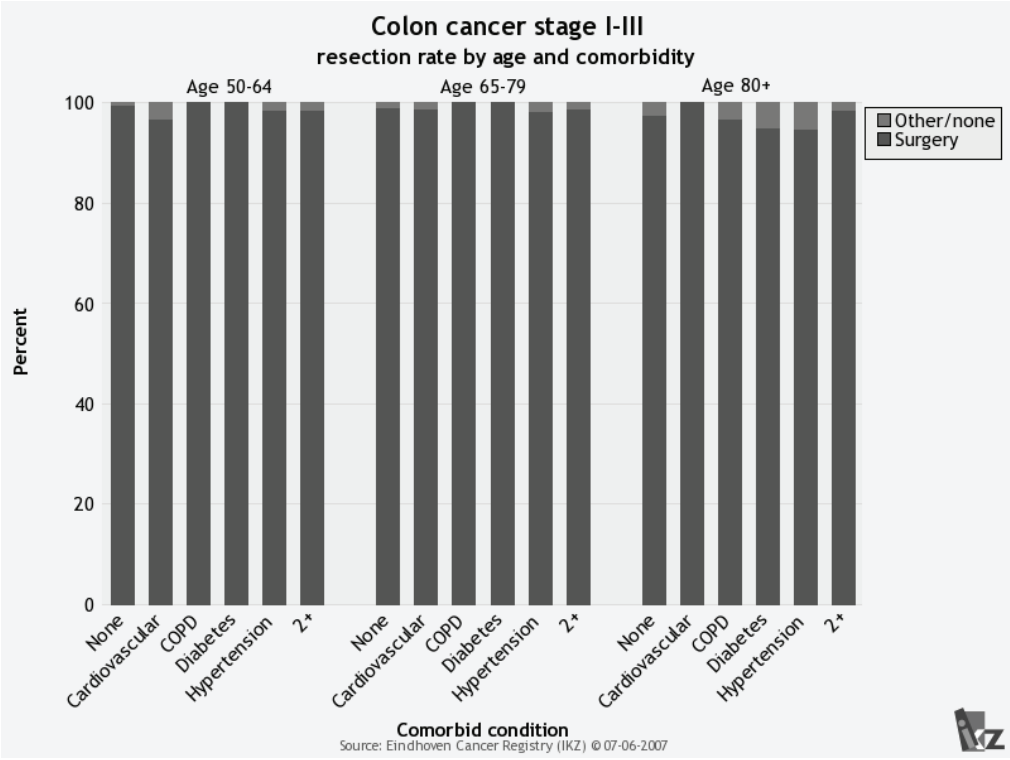
3. Prospective studies are needed for evaluating:
    a. Screening tools or selection criteria for surgery in elderly or those with comorbidity;
    b. Complications and recurrence rates in elderly cancer patients;
    c. Quality of life in elderly cancer patients.

Acknowledgements

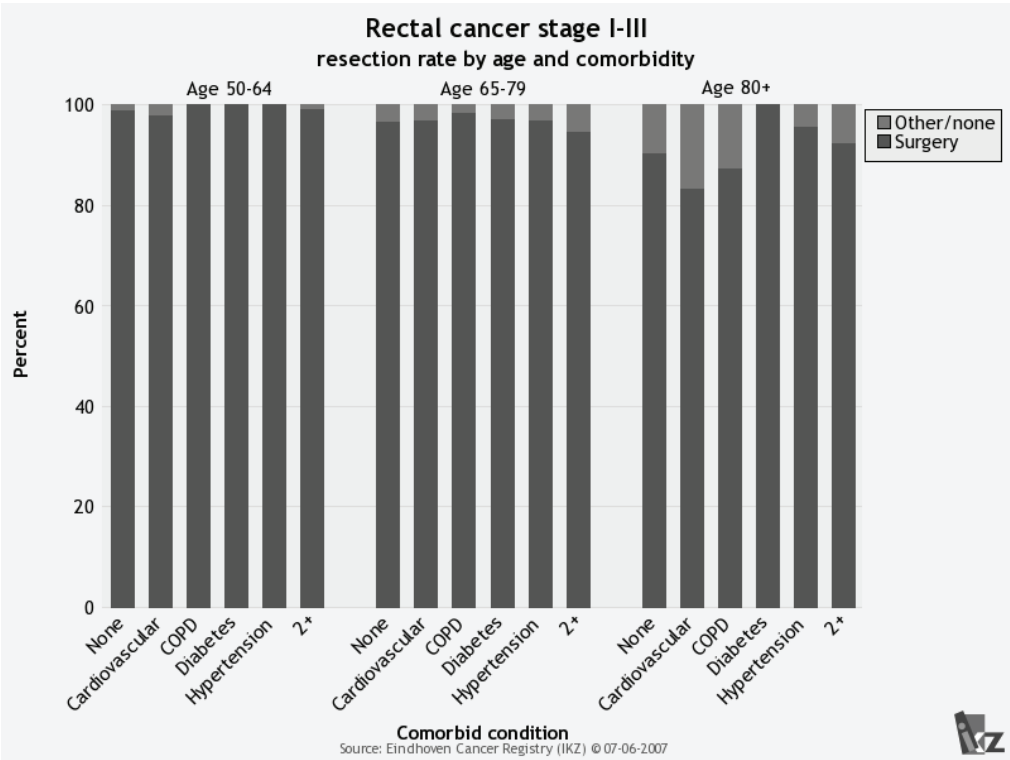
This work was carried out with grants from the Dutch Cancer Society (IKZ 2000-2260).

Figure 1 Resection rate according to age and type of comorbidity

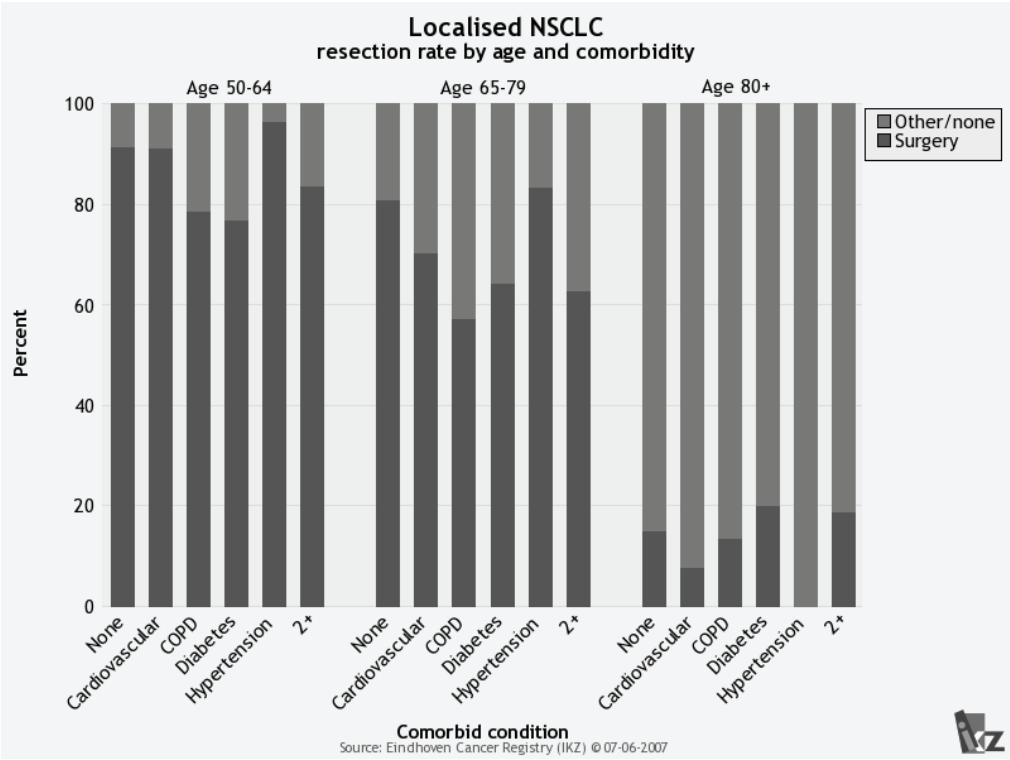
a. Colon cancer (stage I-III)



b. Rectal cancer (stage I-III)



c. NSCLC (stage I-II)



d. Breast cancer (stage I-III)

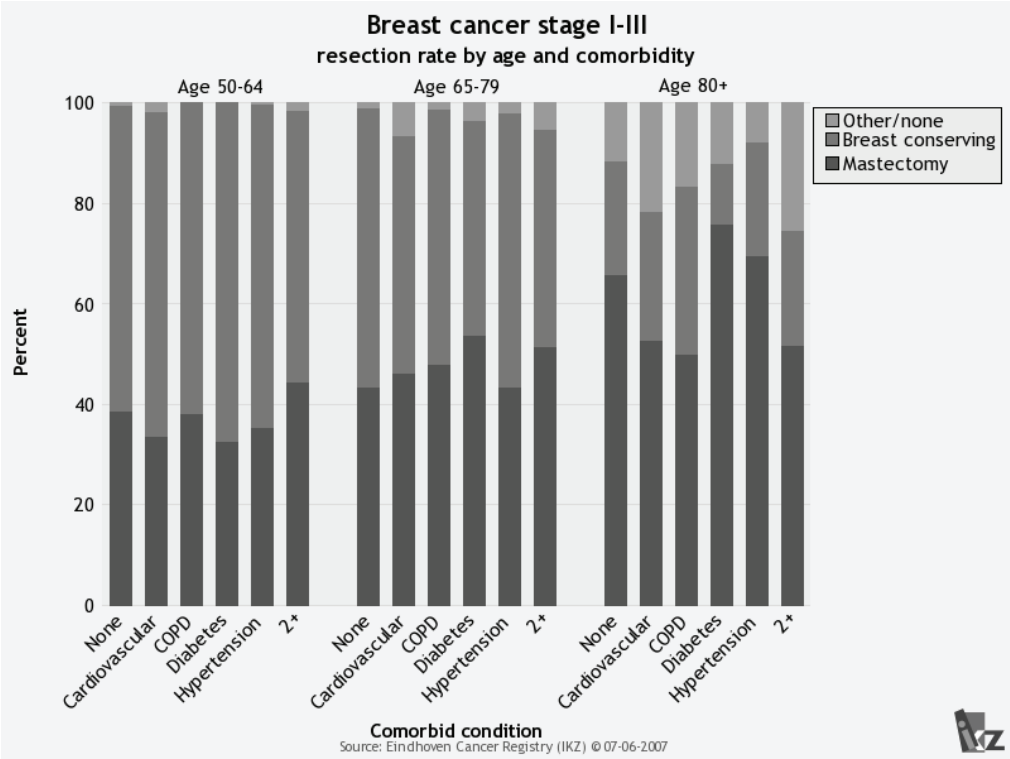
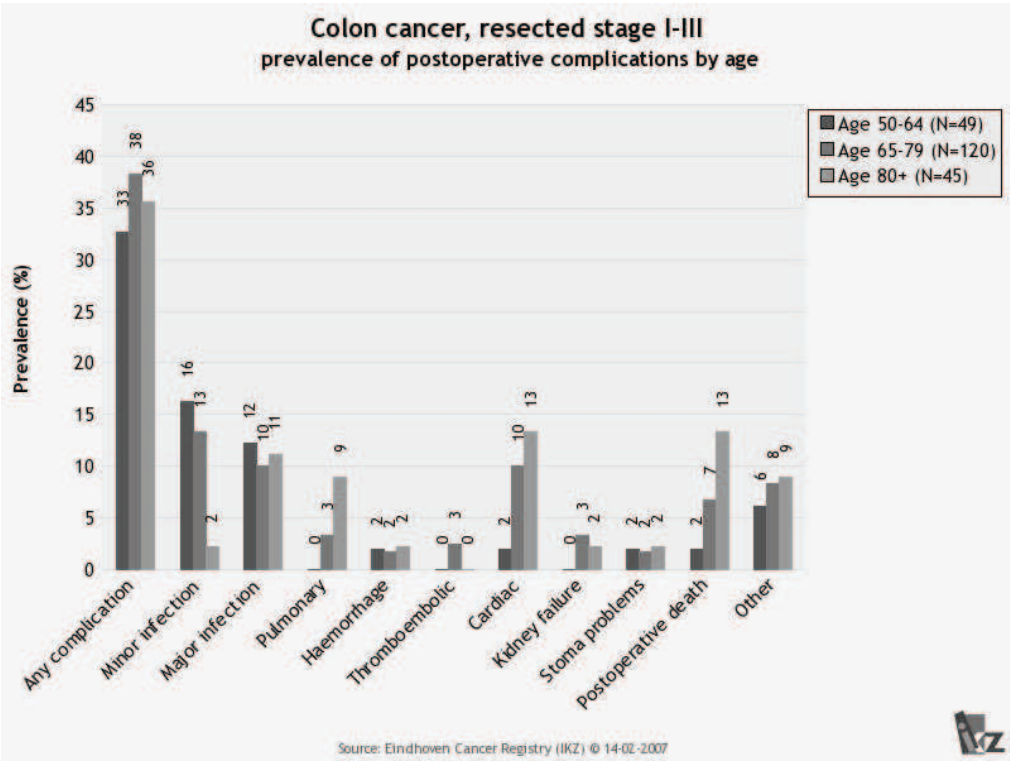
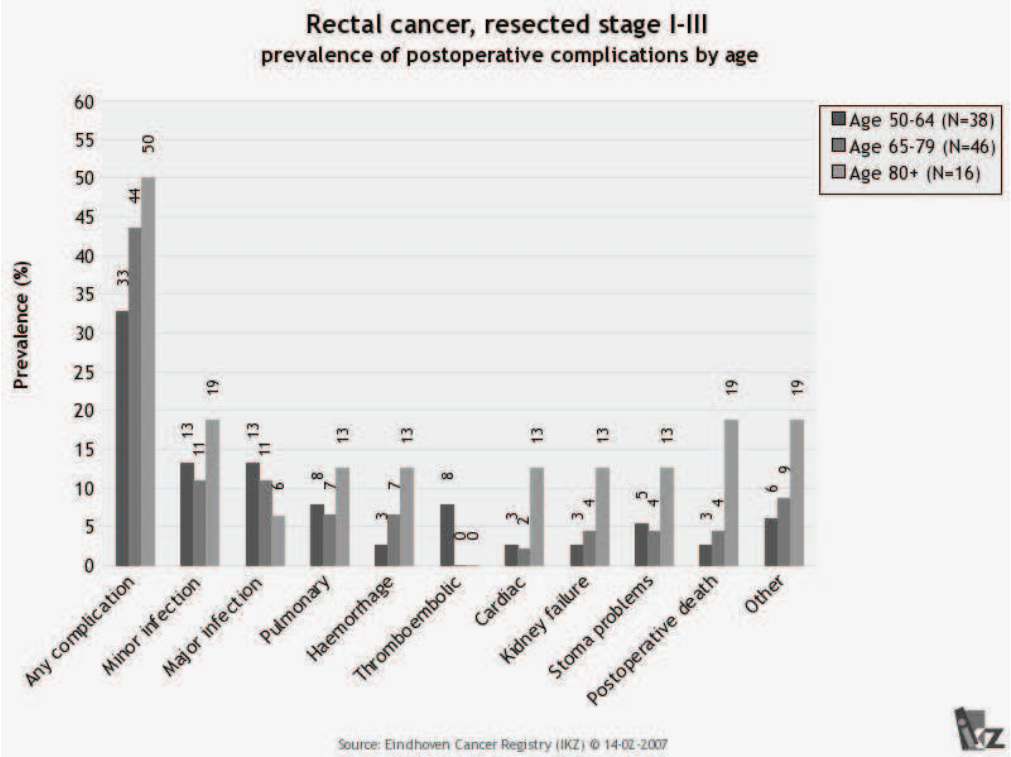


Figure 2 Age-specific prevalence of postoperative complications during the first 3 months after diagnosis (1995-99)

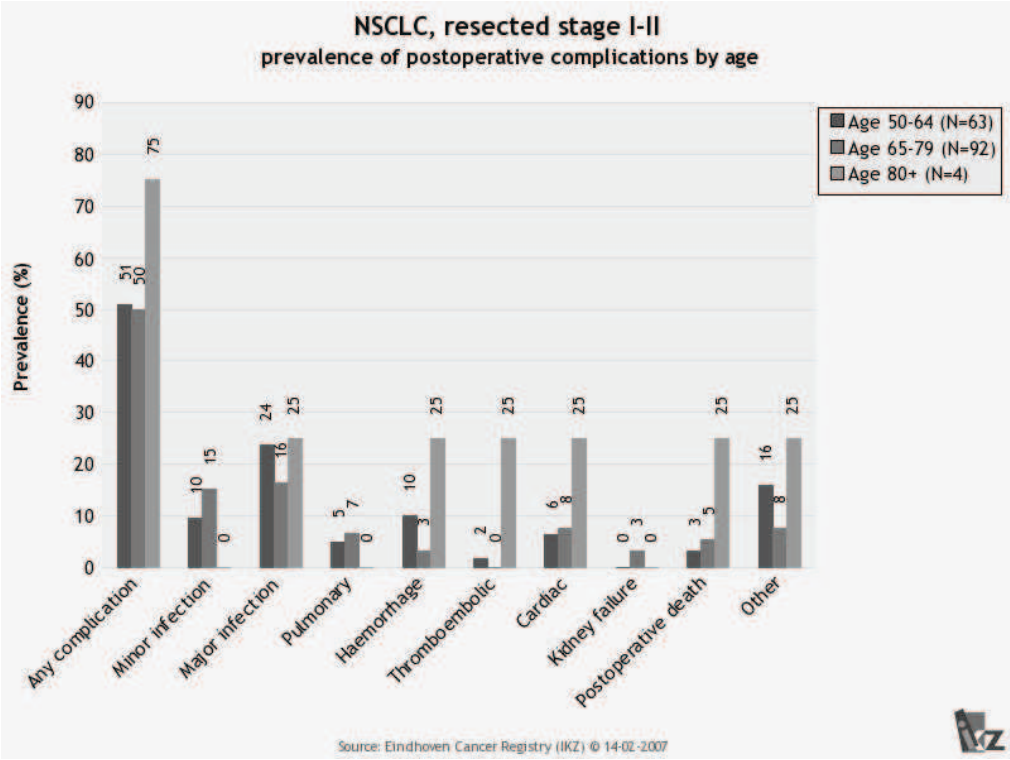
a. Colon cancer, resected stage I-III



b. Rectal cancer, resected stage I-III



c. NSCLC, resected stage I-II



d. Breast cancer, resected stage I-III

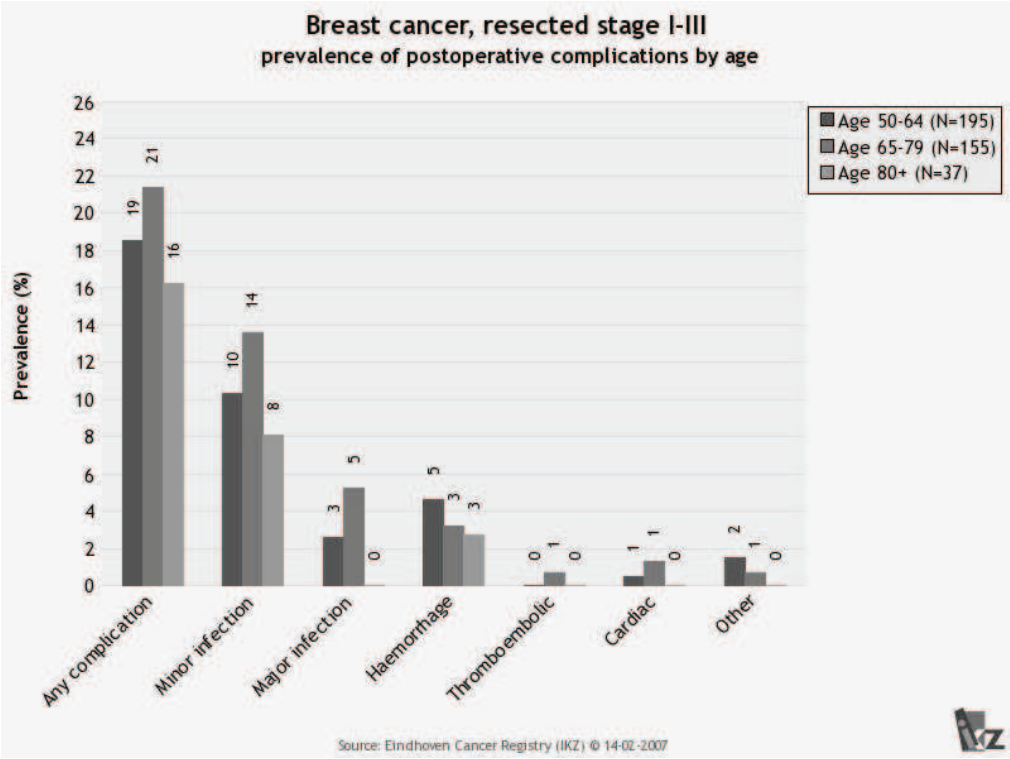
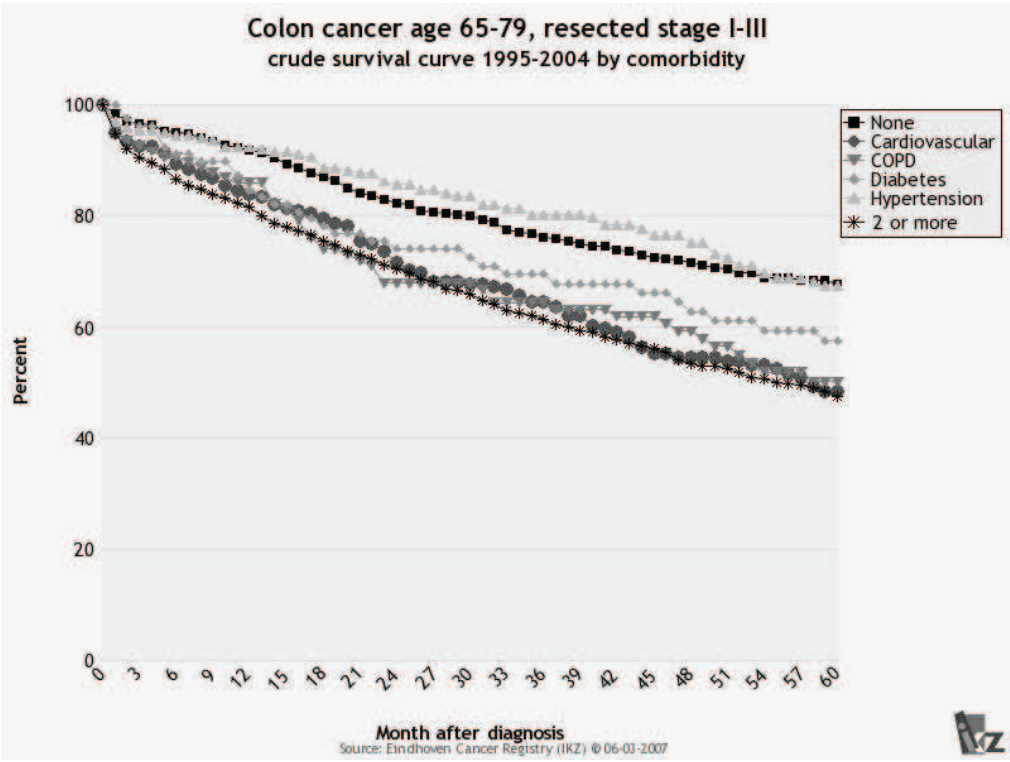
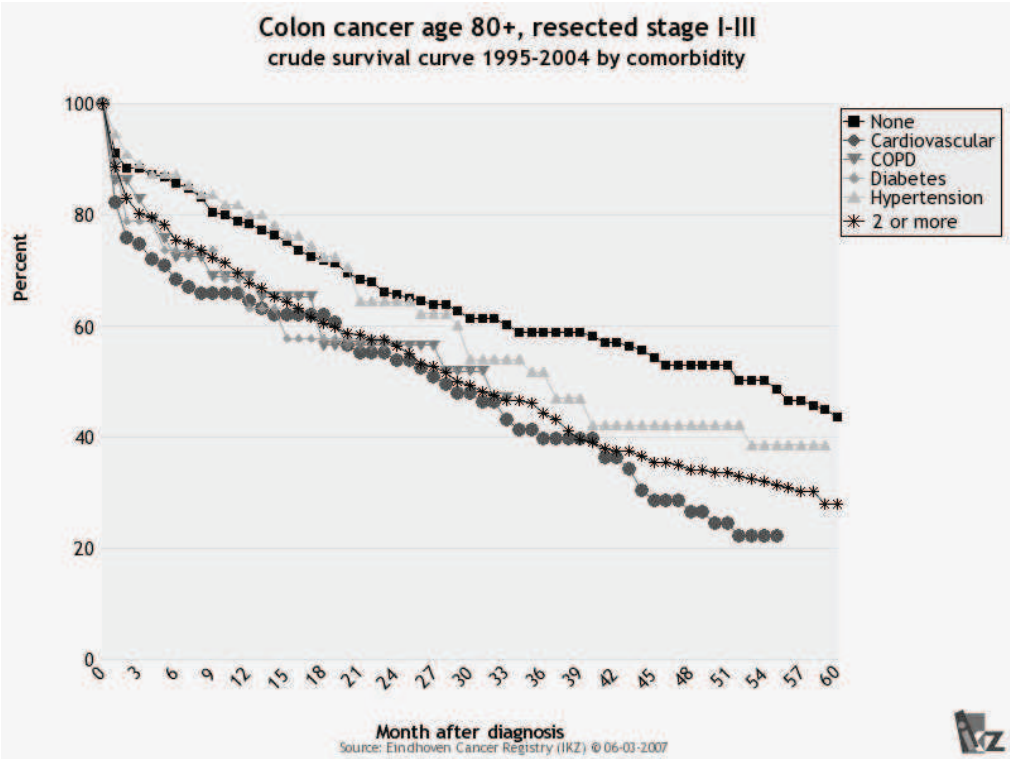


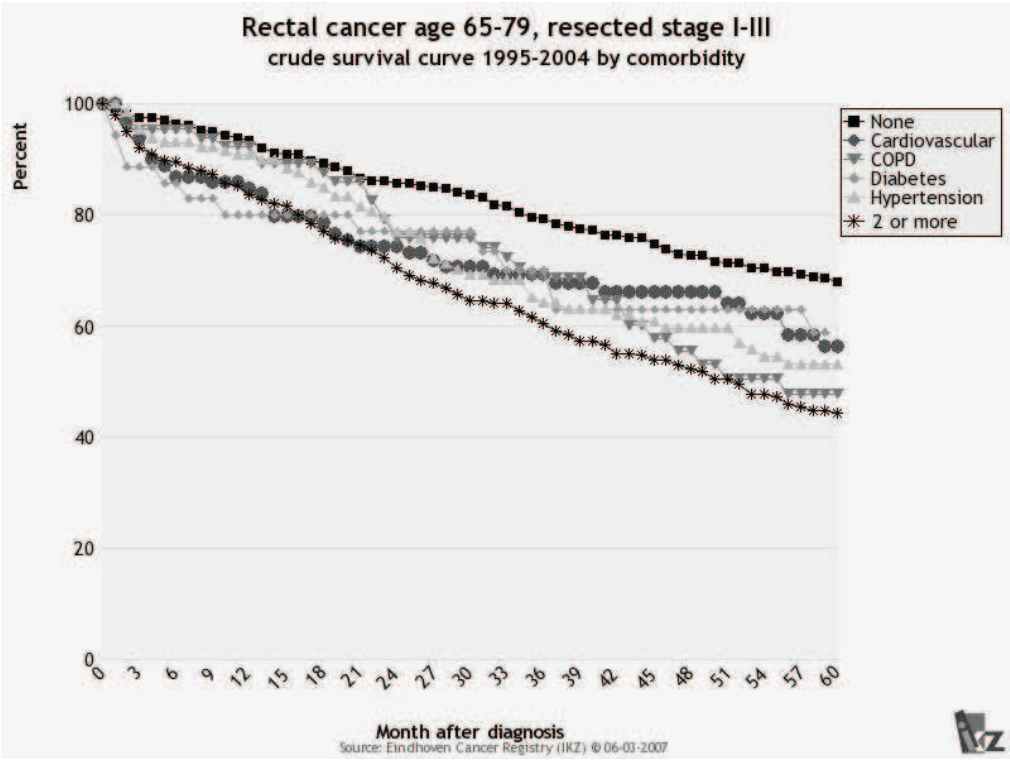
Figure 3 Overall survival, according to age and comorbidity

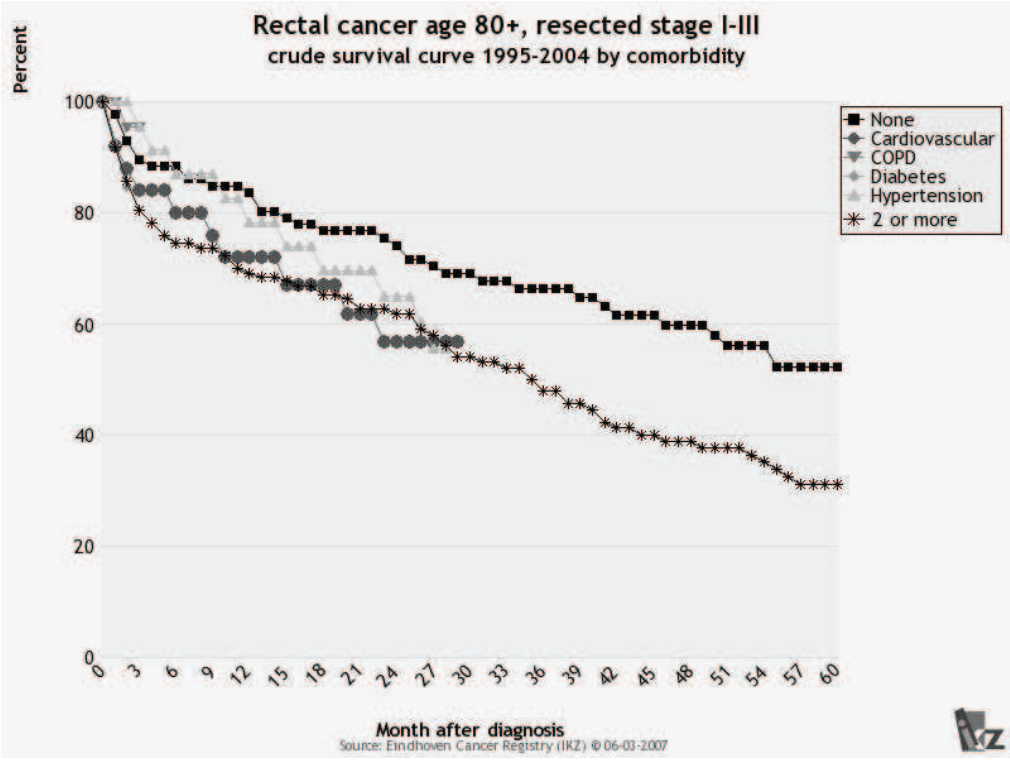
a. Colon cancer stage, resected I-III



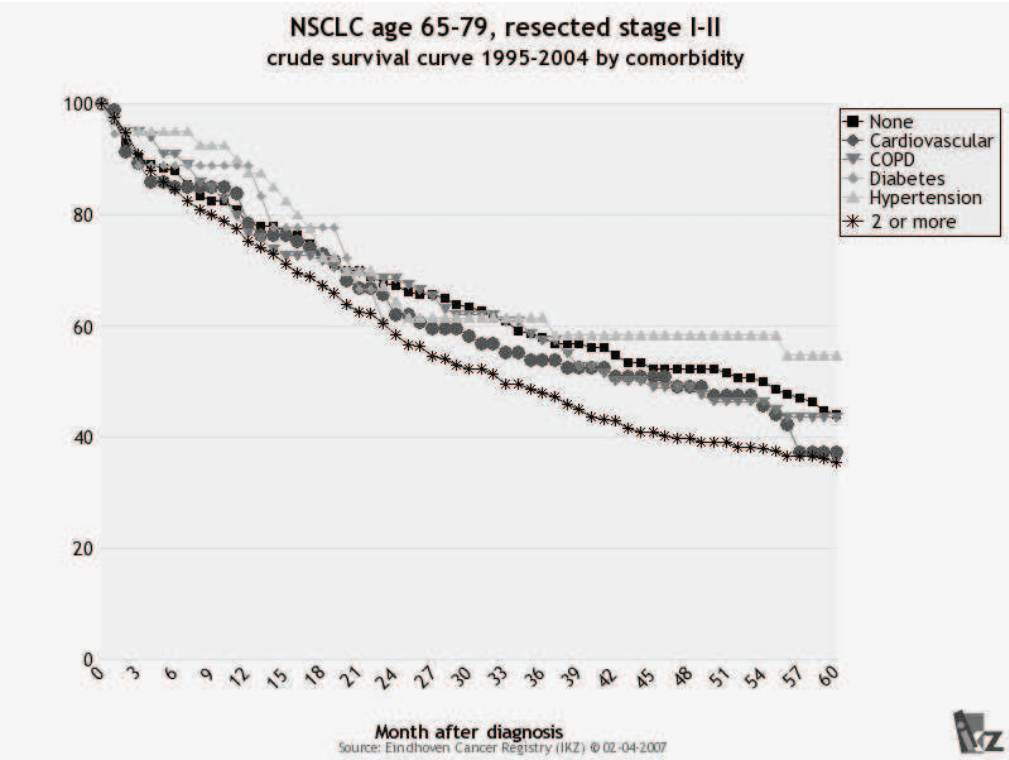


b. Rectal cancer stage, resected I-III

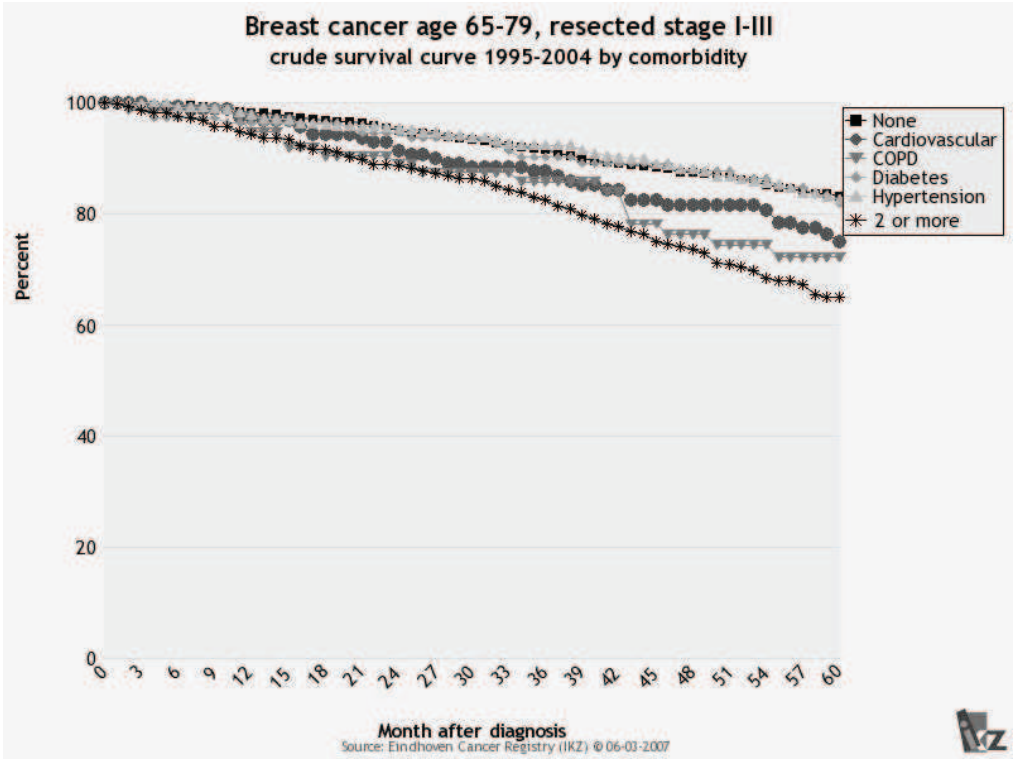


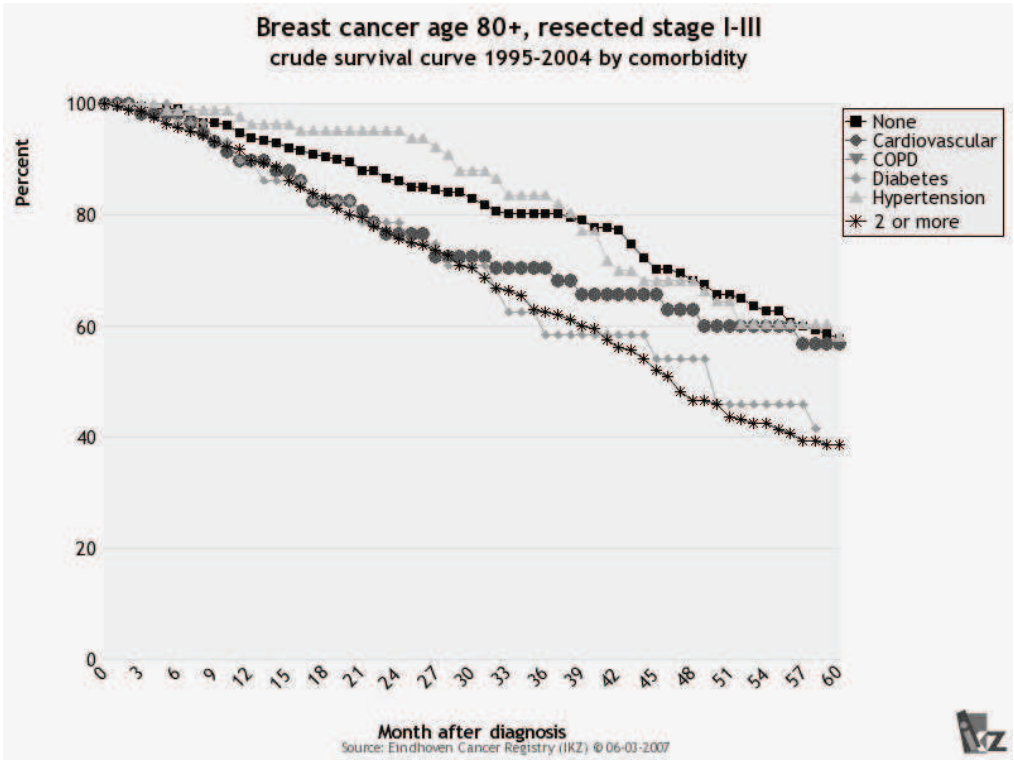


c. NSCLC cancer, resected stage I-II



c. Breast cancer, resected stage I-III





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Chapter 2.2

The effects of age and comorbidity on treatment patterns for radiotherapy and survival in patients with mobile rectal cancer: a population-based study

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European Geriatric Medicine, in press
doi: 10.1016/j.eurger 2011.07.07

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Abstract:

Purpose: To describe treatment patterns and outcome for short-course pre-operative radiotherapy in patients with mobile rectal cancer according to age and comorbidity.

Material and methods: All 914 patients, aged ≥ 50 years, with T2/3N0-2M0 rectal cancer, newly diagnosed in Southern Netherlands between 2002 and 2006 were included. The influence of age, patient and tumour characteristics and type of surgery on treatment with 5*5 Gy preoperative radiotherapy and survival was analysed.

Results: Patients younger than 70 years received radiotherapy less frequently if they had multiple co-morbid conditions (OR=0.4), a history with previous cancer (OR=0.2) or had undergone low anterior resection (OR=0.5). Among patients aged 70 years or older, men received radiotherapy more often than women (OR=2.0) and withholding radiotherapy was associated with multiple comorbid conditions (OR=0.3), low anterior resection (OR=0.3), diabetes mellitus (OR=0.5) or age above 80 years (OR=0.5). Among patients ≥ 70 years hazard ratios for death were significantly increased for males (HR=1.5), higher age (HR=1.06 per year of age), multiple co-morbidities (HR= 1.7) and pulmonary disease (HR=1.6) independently. Receiving radiotherapy had no significant influence on survival after adjustment for other prognostic variables.

Conclusion: As a rule, factors that predict life expectancy, determine also the decision to withhold preoperative radiotherapy. With the exception that women receive radiotherapy less frequently as compared to men, although women survive longer. Increasing age determines withholding radiotherapy only among patients aged 70 years and older.

Introduction

Treatment guidelines for rectal cancer were updated in the Netherlands in 2001: short-course pre-operative radiotherapy (5x5 Gray (Gy)) and a total mesorectal excision (TME) were introduced.[1] In clinical trials addition of short-course pre-operative radiotherapy to TME reduces the incidence of local recurrences in all age groups.[2] [3] In population-based studies overall survival of rectal cancer has improved further since introduction of TME-surgery and preoperative radiotherapy.[4] Only patients older than 75 years did not exhibit improvement of overall survival although combined therapy did lead to an increase in distant metastasis-free survival as well as cancer-free survival.[4]

In 2002, 90% of patients in the Southern part of the Netherlands with a mobile rectal tumour underwent TME procedure according to the national guidelines and 78% received preoperative radiotherapy according to the guidelines.[5] However, several studies have shown that radiotherapy was less often applied for the elderly and those with comorbidity.[5] [6]

We conducted a population-based study to determine factors associated with withholding preoperative radiotherapy and survival of patients with resectable rectal carcinoma (stage pT2 and pT3) between 2002 and 2006. In addition, a questionnaire focussing on factors that might influence referral for radiotherapy was sent to surgeons conducting rectal surgery to gain insight into the decision making process.

Material and methods

Data from the population-based Eindhoven Cancer Registry were used. Data were collected on all patients with newly diagnosed cancer in a large region of the southern Netherlands, with a population of 2.4 million. The registry is notified by six pathology departments, 10 community hospitals and two radiotherapy institutes. Information on diagnosis, staging, comorbidity at time of diagnosis and treatment is routinely extracted from the medical records by trained registration clerks.

We included all patients aged 50 years or older with rectal cancer stage pT2-pT3 and M0, diagnosed between January 2002 and December 2006 in the area of the Eindhoven cancer registry. Patients with rectosigmoid carcinoma, those undergoing a sigmoid resection/colotomy and patients with a resection other than low anterior resection or abdomino-perineal resection were excluded (N= 74). Furthermore, patients who had received pre-operative chemotherapy or intra-operative radiotherapy (N=127) were excluded because this type of treatment suggests the presence of resectable but more locally advanced tumours i.e. cT4. Patients with rectal cancer diagnosed at autopsy were also not selected. A total of 914 patients could be included. Preoperative radiotherapy consisted of short-course radiotherapy with 5x5 Gy, often referred to as short-course radiotherapy. As treatment plans are made before pathological staging and downstaging is not plausible within the short time between end of radiotherapy and time of surgery, clinical stages are supposed to be equal to pathological stages.

In this study primary endpoints were undergoing preoperative radiotherapy and crude survival. The percentage of patients who received preoperative radiotherapy was calculated according to sex (female versus male), age (50-59, 60-69, 70-79, 80+), number (0, 1, 2+) and most common types of comorbidity (cardiac disease, diabetes mellitus, chronic obstructive

pulmonary disease (COPD) and previous cancer), differentiation grade (well/moderate, poor/undifferentiated, unknown) and type of resection (rectum amputation versus low anterior resection).[7] Cardiovascular disease includes valvular disease, myocardial infarction, angina pectoris, congestive heart failure, cardiomyopathy, arrhythmias, deep vein thrombosis, abdominal aorta aneurysm, claudicatio intermittens and cerebrovascular disease. Hypertension was coded as a separate comorbid condition. Chi-square analysis was used to test whether the percentage of patients who received preoperative radiotherapy within a certain category differed from the reference category of that specific variable. Multivariable logistic regression analyses of the independent odds ratio for those undergoing preoperative radiotherapy were carried out with the proc logistic procedure of the SAS package. Since the effects were different for age <70 and 70+, we stratified according to age.[4]

Information concerning vital status of all patients was available up to 1 January 2008. In addition to passive follow-up via the hospitals, this information was also obtained from the municipal registries in the area of the Eindhoven Cancer Registry and the Municipality Administrative Database. The latter database contains data on all deceased and emigrated persons in the Netherlands since October 1994.Therefore, information on patients who moved outside the registry area was also obtained. Patients who emigrated outside the Netherlands were considered lost-to follow-up at the date of emigration.

To determine the surgeons' policy for referral for radiotherapy, we sent a questionnaire to 43 gastro-intestinal surgeons specialized in rectal cancer surgery in the Eindhoven Cancer Registry region. In the procedure to preoperative radiotherapy, surgeons propose radiotherapy to patients. All surgeons have the opportunity to discuss their patients (before their proposal to an individual patient) in a multidisciplinary team. As a rule this team

consists of gastro-intestinal surgeons, radiotherapists, medical oncologists and a oncology nurse. It depends on the hospital whether general practitioners or geriatricians are involved. In the questionnaire we categorised several tumour- and patient-characteristics and asked whether these characteristics played an important, a moderately important or a minor/no role in recommending radiotherapy to patients. Tumour characteristics included tumour localisation (proximal, distal), size, positive lymph nodes; patient characteristics were age, comorbid burden, specific diseases such as cardiac or pulmonary disease and dementia, distance to radiotherapeutic centre, functional status and presence of residential care. Surgeons were also asked to categorize the three most important factors that guided them in their decision to propose short-course pre-operative radiotherapy. In total 28 questionnaires were returned (response rate:65%), all returned questionnaires were filled in completely.

Statistical analysis: Crude survival rates were computed. Survival time was defined as the time from diagnosis until death or the end of the study (if the patient was still alive on January 1st, 2008). The log rank test was performed to evaluate significant differences in survival in univariate analyses. For evaluation of the independent effects of the prognostic factors, a multivariable Cox regression model was built. Due to the different effects of predicting variables between the age groups these analyses were stratified according to age (<70/70+). The independent prognostic effects of age, sex, type of surgery, grade and preoperative radiotherapy were first estimated using a model without comorbidity. Subsequently comorbidity was included in the model to investigate whether the prognostic effect of age could be fully explained by comorbidity. With respect to comorbidity, the prognostic effects of the number of comorbid conditions were evaluated first. Subsequently, the specific diseases were evaluated in separate models, including all aforementioned

variables, except for the number of comorbid conditions. All tests were 2-sided. A p-value < 0.05 was considered significant. SAS/STAT (version 9.1) software was used for statistical analyses.

Results

Patient characteristics

Nine hundred and fourteen patients were diagnosed with rectal cancer (534 men and 380 women). Table 1 shows general characteristics of these patients. Forty-two percent had no other serious chronic diseases at time of diagnosis of rectal cancer; 29% had one comorbid condition and 20% had 2 or more comorbid conditions. Almost one-fourth of all patients suffered from cardiac diseases, 12% had diabetes, 10% a previous cancer and 9% a chronic obstructive pulmonary disease. Fourty-six percent of all patients was older than 70 years. Sixty-one percent of patients underwent low anterior resection and 39% rectum amputation.

Table 1. General characteristics of patients with rectal cancer diagnosed in 2002-2006 in the southern Netherlands and percentage who received preoperative radiotherapy.

		(%)	Preoperative RT (%)	P
Gender				
Male	534	(58)	85	0.01
Female	380	(42)	79	
Age (years)				
50-59	194	(21)	88	<0.0001
60-69	300	(33)	87	
70-79	302	(33)	82	
80+	118	(13)	65	
Comorbidity				
No comorbidity	390	(42)	88	<0.0001
1 comorbid condition	262	(29)	82	
2 or more comorbid conditions	179	(20)	72	
Unknown comorbidity	83	(9)	86	
Cardiac	200	(22)	77	
Pulmonary	78	(9)	81	
Diabetes	107	(12)	72	

Previous cancer	94	(10)	66	
Differentiation grade				
1 or 2	570	(62)	78	<0.0001
3 or 4	94	(11)	80	
Unknown	250	(27)	96	
Type of surgery				
abdomino-perineal resection	360	(39)	90	<0.0001
Low anterior resection	554	(61)	78	

Pre-operative radiotherapy

The proportion receiving preoperative radiotherapy decreased from 87% among patients aged 60 to 69 years old to 65% in the group aged 80 years or older; In the latter age group 77% received radiotherapy if comorbidity was absent. If cardiovascular disease/pulmonary disease, diabetes or multiple co-existing diseases were present in these oldest old, radiotherapy was given in 58%, 63% and 64%, respectively (figure 1).

Multivariable analyses for the odds of receiving preoperative radiotherapy were stratified according to age (table 2). Among those younger than 70 (model without comorbidity) the odds ratio (OR) for receiving radiotherapy was significantly lower for those undergoing low anterior resection as compared to those undergoing abdomino-perineal resection. When comorbidity was included, suffering from 2 or more comorbid conditions or a history of previous cancer significantly decreased the odds for receiving preoperative radiotherapy.

For patients aged 70 or older, presence of least 2 comorbid diseases, age above 80 years old, and low anterior surgery significantly decreased the odds for receiving radiotherapy. Men received radiotherapy more often. In a model with comorbidity, diabetes mellitus in particular decreased utilization of radiotherapy, while cardiac disease or a history of previous cancer reached borderline significance. COPD had no impact on receiving radiotherapy. The odds for receiving preoperative radiotherapy in men remained was twice as high as compared to females.

Among patients younger than 70 years the proportion receiving preoperative radiotherapy remained stable over time. However, among patients aged 70-79 this proportion increased from 78% in 2002 to 88% in 2006. In contrast, among those older than 80 this proportion first increased from 61% in 2002 to 75% in 2004, and then decreased to 48% in 2006 (data not shown).

Table 2 *Multivariable analyses of referral for preoperative radiotherapy among patients with pT2/pT3 rectal carcinoma, according to age*

	Age <70				*Age 70+*			
	Model without comorbidity		**Model with comorbidity**		**Model without comorbidity**		**Model with comorbidity**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age								
50-59[1]	1		1					
60-69	1.0	*0.6-1.7*	1.1	*0.6-1.9*				
70-79[1]					1		1	
80+					0.4	*0.2-0.7*	0.5	*0.3-0.8*
Gender								
Female[1]	1		1		1		1	
Male	1.3	*0.7-2.2*	1.4	*0.8-2.5*	1.7	*1.0-2.7*	2.0	*1.2-3.4*
Type of surgery								
abd-perineal res[1]	1		1		1		1	
Low anterior res.	0.5	*0.3-0.9*	0.5	*0.3-0.9*	0.3	0.2-0.5	0.3	0.2-0.5
Comorbidity								
0[1]			1				1	
1			0.7	*0.3-1.3*			0.5	*0.3-1.0*
2+			0.4	*0.2-0.8*			0.3	*0.2-0.6*
Cardiac			0.8	*0.4-1.7*			0.6	*0.4-1.0*
COPD			0.8	*0.3-2.3*			0.6	*0.3-1.4*
Previous cancer			0.2	*0.1-0.5*			0.6	*0.3-1.0*
Diabetes mellitus			0.5	*0.2-1.3*			0.5	*0.3-0.9*

[1] Reference category

OR = odds ratio

95% CI = 95% confidence interval

COPD = chronic obstructive pulmonary diseases

Survival

Survival was significantly worse for patients who were older (figure 2). Among those younger than 70 years survival was not significantly associated with preoperative radiotherapy or comorbidity. In contrast, among those aged 70 or older, survival was significantly worse for those who did not receive preoperative radiotherapy and also for those with comorbidity (figures 3 and 4). In multivariable analysis of patients younger than 70 no significant independent prognostic factors for mortality were found (table 3). Among those aged 70 or older predictors for mortality (model without comorbidity) were higher age, male gender and less differentiated tumours. In a full model with comorbidity survival was significantly worse for higher age, males, patients suffering from COPD or at least 2 comorbid conditions (table 3).

Table 3 *Multivariable analyses of survival among patients with pT2/pT3 rectal carcinoma, according to age*

	Age <70				*Age 70+*			
	Model without comorbidity		**Model with comorbidity**		**Model without comorbidity**		**Model with comorbidity**	
	HR	*95% CI*	**HR**	*95% CI*	**HR**	*95% CI*	**HR**	*95% CI*
Age (continuous)	1.05	*1.00-1.10*	1.03	*0.98-1.09*	1.06	*1.03-1.10*	1.06	*1.02-1.10*
Gender								
Female[1]	1		1		1		1	
Male	1.42	*0.86-2.37*	1.35	*0.78-2.34*	1.68	*1.19-2.36*	1.50	*1.05-2.15*
Type of surgery								
abd-perineal res.[1]	1		1		1		1	
Low anterior res.	0.81	*0.49-1.32*	0.77	*0.45-1.31*	0.81	0.58-1.12	0.78	0.55-1.09
Grade								
1-2[1]	1		1		1		1	
3-4	1.04	*0.98-1.12*	1.06	*0.98-1.14*	1.06	*1.00-1.10*	1.05	*1.00-1.10*
Preoperative RT								
No[1]	1		1		1		1	
Yes	0.68	*0.35-1.35*	0.65	*0.33-1.30*	0.71	*0.48-1.04*	0.76	*0.51-1.14*
Comorbidity								
0[1]			1				1	
1			1.12	*0.61-2.03*			1.40	*0.91-2.14*
2+			1.49	*0.74-3.02*			1.74	*1.12-2.68*
Cardiac							1.06	*0.73-1.44*
COPD							1.60	*1.02-2.52*
Previous cancer							0.96	*0.60-1.53*
Diabetes mellitus							1.20	*0.78-1.85*

[1] Reference category

HR = hazard ratio for mortality

95% CI = 95% confidence interval

COPD = chronic obstructive pulmonary diseases

Questionnaire

Surgeons indicated that tumour characteristics are the main issue in referral for radiotherapy. Major determinants were tumour localisation (39% mentioned radiotherapy was less important for proximal tumours), tumour size and lymph node metastases. Comorbidity or age were regarded as less important. Distance to a radiotherapy centre was not regarded as an important factor.

Comorbid burden as indicated by the actual presence of two or more comorbid diseases was regarded as moderately important by 50% of the surgeons. Many surgeons viewed dementia as a reason to withhold radiotherapy: 48% considered dementia as moderately important, 40% as a very important reason to refrain from radiotherapy.

Disturbed mobility, use of walking-aids or requiring assistance had no impact on their therapeutic decisions for 54% of the surgeons. Half of the respondents mentioned that ADL-dependency influenced their referral for radiotherapy. Otherwise, 58% considered the need for residential care in a nursing home as an important reason to refrain from pre-operative radiotherapy. From a surgical point of view age did not matter until the age of 80; half of the surgeons took the age of 80 years and over as a moderately important factor in deciding whether a patient should receive radiotherapy.

Discussion

In patients with mobile rectal cancer preoperative radiotherapy was carried out in over 82% of patients, as far as these patients were younger than 80 years and had less than two comorbid conditions. Above 80 years utilization of radiotherapy dropped to 65%, although 77% of patients in this oldest group received radiotherapy if comorbidity was absent. In an

earlier study of our group (including patients diagnosed before 2002) comorbidity did not affect the resection rate of patients with rectal cancer, but led to less frequent use of radiotherapy in patients with at least 2 co-morbid conditions. Previous malignancy or a combination of diabetes and hypertension were conditions that had the greatest effect on decreased use of radiotherapy.[5] In our present study female gender, age above 80 years and again multiple co-morbid conditions and diabetes mellitus were associated with less frequent referral for radiotherapy. Despite an update on treatment guidelines in 2001 (advocating the combination of short course pre-operative radiotherapy and TME-surgery), the associations between specific comorbidities and less frequent use of radiotherapy have remained the same.

One can argue that once the decision has been made to operate patients with rectal cancer using major surgical procedures, short-course preoperative radiotherapy is not expected to be troublesome. This is only partly true, since radiotherapy is associated with increased rates of impaired wound healing, bowel dysfunction and faecal incontinence.[11] [12] [13] [14] Especially in elderly patients complications due to the combination of rectal surgery with preoperative radiotherapy lead to high mortality rates both in population-based and trial populations.[10] Patients aged 75 years or older had a 30-day mortality rate of 7% and a 6-month mortality of 13%, versus 26% and 39%, respectively, for those over 90 years old.[10] Nevertheless, preoperative radiotherapy reduces the incidence of local recurrent disease and is less demanding in terms of logistics, costs and compliance considering postoperative chemoradiotherapy in rectal cancer.[9]

In patients above 75 years of age Rutten and colleagues showed no survival benefit of pre-operative radiotherapy, so prevention of local recurrent disease remains the primary goal of radiotherapy. [4] Since time to benefit from radiotherapy is crucial, probably factors that are

associated with decreased survival may also determine the choice for radiotherapy. In our study higher age, male sex , pulmonary disease and presence of multiple co-morbid conditions were associated with decreased survival in patients aged 70 years and older. Discrepancies between factors that determine referral for radiotherapy and survival apparently occur in male patients and in patients with pulmonary disease. Co-existent pulmonary disease was associated with early death in patients over 70 years but pulmonary disease did not have any impact on receiving radiotherapy. Male gender was associated with early death if men were older than 70 years, but women received radiotherapy less frequently. Additional analyses in our study showed that men were not significantly older as compared to women, but men suffered significantly more often from COPD and cardiac disease ($p< 0.04$). However, the gender effect on survival persisted when co-morbidity was taken into account. Interestingly, an earlier report showed that short-course radiotherapy was associated with fewer complications among women as compared to men.[11] Our study therefore suggests the existence of undertreatment in elderly women. Patient preferences might explain the gender effect: female patients are more often single (separated or widowed) and, indeed, being single is associated with decreased use of radiotherapy in patients with breast conserving surgery combined with radiotherapy.[8] Reservations towards pre-operative radiotherapy can be advocated in patients with high risk of dying within 2 years due to other causes than cancer. Eighty-three percent of patients without comorbidity and older than 70 years were alive after 2 years. In a substantially younger trial-population survival rate at two years was also 83% [15]. Number of patients needed to undergo treatment to prevent one local recurrence in the trial was 17.[15] In our population-based study patients with diabetes mellitus and COPD showed decreased survival rates after 2 years: 75% and 58%, respectively. Overall 2-year survival of our patients

of 80 years and older was 63%. The number needed to prevent local recurrence will be marginally higher in our study population compared to younger or fitter study populations with a better 2-year survival. Therefore, we argue that physicians should only withhold pre-operative radiotherapy in case patients do not accept its disadvantages or death within the next two years seem to be inevitable.

If surgery cannot be performed in the elderly, due to frailty or high comorbid load, the goals of therapy should be local tumour control and management of local complications instead of prevention of local recurrences and increased cancer-free survival. In these cases combinations of contact radiotherapy, external beam radiotherapy and brachytherapy may be a safe and modestly effective alternative therapy. With this combination of therapies a French study showed a recurrence rate of 28% and a 5-year survival rate of 63%.[16]

Radiotherapy was proposed less often if low anterior resection had been performed. The questionnaire indicated some reluctance to refer patients with proximal tumours for radiotherapy. We argue that proximal tumours are present predominantly in patients who have undergone low anterior resection (LAR). Indeed local recurrences occur less frequently in tumours treated with LAR (7.8%) versus abdomino-perineal resection (11.7%). Pre-operative radiotherapy reduces local recurrences in all subsites, except in patients with LAR and distal margins of less than 5 mm.[20]

In response to our questionnaire surgeons revealed that tumour characteristics such as size and localisation predominantly determine referral for radiotherapy. Moreover, age over 80 years and overt comorbidity, e.g. 2 or more concomitant conditions, influenced their decision-making. Pulmonary disease is viewed as a minor issue in the decision-making process by surgeons. A European multicentered study of pre-operative assessment of elderly cancer patients found no relationship between comorbidity and post-surgical outcomes.[17]

This study however was not population-based and used Satariano's comorbidity index, an index without notification of severity or impact on daily functioning. In contrast, ADL and IADL-dependency predicted more accurately extended hospital stay and post-operative complications.[17] In our study, only half of the surgeons indicated that they had incorporated items concerning (I)ADL-dependency into their decision-making process, although (I)ADL-dependency is a strong predictor of early and late mortality of hospitalized elderly patients.[18]

Limitations of our retrospective population-based study are clear. The observed variation is at least partially based on deficient documentation and/or arbitrary decision-making. The increased survival of older patients with pre-operative radiotherapy compared to older patients without radiotherapy is likely to be an example of selection bias in our study. Direct comparison between these groups in trials with relatively healthy elderly showed no difference in survival.[4] Furthermore, our data did not comprise all relevant parameters involved in the decision-making process on referral for radiotherapy, especially on gender data lack. Data on malnutrition, dependency on (I)ADL, geriatric syndromes and detailed information on mental functions are regularly described in a comprehensive geriatric assessment and determine survival. [21] Unfortunately these data are regularly lacking in cancer registries worldwide. Patient preferences were not studied, also because they are often not documented. On the other hand, the registration process and extraction of data from medical files of our population-based data derived from community hospitals only were judged as very reliable.[19].

Our study shows that among patients up to 80 years old more than 82% received short course pre-operative radiotherapy according to treatment guidelines. For patients ≥ 70 years, the co-morbid load (diabetes mellitus, previous cancers or multiple comorbidities)

was associated with decreased survival, which might explain the significantly lower rates for receiving radiotherapy. This balance between decreased survival and less utilization of radiotherapy was less clear among male patients or patients with COPD. Although survival in these groups was relatively low, utilization of radiotherapy did not seem to be affected by COPD or was even increased in men compared to women. Therefore especially older women seem either to be undertreated or avert radiotherapy themselves.

It seems worthwhile to evaluate prospectively whether factors, associated with decreased survival are indeed responsible for the absence of potential benefits of radiotherapy, i.e prevention of local recurrences.

Acknowledgments

This research was performed within the framework of the project 'Treatment and outcome for cancer patients aged 75 or older: a national population-based study' (Dutch Cancer Society Grant IKZ 2007-3865) and GeriOnNe (Geriatric Oncology in the Netherlands). We thank the registrars of the Eindhoven Cancer Registry for their dedicated data collection.

Figure 1 *Referral (%) for preoperative radiotherapy among patients with pT2/3 rectal cancer, according to age and comorbidity*

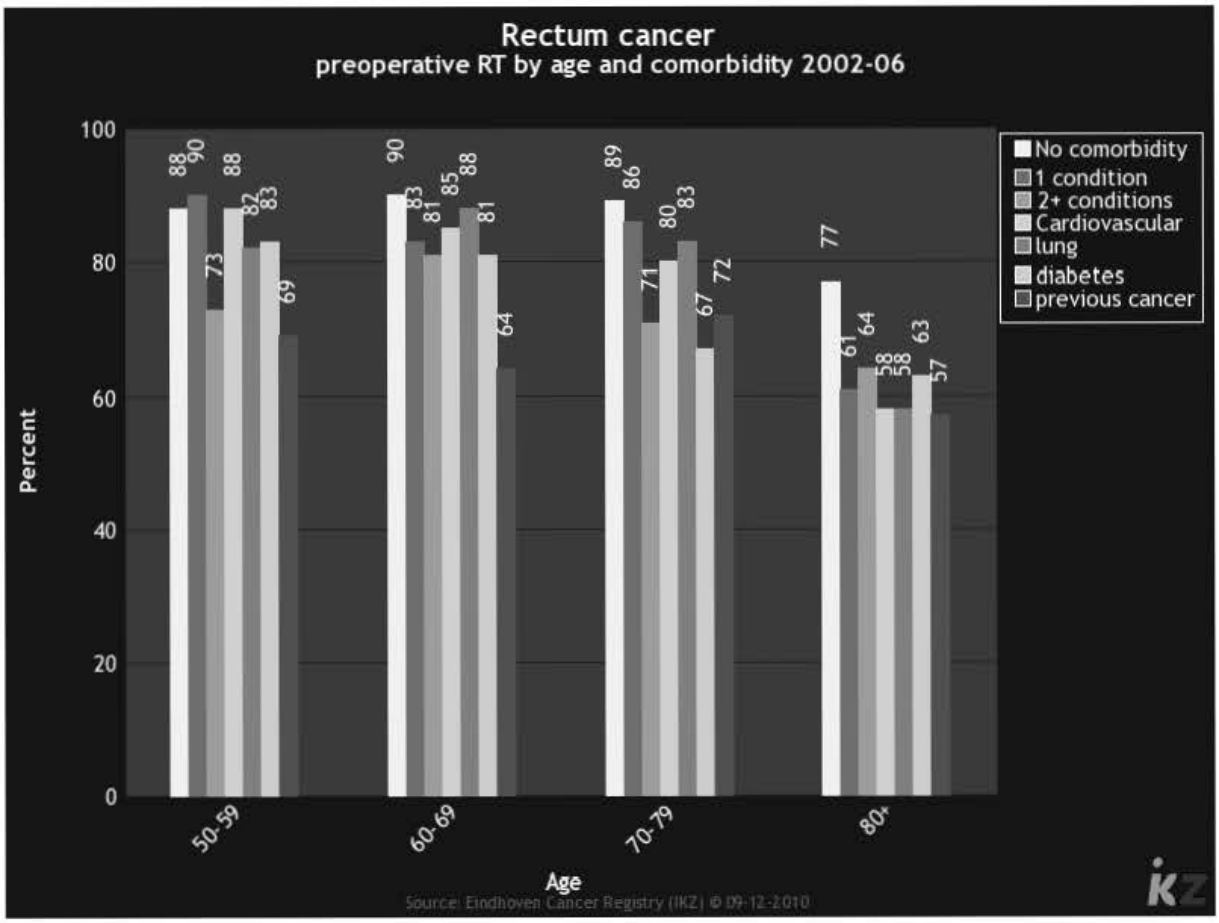


Figure 2 *Crude survival of patients with pT2/3 rectal carcinoma according to age.*

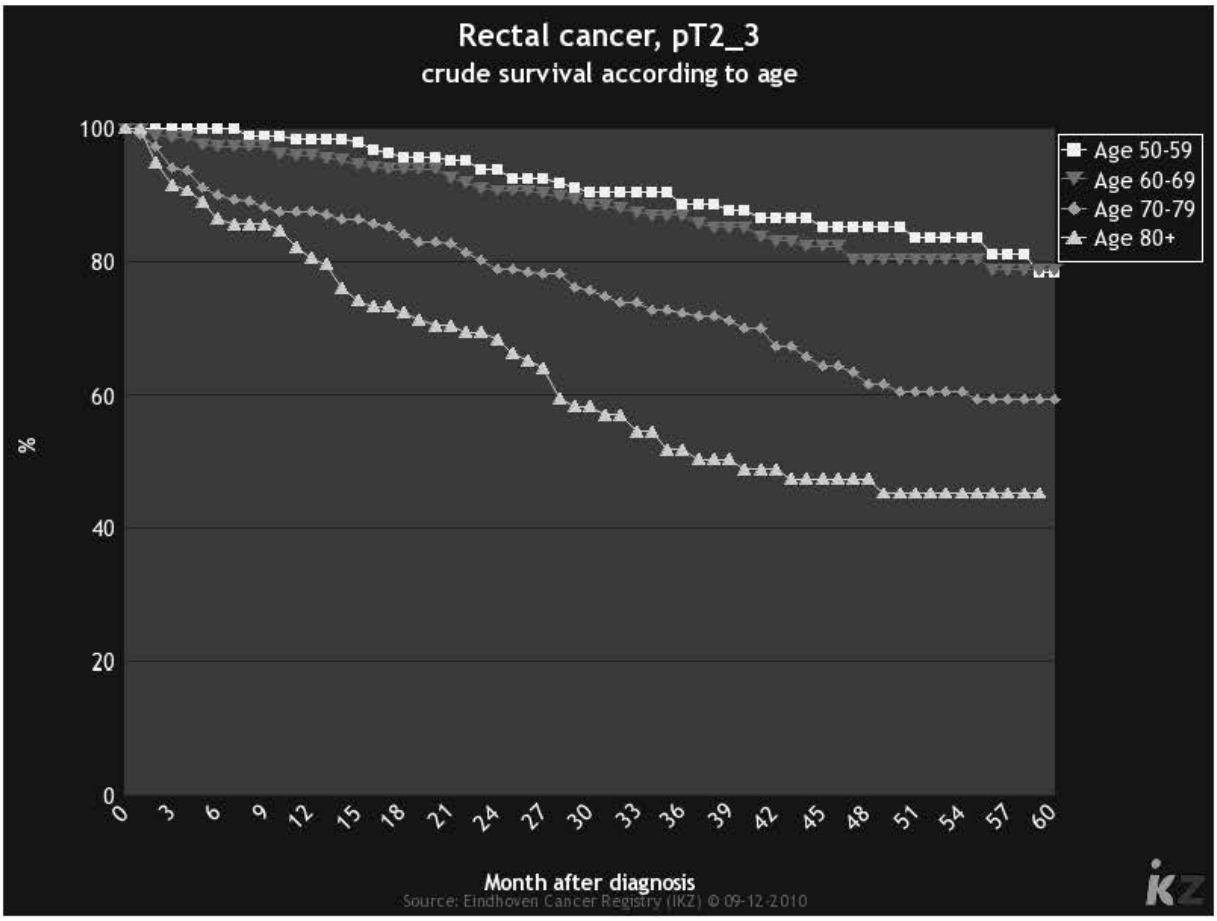


Figure 3 *Crude survival of patients with pT2/3 rectal carcinoma (age 70+) according to comorbidity*

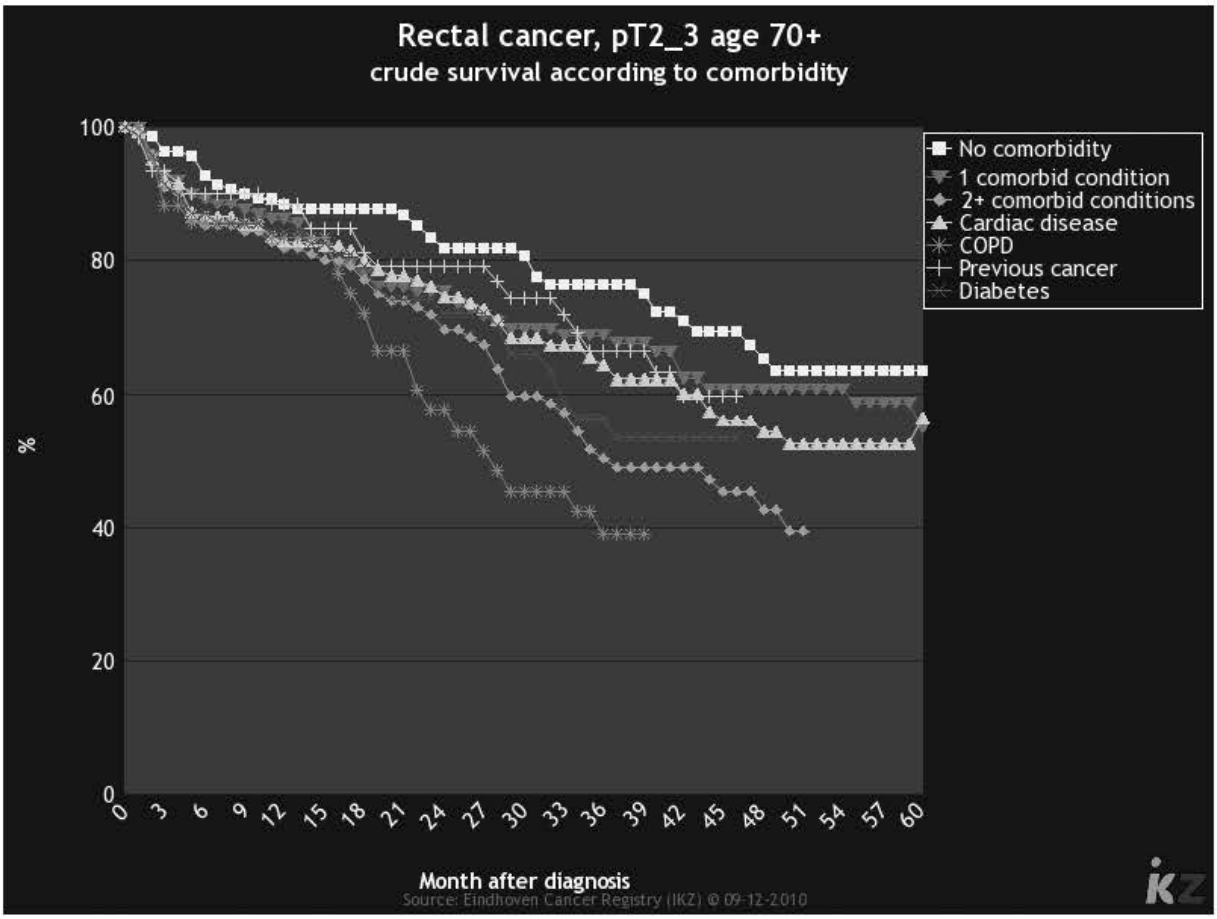
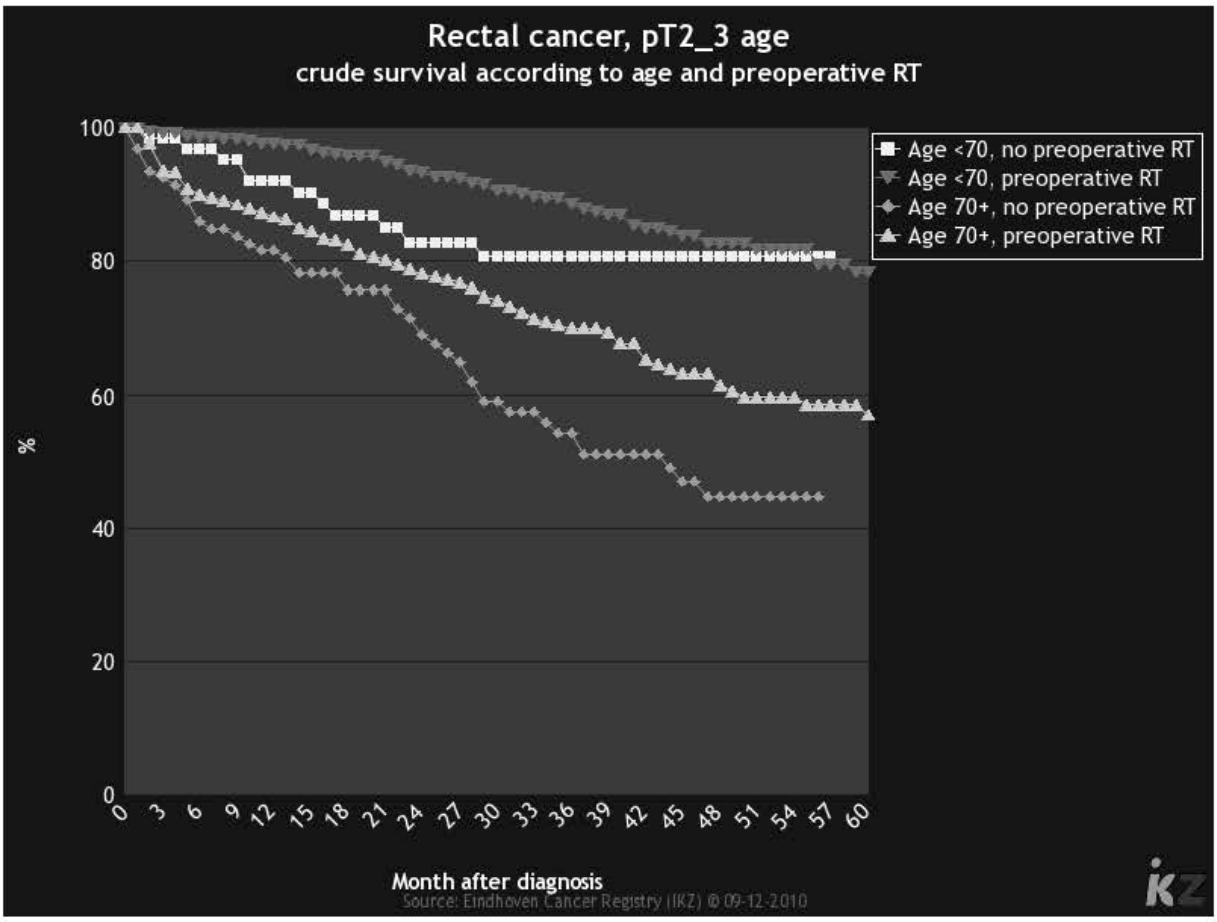


Figure 4 *Crude survival of patients with pT2/3 rectal carcinoma according to age and preoperative radiotherapy*



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Chapter 2.3

Benefits and drawbacks of short-course preoperative radiotherapy in rectal cancer patients aged 75 years and older

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Abstract

Purpose: to study incidence of local recurrences, postoperative complications and survival, in patients with rectal carcinoma aged 75 years and older, treated with either surgery and pre-operative short course radiotherapy or surgery alone.

Patients and methods: A random sample of patients aged over 75 years with pT2-T3,N0-2,M0 rectal carcinoma diagnosed between 2002 and 2004 in the Netherlands was included, treated with either surgery alone (N= 296) or surgery in combination with pre-operative 5x5Gy radiotherapy (N=346). Information on local recurrent disease, postoperative complications ECOG-perfomance score and Adult Comorbidity Evaluation-27 scores (ACE-27) was gathered from the medical files.

Results: Local recurrent disease developed less frequently in patients treated with pre-operative radiotherapy compared to surgery alone (2% vs 6%, p=0.002). Postoperative complications developed more frequently in irradiated patients (58% vs 42%, p<0.0001). Especially deep infections (anastomotic leakage, pelvic abcess) and wound infections were significantly increased in this group (16% vs 10%, p=0.02 and 14% vs 7%, p<0.005, respectively). 30-day mortality was equal in both groups (8%). A significant increase in postoperative complications rate and 30-day mortality was only seen in those with “severe comorbidity” compared to patients without comorbidity (respectively 58% and 10% versus 43% and 3%), COPD (59% and 12%), diabetes (60% and 11%) and cerebrovascular disease (62% and 14%). In multivariable analysis postoperative complications and re-operations, ACE-27 categories predicted 5-year survival, but pre-operative radiotherapy did not.

Conclusion: In elderly patients pre-operative radiotherapy decreases the incidence of local recurrent rectal cancer. Comorbidity and its influence on survival does not neutralize this

benefit, although especially severe comorbidity, COPD, diabetes and cerebrovascular disease induce high postoperative complication rates and a 4-fold increase in 30-day mortality rates.

Introduction

The prognosis of patients with rectal carcinoma (pT2-T3) has improved during the last decades.[1-5] Earlier stage diagnosis, progress in anesthesia, less emergency procedures and the introduction of total mesorectal excision (TME) led to an improvement in survival and less local recurrent disease.[1,6] Addition of pre-operative radiotherapy to TME-surgery led to a further decrease in local recurrence rate and to an increase in cancer-free survival. [7, 8] Over time, the introduction of TME-surgery and pre-operative radiotherapy did not result in better overall survival in patients older than 75 years.[8]

A previous publication from our group has shown that elderly patients with rectal cancer showed an increased incidence of treatment-related complications compared to patients younger than 70 years (65% versus 51%). Apart from age, comorbidity and pre-operative radiotherapy were associated with higher complication rates.[9] Also, compared to younger patients a stronger relation was observed between complications and mortality among elderly patients.[9,10, 11] As the risk-benefit ratio of pre-operative 5x5 Gy radiotherapy among elderly patients is less clear we conducted a study among unselected patients aged 75 years or older with rectal cancer (stage pT2-pT3) comparing post-operative complications, recurrence rates and survival between patients undergoing surgery with and without pre-operative radiotherapy.

Patients and methods

Data collection

Population-based data from patients diagnosed between 2002 and 2004 in six regional Dutch cancer registries were used. The cancer registries are based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). An additional source is the national registry of hospital discharge, which accounts for only a small subset of new rectal cancer cases since tumour tissue is available through biopsy and/or tumour resection for the vast majority of these patients. Information on patient characteristics (e.g. gender, date of birth), tumour characteristics (e.g. date of diagnosis, histology, stage, grade), and treatment is obtained routinely from the medical records about 6 months after diagnosis. The quality of the data is high, due to thorough training of the administrators and computerized consistency checks at regional and national levels. Survival and time to recurrence was calculated as the time from diagnosis to recurrence and/or death. The information on vital status was actively obtained from the municipal registries (complete up to 01-01-2010).

For the present study, we randomly selected 2 groups out of all patients aged 75 years or older with rectal cancer pT2-3N0-2M0 who were surgically treated. One group was treated with preoperative radiotherapy 5x5 Gy, the other was treated with surgery alone. Patients who underwent emergency surgery were excluded. Age was classified as 75-79, 80-84 and 85+ years. Additional data on performance status (ECOG), living alone, living independently, detailed information on re-operations and postoperative complications were gathered from the medical records. Also the Adult Comorbidity Evaluation-27 (ACE-27) was calculated. The ACE-27 index is a validated 27-item co-morbidity index for patients with cancer.[12]

Twenty-seven comorbid conditions were scored from the medical records. Each condition was graded to severity, classified as absent, grade 1 (mild decompensation), grade 2 (moderate decompensation) and grade 3 (severe decompensation). In case of two or more comorbid conditions the highest grade was counted, and two or more grade 2 conditions were counted as grade 3. Patients who were not living in institutions were classified as 'living independently".

Complications were categorized as wound infections (wound abscess, wound dehiscence), deep infection (anastomotic leakage, pelvic abscess), cardiovascular complications, thromboembolic events (deep venous thrombosis, pulmonary or peripheral embolism), pulmonary complications, urinary tract complications, bleeding, or other complications.

Statistical analyses

Treatment was described as percentages per patient group. Differences in treatment between patient groups were tested with the chi-square test. Crude survival was calculated. Survival and time to recurrence was calculated as time from diagnosis until recurrence/death or end of the study. The log-rank test was performed to evaluate differences between patient groups with respect to recurrence-free and overall survival. To evaluate independent prognostic effects, multivariable Cox regression was used.

Results

Patient characteristics

Of the 642 patients included, 346 patients received pre-operative radiotherapy and 296 did not. General patient characteristics and proportions receiving radiotherapy are shown in table 1. Older patients, patients with ECOG-performance scores 2-4, living in nursing or elderly homes, and patients with previous malignancies, diabetes mellitus and cerebrovascular disease received radiotherapy less often. Social parameters like living alone or living independently were frequently unknown (respectively in 46% and 32%).

Treatment outcome

Postoperative complications (table 2) occurred more frequently in patients who had received radiotherapy (58 % vs 42%, $p<0.0001$). Especially deep infections (anastomotic leakage, pelvic abcess) and wound infections (woundabcess, dehiscence) were more frequent among irradiated patients (16% vs 10%, $p=0.02$ and 14 vs 7%, $p<0.005$, respectively). The incidence of ileus also doubled in those receiving pre-operative radiotherapy but did not reach statistical significance (7% vs 3%, $p=0.08$). Thirty-day mortality was equal in both groups (8%). There was a trend among irradiated patients towards more frequent re-operations within 6 months after primary resection (19% vs 14%, $p=0.09$).

In the total group of patients, “severe comorbidity” was associated with a significant increase in postoperative complications (58%), postoperative cardiovascular complications (13%) and 30-day mortality (10%). (table 3) Patients without comorbidity showed a postoperative complication rate of 43%, incidence of deep infections of 11% and 30-day mortality rate of 3%. COPD was associated with a significant increase in postoperative

complications (59%), deep infections (21%), cardiovascular complications (16%) and 30-day mortality rate (12%). Also pre-existent cardiovascular comorbidity, diabetes and cerebrovascular disease led to a significant increase in postoperative complications (respectively 54%, 60% and 62%) and 30-day mortality (respectively 11%, 11% and 14%); these co-morbid conditions did not lead to a significant increase in deep infections (respectively 16%, 11%, 14%).

The local recurrence rate was lower among patients receiving pre-operative radiotherapy (2% vs 6%, p=0.002; 2% vs. 8%, p=0.002 among patients surviving at least 12 months). In a multivariable model including age, sex, dependency, comorbidity, tumour localization, tumour stage and postoperative complications, the hazard ratio for local recurrent disease was significantly decreased in the group with radiotherapy (HR pre-operative radiotherapy versus no radiotherapy = 0.2, p=0.002).

In a multivariable logistic regression analysis (table 4) increasing age was not associated with higher postoperative complication rates. Women were less likely to develop complications (OR=0.63, p=0.006). Severe comorbidity was associated with higher risk of complications (OR=1.72, p=0.04). ECOG-performance score showed a trend towards a relation with complications, OR=1.52 for ECOG-score 1 (p=0.07) and OR 1.81 for ECOG-score 2-4 (p=0.06). Pre-operative radiotherapy was associated with a doubled risk of postoperative complications (OR=2.06, p=0.0002).

Patients aged 85 or older exhibited a higher risk of death (Hazard Ratio (HR) 1.74, p=0.0002), as did “mild”, “moderate” and “severe comorbidity” (HR 1.57, 1.55 and 2.03 respectively), and stage pT3 (HR 1.46, p=0.001 compared tot pT2) (table 5). Post-operative complications and re-operation within 6 months after primary resection were significantly associated with a higher risk of death: HR 1.43 (p=0.003) and HR 1.47 (p=0.008) respectively. In multivariable

regression analysis radiotherapy was not a significant prognostic parameter (HR 0.81, p=0.09).

Discussion

In two random samples of unselected elderly patients with rectal cancer (pT2 and pT3) local recurrent disease developed less frequently in the patients who received pre-operative radiotherapy compared to TME surgery alone (2% versus 6%). Apparently neither comorbidity nor age itself influences survival to an extent that this benefit is neutralized. 30-day mortality and systemic complications were equally present in both groups. Nevertheless pre-operative radiotherapy has a price: the risk for complications doubled, especially deep infections and local woundproblems were significantly increased in patients who had received radiotherapy. In rectal surgery, regardless of receiving radiotherapy, comorbid conditions were associated with a significant increase of postoperative systemic complications: COPD and severe comorbidity (ACE-27) were associated with a significant increase of cardiovascular complications and severe comorbidity, COPD, diabetes and cerebrovascular disease led to a 4-fold increase in 30-day mortality compared to patients without comorbidity.

Compared to earlier studies our results show low local recurrence rates in both treatment groups (2% and 6%). Data from randomized controlled trials after introduction of TME-surgery show recurrence rates from 4.4% to 5.6% after pre-operative radiotherapy and from 10.9 to 11.5% in groups with surgery alone or postoperative chemoradiotherapy.[7, 13] Involvement of circumferential resection margin and attained plane of surgery are strongly associated with developing local recurrent disease, leading to 3-year local recurrence rate that varies from 4% to 17%.[14] Low recurrence rate in our study may be related to the fact

that TME surgery was already considered standard for rectal cancer care in the study period. Nevertheless, several alternative hypotheses may explain our low recurrence rates: if local recurrent disease would remain asymptomatic in elderly patients, incidence of local recurrences in our study will remain artificially low. Another explanation may be that local recurrent disease is not always documented in clinical records. For instance, if a manifest recurrent tumour is solely treated by a family physician and this information is not included in the clinical records, these data will not be found in the registry.

Apart from the beneficial effects of pre-operative 5x5 Gy radiotherapy, it also resulted in an increased complication rate in the post-operative period. Especially wound infections were significantly more prevalent in patients with pre-operative radiotherapy. However, systemic complications or 30-day mortality were not increased in these patients.

The high incidence of deep local infections in patients with COPD (21%) is remarkable. Both earlier Dutch and US studies showed that, compared to other pre-surgical conditions, especially chronic obstructive pulmonary disease led to a higher incidence of postoperative complications. [15, 16] Maybe a pre-operative work-up with corticosteroid therapy induces a higher risk for infections or anastomotic leakage. As short-course radiotherapy also has a significant impact on the leucocyte response after surgery, and as with age subtle changes in the immune system occur, multiple factors may however explain the increased complication rates in elderly patients with COPD and radiotherapy.[17, 18]

Our study did not show an increased rate of systemic complications or 30-day mortality in the radiotherapy group. In contrast, the Stockholm I trial showed an increase in postoperative mortality after radiotherapy, 8% versus 2%.[19] The Stockholm II trial reduced the irradiation volume which led to a reduced overall mortality rate. However, 6-months mortality rate was still higher in the irradiated group (5% versus 1% in the non-irradiated

group).[20] Others in the pre-TME era reported an increase in cardiovascular death after preoperative radiotherapy for rectal cancer.[21, 22] More recently, Rutten found no influence on 6-month mortality with regard to pre-operative versus no radiotherapy, studying datasets from the TME-trial and Cancer Registries.[8] Of importance to note is that we observed an increase in both the risk of complications and the risk of death in the presence of mild comorbidity. Also patients with an ECOG score of 1 already exhibited an increased risk of developing postoperative complications. Survival rates in our study are comparable to the results in randomized controlled trials as long as patients above 75 years old do not suffer from any comorbidity or have ECOG performance scores 0-1.

Our study has several limitations: first, patients were not prospectively nor randomly assigned to both groups. Instead, a selection for pre-operative radiotherapy was made by the treating physician. Bias by indication will be present and we assume that increased "vulnerability" may guide patients into less intensive treatment plans. In a recent study on mobile rectal cancer we reported that 35% of patients older than 80 years did not receive radiotherapy despite the fact that combination therapy is recommended in the guidelines.[23] Although patients not receiving radiotherapy may represent a selected group of less fit patients, these patients are not exceptional in old age categories. Apparently physicians (and/or patients) show a restraint to combine surgery with short course pre-operative radiotherapy.

Generally, an advantage of using population-based data is the potential avoidance of several sources of bias, such as referral bias and exclusion. In this study on elderly cancer patients this may only partly be the case: In the present study 5% of the patients did not live independently. According to the national demographic registry almost 9% of the study population should live in elderly or nursing homes (http://statline.cbs.nl/statweb). This

discrepancy suggests a referral bias for patients living in these homes to diagnostic procedures or surgical treatment in rectal cancer.

Irrespective of the limitations, the present study gives unique in-depth information on the course of disease in elderly patients with rectal cancer who underwent rectal surgery, both with or without pre-operative radiotherapy. The study shows that pre-operative radiotherapy decreases the local recurrence rate and does not influence 30-day survival rate. However, this benefit is achieved at the cost of an increased postoperative complication rate. Development of a local recurrence is notorious for its devastating consequences (intractable pain, disturbed micturition or defecation) and is almost always fatal in elderly patients. Therefore we believe that pre-operative 5x5 Gy radiotherapy should also be offered to patients aged 75 years and older, once the decision for undergoing surgery has been made. Nevertheless an essential modification to this statement is necessary in case of severe comorbidities or conditions with high complication and mortality rates (cerebrovascular disease, COPD). A restricted treatment plan without short course pre-operative radiotherapy should be considered among these carefully selected patients.

Acknowledgments

The work on this research was performed within the framework of GeriOnNe (Geriatric Oncology in the Netherlands). We thank the registrars of the cancer registries of the comprehensive cancer centres South, Limburg, East, Stedendriehoek Twente, Middle Netherlands and Rotterdam for their dedicated data collection.

Funding

The work on this research was performed within the framework of the project 'Treatment and outcome for cancer patients aged 75 or older: a national population-based study' (Dutch Cancer Society Grant IKZ 2007-3865).

Table 1. General characteristics of patients aged 75 years or older with $pT_{2-3}N_{any}M_{0,}$ rectal carcinoma, including proportions receiving preoperative radiotherapy.

	Total number of patients (%)		**Number and proportion (%) receiving preoperative radiotherapy**		**P-value[a]**
Age (yrs)					
75-79	**344**	**(53%)**	**212**	**(62%)**	
80-84	203	(32%)	101	(50%)	
85+	95	(15%)	33	(35%)	<0.0001
Gender					
Male	327	(51%)	183	(56%)	
Female	315	(49%)	163	(53%)	0.2
Year of diagnosis					
2002	212	(33%)	110	(52%)	
2003	205	(32%)	121	(59%)	
2004	225	(35%)	115	(51%)	0.2
Performance score (ECOG)					
0	164	(26%)	114	(70%)	
1	196	(31%)	97	(49%)	
2-4	83	(13%)	36	(43%)	
Unknown	199	(31%)	99	(50%)	<0.0001
Severity of comorbidity					
None	159	(25%)	92	(58%)	
Mild	205	(32%)	123	(60%)	
Moderate	149	(23%)	68	(46%)	
Severe	119	(19%)	61	(51%)	
Unknown	10	(2%)	2	(20%)	0.07
Comorbid condition					
Cardiovascular diseases	234	(36%)	114	(49%)	0.7 [b]
Previous malignancies	98	(15%)	44	(45%)	0.04 [b]
COPD	75	(12%)	36	(48%)	0.2 [b]

Diabetes	96	(15%)	38	(40%)	0.005[b]
Hypertension	205	(32%)	125	(61%)	0.5 [b]
Cerebrovascular diseases	71	(11%)	30	(42%)	0.03 [b]
Living alone					
Yes	146	(23%)	76	(52%)	
No	200	(31%)	99	(50%)	
Unknown	296	(46%)	171	(58%)	0.6
Living independently					
Yes	402	(63%)	221	(55%)	
No	33	(5%)	11	(33%)	
Unknown	207	(32%)	114	(55%)	0.02
pT					
2	238	(37%)	133	(56%)	
3	404	(63%)	213	(53%)	0.4

[a] Chi-square test of equal proportions receiving preoperative radiotherapy, excluding category 'unknown' (ECOG, severity of comorbidity, living alone, living independently).
[b] Chi-square test comparing proportions treated with preoperative radiotherapy between patients with the respective comorbid condition and patients without comorbidity.

Table 2. Outcome of treatment of patients with pT2-3 rectal carcinoma aged 75 years or older; postoperative complications, re-operations, 30-day mortality, and local recurrence rates according to receipt of preoperative radiotherapy [a].

	RTx+ **N (%)**	**RTx-** **N (%)**	**P-value**
Total	346 (100%)	296 (100%)	
Any postoperative complication [b]	196 (58%)	123 (42%)	<0.0001
Wound infection (wound abcess, wound dehiscence)	48 (14%)	21 (7%)	0.005
Deep infection (anastomotic leakage, pelvic abcess)	53 (16%)	28 (10%)	0.02
Ileus	22 (7%)	10 (3%)	0.08
Cardiovascular complication	30 (9%)	24 (8%)	0.8
Thromboembolic event	6 (2%)	5 (2%)	0.9
Pulmonary complication	16 (5%)	13 (4%)	0.9
Urinary tract complication	46 (14%)	29 (10%)	0.2
Bleeding requiring surgical re-intervention or blood transfusion	6 (2%)	4 (1%)	0.7
Other postoperative complication [c]	62 (18%)	41 (14%)	0.2
Re-operation [d]	65 (19%)	41 (14%)	0.09
30-day mortality after elective surgery	26 (8%)	22 (8%)	0.9
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Local recurrence	6 (2%)	19 (6%)	0.002
Local recurrence, among patients at least 12 months alive	6 (2%)	18 (8%)	0.002

[a] Excluding patients of whom the medical files did not provide sufficient information regarding presence or absence of postoperative complications (N=14).
[b] Postoperative complications up to 1 year after diagnosis; only complications requiring medical intervention.
[c] E.g. nausea, stoma problems, diabetes complications, liver function disorders, kidney function disorders, haematological complications.
[d] Any surgical intervention within 6 months after elective tumour resection.

Table 3. Postoperative complications and 30-day mortality according to severity of comorbidity (ACE-27) and specific comorbid conditions, among patients with pT2-3 rectal carcinoma aged 75 years or older.

	postoperative complications	**postoperative deep infections**	**postoperative cardiovascular complications**	**30-day mortality**
Severity of comorbidity				
None	43%	11%	6%	3%
Mild	54%	11%	7%	8%
Moderate	51%	11%	10%	11%
Severe	58% [a]	21%	13% [a]	10% [a]
Comorbid condition				
Cardiovascular diseases	54% [b]	16%	12% [b]	11% [b]
Previous malignancies	44%	15%	10%	5%
COPD	59% [b]	21% [b]	16% [b]	12% [b]
Diabetes	60% [b]	11%	9%	11% [b]
Hypertension	53%	15%	8%	9% [b]
Cerebrovascular diseases	62% [b]	14%	7%	14% [b]

[a] Cochran-Armitage trend test (two-sided) of effect of severity of comorbidity: $p<0.05$.
[b] Chi-square test comparing patients with the respective comorbid condition vs. patients without comorbidity: $p<0.05$.

Table 4. Risk of developing postoperative complications among patients with pT2-3 rectal carcinoma aged 75 years or older; a multivariable logistic regression analysis [a].

	Unadjusted % postoperative complications	**Adjusted OR**	**p-value**
Age (yrs)			
75-79 [b]	51%	1.00	
80-84	49%	1.03	0.9
85+	52%	1.35	0.2
Gender			
Male [b]	56%	1.00	
Female	46%	0.63	0.006
Severity of comorbidity			
None [b]	43%	1.00	
Mild	54%	1.51	0.07
Moderate	51%	1.40	0.2
Severe	58%	1.72	0.04
Performance score (ECOG)			
0 [b]	44%	1.00	
1	52%	1.52	0.07
2-4	59%	1.81	0.06
pT			
2 [b]	48%	1.00	
3	53%	1.25	0.2
Subsite			
Rectosigmoid [b]	40%	1.00	
Rectum	54%	1.39	0.1
Preoperative radiotherapy			
No [b]	42%	1.00	
Yes	58%	2.06	0.0002

[a] Adjusted for all variables listed and year of diagnosis.
[b] Reference category.

Table 5. Risk of death among patients with pT2-3 rectal carcinoma aged 75 years or older; a multivariable proportional hazards regression analysis.

	Unadjusted 5-yr survival rate (%)	**Adjusted HR**	**p-value**
Age (yrs)			
75-79 [b]	49%	1.00	
80-84	43%	1.17	0.2
85+	31%	1.74	0.0002
Gender			
Male [b]	42%	1.00	
Female	47%	0.85	0.14
Severity of comorbidity			
None [b]	60%	1.00	
Mild	43%	1.57	0.004
Moderate	45%	1.55	0.009
Severe	28%	2.03	<0.0001
Performance score (ECOG)			
0 [b]	60%	1.00	
1	49%	1.27	0.2
2-4	22%	2.20	<0.0001
pT			
2 [b]	54%	1.00	
3	40%	1.46	0.001
Subsite			
Rectosigmoid [b]	42%	1.00	
Rectum	45%	0.90	0.5
Reoperation			
No [b]	48%	1.00	
Yes	30%	1.47	0.008
Postoperative complications			
No [b]	53%	1.00	

Yes	38%	1.43	0.003
Preoperative radiotherapy			
No [b]	42%	1.00	
Yes	48%	0.81	0.09

[a] Adjusted for all variables listed and for year of diagnosis.
[b] Reference category

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Chapter 2.4

Chemotherapy in elderly small-cell lung cancer patients: yes we can, but should we do it?

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Published, Annals of Oncology. 2011;22:821-826

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Abstract

Background: Twenty percent of all newly diagnosed patients with small-cell lung cancer (SCLC) are over 75 years. Elderly patients may show more toxicity due to co-morbidity. We evaluated motives for adherence to treatment guidelines, completion of treatment, and toxicity.

Patients and method: Population-based data from patients aged 75 or older and diagnosed with SCLC in 1997-2004 in the Netherlands were used (368 limited disease and 577 extensive disease). Additional data on co-morbidity (ACE27), WHO performance status (PS), treatment, motive for no chemotherapy, adaptations and underlying motive, and grade 3 or 4 toxicity were gathered from the medical records.

Results: Forty-eight percent did not receive chemotherapy. The most common motives were refusal by the patient or family, short life expectancy or a combination of high age, co-morbidity and poor PS. Although only relatively fit elderly were selected for chemotherapy, 60-75% developed serious toxicity, and two-thirds of all patients could not complete the full chemotherapy.

Conclusion(s): We hypothesize that a better selection by proper geriatric assessments is needed to achieve a more favourable balance between benefit and harm.

Background

Small-cell lung cancer (SCLC) accounts for approximately 17% of all lung tumours among males and 25% among females in the southern part of the Netherlands [1]. SCLC is an aggressive tumour which is frequently metastasized at time of diagnosis; median survival for limited disease is approximately 23 months and for extensive disease 8-12 months [2]. Since SCLC is considered as a disseminated disease with subclinical distant metastases,

chemotherapy plays an important role. Nowadays standard treatment for patients with limited disease who have a good performance status is combined chemoradiotherapy, while for those with extensive disease chemotherapy alone is the standard [3]. Due to the high probability of brain metastases, prophylactic cranial irradiation (PCI) is recommended [4]. This results in better overall quality of life.

Seventy-five percent of all newly diagnosed patients with SCLC are 60 years or older, and over 20% are aged 75 years or older [5]. Elderly patients may show higher drug related toxicities due to serious co-morbidity or reduced organ functions. For this reason clinical trials have usually excluded older patients and those with serious concomitant conditions [6]. Although more trials for SCLC include elderly patients, mainly relatively healthy elderly are included. A previous population-based study from our group has shown that a substantial part of elderly patients with SCLC did not receive the standard treatment and prognosis was worse for elderly compared to younger patients [5]. In this study we evaluated which patient characteristics were associated with adherence to treatment guidelines (and motives for non-adherence), completion of planned treatment (and motives for adaptations) and toxicity in unselected elderly Dutch SCLC patients.

Methods

Study population and data collection

Population-based data from six regional Dutch cancer registries was used. These registries record data on patients newly diagnosed with cancer in all hospitals in their region. Trained registrars routinely collect data on patient and tumour characteristics, like histology, tumour grade, localisation, morphology, and stage directly from the medical records. For the present study, all patients aged *75* years or older with primary small-cell lung cancer (C34.0-C34.9

and ICD-O codes 8040-8045), diagnosed during 1997-2004 in the Netherlands were included (n=945). Patients diagnosed at autopsy were excluded. Age was classified as 75-79, 80-84 and 85+. Clinical stage of disease was classified as limited (tumours confined to one hemithorax without pleural effusion and no distant metastases) and extensive (distant metastases in the contralateral chest or at distant sites). Treatment of SCLC was classified as chemoradiation (CT+RT), chemotherapy alone (CT), and other including 'best supportive care' (BSC). Recommended treatment for limited disease in this period was cyclophosphamide-doxocubicin-etoposide (CDE) followed by thoracic irradiation (45-50 Gy) or cisplatinum-etoposide (CE) with concurrent thoracic irradiation. Recommended treatment for patients with extensive disease was CDE. Prophylactic cranial irradiation (PCI) was analysed separately.

Additional data on co-morbidity (according to the Adult Co-morbidity Evaluation 27 (ACE-27) classification [7], WHO performance status (PS), living alone, living independently, detailed information on type of treatment, number of cycles, motive for no chemotherapy, adaptations and underlying motives, and grade 3 or 4 toxicity according to CTC-toxicity criteria [8] were gathered from the medical records.

The ACE-27 index is a validated 27-item co-morbidity index for patients with cancer. Twenty-seven co-morbid conditions were gathered from the medical records. Each condition was graded to severity and classified as absent, grade 1 (mild decompensation), grade 2 (moderate decompensation) and grade 3 (severe decompensation). In case of two or more co-morbid conditions the highest grade was count, and two or more grade 2 conditions were counted as grade 3. Patients who were not living in institutions were classified as 'living independently' but they could also receive home care.

Statistical analysis

Treatment and completion was described according to patient characteristics. Differences between subgroups were tested with chi-square test. Motives for suboptimal treatment and treatment adaptations were described. Furthermore, toxicity (total, haematological, cardiovascular and renal) was described according to patient characteristics.

Results

Patient characteristics

The general characteristics of the patients are shown in table 1. Three hundred and sixty-eight patients with limited disease were included and 577 with extensive disease. 649 of these patients (69%) were aged 75-79, 239 patients (25%) 80-84 and 57 patients (6%) were diagnosed at age 85 or older. Seventy-eight percent of all patients had co-morbidity at the time of cancer diagnosis (21% grade 1, 31% grade 2 and 26% grade 3). The most common co-morbid conditions were cardiovascular diseases (44%) and chronic obstructive pulmonary diseases (COPD, 29%). Sixty-nine percent of patients were living independently and 27% were living alone. However, for about one third of patients information on institutionalization or cohabitation status was not noted in the medical records. Performance status (PS) was also often (39%) missing, but of those with known PS, 321 (55%) had PS 0 or 1 and 258 (45%) 2-4.

Table 1 Characteristics of patients with small-cell lung cancer, according to stage and age

Stage	Limited			Extensive		
Age	75-79 yrs	80-84 yrs	85+ yrs	75-79 yrs	80-84 yrs	85+ yrs
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Gender						
Male	179 (72)	73 (78)	23 (88)	294 (73)	125 (86)	26 (84)
Female	69 (28)	21 (22)	3 (12)	107 (27)	20 (14)	5(16)
Treatment						
CT+RT*	58 (23)	14 (15)	0			
CT*	98 (40)	35 (37)	10 (38)	222 (55)	46 (32)	7 (23)
Other*	92 (37)	45 (48)	16 (62)	179 (45)	99 (68)	24 (77)
Co-morbidity (total score ACE-27)[#]						
0	33 (13)	9 (10)	9 (35)	78 (19)	21 (14)	8 (26)
1	46 (19)	21 (22)	3 (12)	81 (20)	37 (26)	6 (19)
2	82 (33)	38 (40)	7 (27)	117 (29)	41 (28)	9 (29)
3	77 (31)	21 (22)	6 (23)	103 (26)	36 (25)	5 (16)
Unknown	10 (4)	5 (5)	1 (4)	22 (5)	10 (7)	3 (10)
Performance status (WHO)						
0-1	98 (40)	37 (39)	12 (46)	133 (33)	32 (22)	9 (29)
2-4	48 (19)	23 (25)	6 (23)	120 (30)	47 (32)	14 (45)
Unknown	102 (41)	34 (36)	8 (31)	148 (37)	66 (46)	8 (26)
Living independently[$]	185 (75)	70 (74)	20 (77)	266 (66)	93 (64)	21 (68)
Living alone[$]	66 (27)	40 (43)	12 (46)	88 (22)	38 (26)	15 (48)

*CT=chemotherapy, RT=radiotherapy

[#]0=absent, 1=mild decompensation, 2=moderate decompensation, 3=severe decompensation

[$] Proportion of known; about 1/3 was unknown

Treatment and completion

Of all patients 48% did not receive chemotherapy. Details of treatment and completion of treatment for each stage of disease are described below.

Limited disease

Among patients with limited disease, the proportion receiving chemoradiation decreased from 23% of those aged 75-79 to 15% of those aged 80-84 to zero of those aged 85 or older, while the proportion receiving chemotherapy alone remained almost 40% (figure 1). Women received less frequently chemoradiation as compared to men (12% versus 22%). Combined chemoradiation also decreased with co-morbidity (from 24% of those without co-morbidity to 13% of those with grade 3 co-morbidity) and with decreasing PS (from 27% of those with WHO 0-1 to only 8% of those with WHO 2-4). Prophylactic cranial irradiation was introduced in 1999 and was applied to only 4% between 1999 and 2004 (all younger than 85). Of patients receiving chemotherapy, 56% received cyclophosphamide, doxorubicin and etoposide (CDE), 18% a two-drug combination of cisplatin (or carboplatin) and etoposide (CE, mainly after 2001), and 25% other chemotherapy (mainly oral etoposide). Since 2003, the proportion receiving carboplatin-etoposide was 23% compared to 17% cisplatin-etoposide and 42% CDE.

The two most common motives for not receiving chemotherapy were a combination of high age, co-morbidity and poor PS (30%) on the one hand, and refusal by the patient or family (29%) on the other hand (table 2). Thirteen percent did not receive chemotherapy because of short life expectancy and another 3% had died before start of treatment. For only 7% the motive for not receiving chemotherapy was unknown. The motive for not receiving radiotherapy was unknown in 31%, wait-and-see policy in 40% and high age, co-morbidity or

poor PS in 9%. In seven percent the patient had already died before start of radiotherapy. In 70% of all patients receiving chemotherapy dose (32%), number of cycles (42%), type of chemotherapy (8%) or time between courses (25%) were adapted (table 3). Dose of chemotherapy was reduced before start of treatment in 13%. The most common motives for adaptations were haematological toxicity (30%, of which 3% were due to decreased bone marrow function in combination with an infection), dying during treatment (10%) or progression (8%) (table 4). The proportion of adaptations in chemotherapy was clearly higher among men (74%) than among women (56%) and was 54% among patients without co-morbidity compared to 73% among those with co-morbidity. Adaptations were not associated with age or PS. The proportion of patients receiving less than 4 cycles of chemotherapy was 44% among patients receiving CDE and 35% among those receiving CE. The number of cycles was not significantly associated with gender, age, co-morbidity or PS.

Table 2 Motives for not receiving chemotherapy, according to stage

Motive	**Limited** **N (%)**	**Extensive** **N (%)**
Patient's or family's choice	43 (29)	60 (21)
High age, co-morbidity or poor PS	46 (31)	98 (34)
Short life expectancy	19 (13)	62 (21)
Dead before start of CT	4 (3)	23 (8)
Other	26 (18)*	24 (8)
Unknown	10 (7)	22 (8)

*of whom 4% underwent surgery

Table 3 Adaptations of chemotherapy, according to stage (more adaptations per patient possible)

Adaptation in chemotherapy	**Limited** **N (%)**	**Extensive** **N (%)**
Total	151 (70)	171 (62)
Dose reduced before start chemo	28 (13)	38 (14)
Dose reduced during chemo	41 (19)	39 (14)
Number of cycles reduced	91 (42)	120 (44)
Time between cycles	53 (25)	50 (18)
Change in type of chemotherapy	17 (8)	8 (3)

Extensive disease

Among patients with extensive disease, the proportion receiving chemotherapy clearly decreased with increasing age from 55% of patients aged 75-79 to 32% of those aged 80-84 and 23% of those aged 85+ (figure 1). In contrast, the proportion receiving only best supportive care was 45% among younger patients, but increased markedly up to 77% among those aged 85 or older. Administration of chemotherapy slightly decreased with co-morbidity (from 54% of those without co-morbidity to 49% of those with grade 3 co-morbidity) and was lower for those with poor PS (69% for those with WHO 0-1 and 34% for those with WHO 2-4). Of patients receiving chemotherapy, 57% received cyclophosphamide, doxorubicin and etoposide (CDE), 13% a two-drug combination of cisplatin (or carboplatin)

and etoposide (CE), and 30% other chemotherapy (mainly oral etoposide).

The three most common motives for not receiving chemotherapy were poor PS (22%), refusal by the patient or family (21%) and short life expectancy (21%) (table 2). Nine percent had already died before the start of treatment. For 8% a motive for not receiving chemotherapy was unknown.

In 62% of all patients receiving chemotherapy dose (28%), number of cycles (44%), type of chemotherapy (3%) or time between courses (18%) were adapted (table 3). Dose of chemotherapy was adapted before start of treatment in 14%. The most common motives for adaptations were haematological toxicity (32%, of which 7% were combined with an infection) and dying during treatment (19%) (table 4). The proportion of adaptations in chemotherapy was lower among men (60%) than among women (74%) and decreased from 66% in age group 75-79 to 53% in age group 80-84 and 33% in those aged 85 or older. It was not associated with co-morbidity or PS. The proportion of patients receiving less than 4 cycles of chemotherapy was 56% among patients receiving CDE and 60% among those receiving CE. The number of cycles was not associated with gender, age, co-morbidity or PS.

Table 4 Motives for adaptations in chemotherapy, according to stage

Motive	**Limited** **(%)**	**Extensive** **(%)**
Hematological toxicity	40 (27)	42 (25)
Infection	5 (3)	12 (7)
Other toxicity	13 (10)	10 (6)
On patient's request	9 (6)	15 (9)
Poor PS	11 (7)	14 (8)
Dead during CT	15 (10)	32 (19)
Progression	12 (8)	11 (6)
Poor renal function	5 (3)	1 (1)
Other	3 (2)	3 (2)
Unknown	37 (24)	33 (19)

Toxicity

Limited disease

Sixty-nine percent of patients with limited disease who received chemotherapy developed any grade 3 or 4 toxicity during or after treatment; 43% consisted of hematological toxicity (of which 10% was combined with an infection). Only 6 patients (3%) developed cardiac toxicity and none of the patients developed renal failure. The proportion developing toxicity

decreased with age from 81% in age group 75-79 to 66% in age group 80-84 to 56% in those aged 85 or older. Furthermore, toxicity was higher in those with co-morbidity (72-90%) as compared to those without co-morbidity (59%), and was also higher in those with PS 2-4 (81%) than PS 0-1 (65%). Seven patients died due to complications of treatment; all of them already suffering from serious co-morbidity at diagnosis of SCLC.

Extensive disease

Sixty-one percent of patients with extensive disease receiving chemotherapy developed any grade 3 or 4 toxicity and 43% hematological toxicity (of which 13% was combined with an infection). Only 7 patients (3%) developed cardiac toxicity and 5 of the patients (2%) developed renal failure. The proportion developing toxicity was somewhat higher in those with co-morbidity (73%) as compared to those without co-morbidity (60%), but was not related to other patient characteristics. Eleven patients died due to complications of treatment; ten of these eleven already suffered from serious co-morbidity at diagnosis of SCLC.

Discussion

Our study shows that almost half of all elderly SCLC patients did not receive chemotherapy. The most common motives for withholding chemotherapy were refusal by the patient or family, short life expectancy or a combination of high age, co-morbidity and poor functional status. Although only relatively fit elderly were selected for chemotherapy or combined chemoradiation, 60-75% developed toxicity, and two thirds of patients could not complete the full chemotherapy. The question raises whether a treatment decision should be supported with better tools to predict toxicities, for instance a more balanced geriatric assessment. On the other hand, it is difficult to deny treatment opportunities after informing

patient and family of all side effects. Toxicity in our population-based study decreased after age 80 years, probably due to a stricter selection. However, treatment among patients aged 80 or older was adapted as often as among those age 75-79. Perhaps toxicity among the oldest old leads to earlier adaptation. Although our study is a unique study since we were able to analyze motives of non-adherence to guidelines, we could not analyze patient-preferences towards acceptance of chemotherapy.

Treatment and toxicity

Up to the year 2000 combination chemotherapy of cyclophosphamide, doxorubicin and etoposide (CDE) was standard treatment for SCLC. Thereafter, the two-drug combination of cisplatin (or carboplatin) and etoposide (CE) has gradually been implemented as the standard of care for both limited and extensive stage SCLC [9]. In our study we found that women received chemoradiation less often as compared to men. Previous studies have shown that women with SCLC suffer from more toxicity of treatment, treatment is more often adapted, but response rates are similar as compared to men [10, 11].

In accordance with previous studies [3, 12, 13], elderly tended to receive less intense treatment, due to less frequent use of chemotherapy or radiotherapy [5, 12-15]. The less intense treatment could be related to either expected toxicity or the reluctancy of physicians to treat elderly patients with full dose treatment. In our study we have shown that the most common motives for not receiving chemotherapy were refusal by the patient or family, short life expectancy or a combination of high age, co-morbidity and poor PS. The same was found in a recent international study [16]. A previous study has shown that elderly patients with lung cancer accept less toxicity for a given gain in survival [17]. In case of highly toxic chemotherapy for a lethal disease more patients preferred best supportive care if survival is less than 6 months [18].

Previous studies report inconsistent findings with regard to increased toxicity for elderly

patients with SCLC [5, 12, 13, 19, 20]. Most of these studies were clinical trials, and may therefore be biased due to trial eligibility criteria (most of them only including relatively healthy elderly patients) [21]. We found a rather high proportion of elderly patients who developed toxicity (60-75%) and this was the underlying motive for adapting treatment in about 40%. In our study almost half of all patients developed grade 3 or 4 haematological toxicity. However, this was lower than proportions found in a study of two clinical trials among patients aged 70-80 years: 64% showed grade 4 neutropenia and 15% grade 3 or 4 thrombocytopenia [22]. In cisplatin-etoposide based studies great differences in toxicities were found once the sub-populations above 70 years were analysed: Yuen et al [23] showed 84% grade 3 and 4 hematological toxicities and 10% fatal toxicities while Schild et al. [24] found these toxicities in 50 and 6%, respectively. Hematological toxicity is significantly higher with doxorubicin-containing regimens [25] that have mainly been used before 2003 in the Netherlands. It should be noticed that many side-effects can be managed better nowadays [26].

Within our study population of elderly patients with limited SCLC, the prevalence of toxicity decreased with every 5 years increase in age, which can be related to stricter selection for chemotherapy at higher age. However, treatment among those aged 80 or older was adapted as often as among those aged 75-79. Perhaps toxicity among the oldest old leads to earlier adaptation. In our population-based study the dose of chemotherapy was already reduced before start of treatment in 14% of patients. Another 50-60% of patients receiving chemotherapy needed adaptations in dose, time between cycles, number of cycles or type(s) of chemotherapy during treatment, mainly due to haematological toxicity (about 30%), early death (10-20%) or progression of disease (6-8%). A previous clinical study has shown that significantly lower doses were delivered to patients aged 70-80 as compared to younger

patients, and only 69% of elderly were able to complete the full treatment, which is comparable to our study [22]. It seems that more modest levels of toxicity led to dose reductions among elderly patients as compared to younger patients, perhaps due to a greater reluctance on the part of both the physician and the older patient to risk or accept severe grade 3 or 4 toxic effects [17].

Once the reduction in efficacy in case of adapted chemotherapeutic regimens is taken into account [27], one can argue that in the elderly the benefit gained by few patients is payed for by a large group of patients that will not achieve the benefits. We hypothesize that a better selection of patients is needed to achieve a more favourable balance between benefit and harm. We found that toxicity was higher among those with serious co-morbidity at cancer diagnosis. Others underlined the association between severe toxicity and, independent from each other, PS, depressive symptoms and IADL-dependency [28]. Therefore, no chemotherapeutic treatment should be started before these effect-modifying parameters are explicitly taken into account. It has to be studied which of the many parameters are most predictive for toxicity [29].

This study gives a rather unique insight into everyday practice, motives for treatment decisions, adaptations of treatment and toxicity in unselected elderly SCLC patients. However, we should keep in mind that this is a retrospective observational study in which there was selection for treatment. Our finding that within the group of elderly patients toxicity decreased with increasing age might confirm this. Furthermore, not all characteristics could be retrieved from the medical records. Performance status, for example, was missing in almost 40%. Prospective studies are needed, not only for giving insight into the risks and benefits of treatment of this group of patients with a short life expectancy, but also for evaluating the predictive value of patient characteristics. This would

enable physicians and elderly patients to balance benefits, efforts and harm on a more individualized basis.

In conclusion, a better selection of patients by proper geriatric assessments is needed to achieve a more favourable balance between benefit and harm.

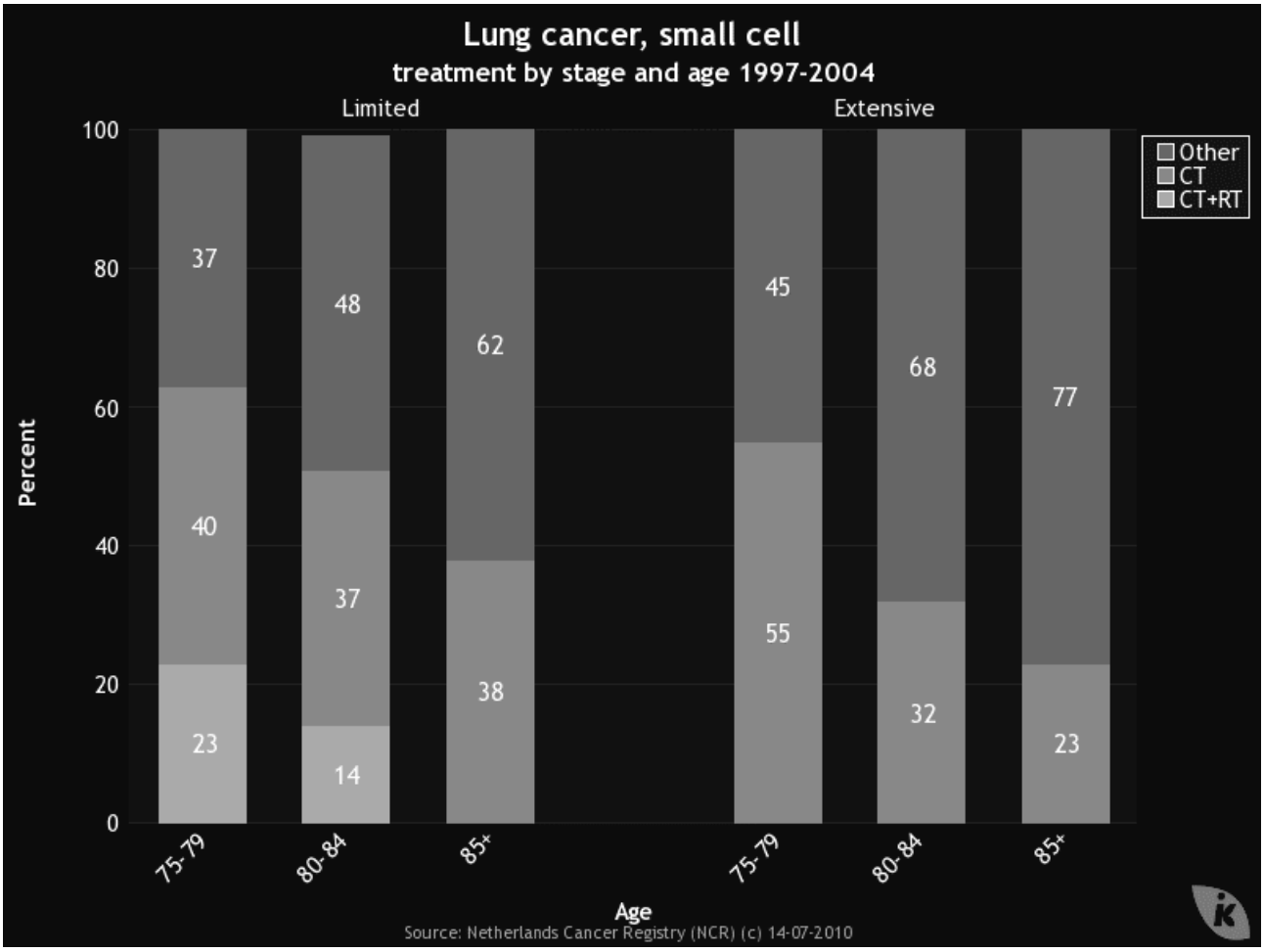
Acknowledgments

We thank the registrars of the cancer registries of the comprehensive cancer centres South, Limburg, East, Stedendriehoek Twente, Middle Netherlands and Leiden for their dedicated data collection, and GeriOnNe (Geriatric Oncology in the Netherlands).

Funding

This work was supported by the Dutch Cancer Society [IKZ 2007-3865].

Figure 1 Treatment according to stage and age.



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Chapter 2.5

Treatment is an independent prognostic factor in elderly patients with limited Small-Cell Lung Cancer (SCLC)

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Abstract

Background: Over twenty percent of all newly diagnosed Dutch patients with small cell lung cancer (SCLC) are over 75 years. Uncertainties still exist about safety and efficacy of chemotherapy and chemoradiation in elderly patients. We evaluated the association between patient characteristics and (completion of) treatment on the one hand, and toxicity, response, time to progression and survival in elderly SCLC patients on the other hand.

Patients and methods: Population-based data from patients aged 75 or older and diagnosed with limited SCLC in 1997-2004 in the Netherlands were used (N=368). Additional data on co-morbidity, performance status, motive for deviating from guidelines, grade 3 or 4 toxicity, response, time to progression and survival were gathered from the medical records.

Results: Although only relatively fit elderly were selected for chemotherapy or chemoradiation, 60-75% developed toxicity, leading to early termination of chemotherapy in over half of all patients. Median time to progression was 4.7 months. Only 8% of patients died of another cause than SCLC. Chemotherapy or chemoradiation had an independent effect on risk of death (HR=0.6 and HR=0.3, respectively).

Conclusion(s): Although toxicity rate was high and many patients could not complete the full chemotherapy, those who received chemotherapy or chemoradiation had a significantly better survival, even after adjustment for differences in age, co-morbidity and performance score.

Introduction

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung tumours among males and 18% among females in the southern part of the Netherlands [1](www.ikcnet.nl). Thirty-five to forty percent of SCLC patients present with limited disease.[2]
Over twenty percent of all newly diagnosed patients with lung cancer SCLC in the Netherlands are 75 years or older [3]. Preferred treatment for patients with limited disease who have a good performance score is concomitant chemoradiation and prophylactic cranial irradiation in case of good response.[4] Elderly patients may experience more toxicities due to serious co-morbidity, functional limitations or reduced organ functions.[5] This is one of the reasons that older patients and those with serious co-morbid conditions are usually underrepresented in clinical trials.[6] Nowadays, more trials for SCLC include elderly patients, but these are often relatively healthy elderly. This means that the results of these studies may not be valid for everyday clinical practice that deals with many elderly patients with serious co-morbidity. A previous population-based study from our group has shown that a substantial part of elderly patients with SCLC did not receive chemotherapy and two thirds of those receiving chemotherapy could not complete the full treatment.[7] In the current study we evaluated the association between patient characteristics and (completion of) treatment on the one hand and toxicity, response to treatment, time to progression and survival on the other hand in elderly Dutch SCLC patients in everyday clinical practice.

Patients and methods

Study population and data collection

Population-based data from six regional Dutch cancer registries was used, reflecting the Dutch population. These registries record data on patients newly diagnosed with cancer in all hospitals in their region. Trained registrars routinely collect data on patient and tumour characteristics, like histology, tumour grade, localisation, morphology, and stage directly from the medical records. The quality of the data is high, due to thorough training of the administrators and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[8] Follow-up of vital status of all patients was completed up to January 1st , 2009. The information on vital status was actively obtained from the municipal registries. For causes of death, data were merged with the database of Statistics Netherlands.

For the present study, all patients aged 75 years or older with primary limited stage SCLC (C34.0-C34.9 and ICD-O codes 8040-8045), diagnosed during 1997-2004 in the Netherlands were included (n=368). Age was classified as 75-79, 80-84 and 85+ years. Clinical stage of limited disease was classified as tumours confined to one hemithorax without pleural effusion and no distant metastases. Recommended treatment for limited disease in this period was cyclophosphamide-doxocubicin-etoposide (CDE) followed by thoracic irradiation (45-50 Gy) or cisplatin-etoposide (CE) with concurrent thoracic irradiation. Treatment of SCLC was classified as combined chemoradiation (sequential or concurrent), chemotherapy alone, radiotherapy alone and best supportive care (BSC). Completion of chemotherapy was classified as: at least 4 cycles of chemotherapy, less than 4 cycles of chemotherapy and no chemotherapy.

Additional data on co-morbidity (according to the Adult Co-morbidity Evaluation 27 (ACE-27) classification[9]), WHO performance status (PS), detailed information on type of treatment, number of cycles, motives for chemotherapy denial, adaptations of chemotherapy and underlying motives, grade 3 or 4 toxicity according to CTC-toxicity criteria version 3.0 [10], tumour response and date of recurrence were gathered from the medical records.

The ACE-27 index is a validated 27-item co-morbidity index for patients with cancer. Twenty-seven co-morbid conditions were gathered from the medical records. Each condition was graded to severity and classified as absent, grade 1 (mild decompensation), grade 2 (moderate decompensation) and grade 3 (severe decompensation). In case of two or more co-morbid conditions the highest grade was counted, and two or more grade 2 conditions were counted as grade 3.

Statistical analyses

Differences in number of cycles of chemotherapy between groups of patient characteristics were tested with the chi-square test. Toxicity rates and response rates were described as percentages per age group. Recurrence and progression rates were calculated for patients who had achieved a complete or a partial remission. Median time to recurrence/progression was calculated as median time between date of recording complete/partial remission and date of recurrence/progression. Date of recording complete remission and/or date of recurrence were unknown for 9 patients who had achieved a complete response and also for 9 patients who had achieved a partial response. These were left out of the analyses for calculating median time to recurrence.

Crude survival was calculated as time from diagnosis until death (any cause) or the end of the study (January 1, 2009). Patients who were still alive at the end of the study were censored. The log rank test was performed to evaluate differences between survival curves

in univariate analyses. For evaluation of the independent effects of age, gender, co-morbidity (yes versus no), performance score (WHO 3-4 versus 0-2) and treatment, a multivariable Cox regression model was built. Cause of death was described, according to age and pre-existing co-morbidity.

Results

Patient characteristics

The general characteristics of the patients are shown in table 1. Three hundred and sixty-eight patients with limited disease were included. 248 of these patients (67%) were aged 75-79, 94 patients (26%) were aged 80-84 and 26 patients (7%) were diagnosed at age 85 or older. Eighty-two percent of all patients had co-morbidity at the time of cancer diagnosis (19% grade 1, 35% grade 2 and 28% grade 3). The most common co-morbid conditions were cardiovascular diseases (44%) and chronic obstructive pulmonary diseases (COPD, 29%). Performance status (PS) was often (39%) missing, but of those with known PS, 205 (92%) had PS 0-2 and 19 (8%) 3-4.

Treatment

The proportion of patients receiving combined chemoradiation decreased from 23% among those aged 75-79 to 14% among those aged 80-84 and none of those aged 85 or older (table 1). The reason for not receiving radiotherapy among those who had only received chemotherapy was often not recorded in the medical file (71%). Among those with known reason, 24% had already died before start of radiotherapy. Thirty-three patients (9%) received only radiotherapy.

The proportion of patients receiving only best supportive care increased from 36% among

those aged 75-79 to 46% among those aged 80-84 and 62% among those aged 85 or older (p=0.01, figure 1). It also increased from 37% among those with PS 0-2 to 84% among those with PS 3-4.

Of patients aged 75-79 years, 64% received any chemotherapy. This proportion decreased to 54% of those aged 80-84 and to 38% of patients aged 85 years or older (figure 1). The proportion of patients receiving at least 4 cycles of chemotherapy decreased from 34% of those aged 75-79 to 15% of those aged 80 or older (p=0.003). This proportion also decreased from 38% among those without co-morbidity or grade 1 co-morbidity to 28% among those with grade 2 co-morbidity and 24% among those with grade 3 co-morbidity (p=0.11). Only 5% of patients with PS 3-4 received at least 4 cycles of chemotherapy, while this was 34% for those with PS 0-2 (p=0.0008). The most common motives for receiving less than 4 cycles of chemotherapy were haematological toxicity (24%), early death (19%) or no effect of chemotherapy/progression during chemotherapy (12%). In 29% of patients the motive for receiving less than 4 cycles of chemotherapy was unknown.

Table 1 Characteristics of patients with limited small-cell lung cancer, according to age

Stage	Limited		
Age	75-79 yrs	80-84 yrs	85+ yrs
	N (%)	N (%)	N (%)
Gender			
Male	179 (72)	73 (78)	23 (88)
Female	69 (28)	21 (22)	3 (12)
Co-morbidity (total score ACE-27)[#]			
0	33 (13)	9 (10)	9 (35)
1	46 (19)	21 (22)	3 (12)
2	82 (33)	38 (40)	7 (27)
3	77 (31)	21 (22)	6 (23)
Unknown	10 (4)	5 (5)	1 (4)
Performance status (WHO)			
0	31 (3)	8 (9)	3 (12)
1	67 (27)	29 (31)	9 (35)
2	38 (65)	15 (16)	5 (19)
3-4	10 (4)	8 (9)	1 (4)
Unknown	102 (41)	34 (36)	8 (31)
Treatment			
Chemoradiation	58 (23)	14 (15)	0
Chemotherapy alone	98 (40)	35 (37)	10 (38)
Radiotherapy alone	22 (9)	10 (11)	1 (4)
Best supportive care	70 (28)	35 (37)	15 (28)

[#]0=absent, 1=mild decompensation, 2=moderate decompensation, 3=severe decompensation

Treatment tolerance and outcome

Sixty-nine percent of patients who received chemotherapy developed any grade 3 or 4 toxicity during or after treatment, mostly haematological toxicity (47%). Of patients receiving only chemotherapy, 65% developed any toxicity compared to 76% of those receiving chemoradiation. The proportion of patients who developed toxicity decreased with age from 81% in age group 75-79 to 66% in age group 80-84 to 56% in those aged 85 or older (p=0.04). This proportion increased from 59% among patients without co-morbidity to 74% among those with co-morbidity. Seven patients died due to complications of treatment; all of them already suffering from serious co-morbidity at diagnosis of SCLC.

Of patients receiving at least 4 cycles of chemotherapy, 35% had a complete remission and 43% a partial remission. The proportion of patients receiving at least 4 cycles of chemotherapy who reached a complete remission decreased from 38% among those aged 75-79 to 30% among those aged 80-84, and none of the 5 patients aged 85 or older who could complete at least 4 cycles of chemotherapy achieved a complete remission. The proportions of patients receiving at least 4 cycles of chemotherapy who achieved a partial remission were 42%, 55% and 20% for age groups 75-79, 80-84 and 85+, respectively. Median time from recording remission to progression for CR+PR was 4.7 months.

Of all 368 patients with limited SCLC, 359 (98%) had died before the end of the study. Ninety-two percent of deceased patients had died of lung cancer, 3.3% of other cancer, 1.4% of cardiovascular diseases, 0.9% of other respiratory diseases and 2.5% of other causes. Cause of death was not significantly related to age at diagnosis or pre-existent co-morbidity. Median survival time for all patients was 6.7 months. For patients who had completed at least 4 cycles of chemotherapy, median survival was 11.5 months. For those who could not complete at least 4 cycles of chemotherapy or did not receive chemotherapy, median

survival was significantly lower (4 and 3 months, respectively, $p<0.0001$, figure 2). After adjustment for age, gender, co-morbidity and performance score, patients receiving at least 4 cycles of chemotherapy had the lowest risk of dying (hazard rate (HR) for mortality = 0.4 compared to those without chemotherapy) (table 2). Patients receiving less than 4 cycles of chemotherapy also had a significantly lower risk of dying compared to those who did not receive chemotherapy (HR=0.6). Besides number of cycles of chemotherapy, age and performance score were other independent prognostic variables (table 2). In a separate model including type of treatment, the risk of dying was lowest for those receiving combined chemoradiation (HR=0.3).

Table 2 Multivariable logistic regression analyses of crude survival of elderly patients (75+) with limited small cell lung cancer.

	Model including type of treatment[#]		Model including completion of chemotherapy[#]	
	HR	**95% CI**	**HR**	**95% CI**
Age (years)				
75-79*	1		1	
80-84	1.2	0.94-1.53	1.2	0.95-1.55
85+	1.6	1.03-2.39	1.6	1.08-2.48
Sex				
Female*	1		1	
Male	1.1	0.85-1.41	1.0	0.81-1.34
Co-morbidity				
No*	1		1	
Yes	1.4	1.07-1.89	1.4	1.03-1.82
Performance score				
0-2*	1		1	
3-4	2.6	1.6-4.2	2.7	1.6-4.4
Unknown	1.6	1.24-2.00	1.5	1.22-1.97
Type of treatment				
BSC*	1		NI	
CT alone	0.6	0.48-0.78	NI	
CT+RT	0.3	0.24-0.45	NI	
Completion of CT				
No CT*	NI		1	
<4 cycles	NI		0.6	0.50-0.84
4+ cycles	NI		0.4	0.28-0.48

HR=Hazard Ratio for death, CT=chemotherapy, RT=radiotherapy, BSC=Best Supportive Care
NI=Not Included *reference category
[#]multivariable model also includes age, sex, co-morbidity and performance score

Discussion

Although only relatively fit elderly were selected for chemotherapy or combined chemoradiation, 60-75% developed toxicity, leading to early termination of chemotherapy in over half of all patients. Elderly and those with poor performance status completed the full treatment significantly less often. The majority of patients who achieved a complete or partial response had a recurrence within a year and 92% died of SCLC. Although toxicity rate was high and many patients could not complete the full chemotherapy, those who received chemotherapy or combined chemoradiation had a significantly better survival, even after adjustment for differences in age, co-morbidity and performance score.

Treatment and toxicity

In accordance with previous studies, the proportion of patients receiving intensive treatment decreased with increasing age.[3, 11-15] This is related to either expected toxicity or the reluctance of physicians to treat elderly patients with full dose treatment, and refusal by the patient. In our study we have shown that the most common motives for not receiving chemotherapy were refusal by the patient or family, short life expectancy or a combination of high age, co-morbidity and poor PS, and radiotherapy was often withheld because of early death (24% of those with known reason for withholding radiotherapy). The same was found in another recent retrospective study.[16] Previous studies have shown that elderly patients with lung cancer accept less toxicity for a given gain in survival compared to younger patients.[17, 18] In case of highly toxic chemotherapy for a lethal disease more patients preferred best supportive care if expected survival is less than 6 months.[19] As we have shown that median survival exceeded 6 months only in case of full dose treatment (≥ 4 cycles of chemotherapy), patients refusal for chemotherapy may be prompted by the limited

benefits. A Canadian study reported 80% use of chemotherapy in LD-SCLC patients older than 75 years.[13] Compared to this small population-based study, our study shows considerable less use of chemotherapy (ranging from 34% to 57%). Apparently, interpretation of benefits and risks differ along Western societies, despite comparable health care systems.

Previous studies report inconsistent findings with regard to increased toxicity for elderly patients with SCLC.[3, 12, 13, 20, 21] Most of these studies were clinical trials, and may therefore be biased due to trial eligibility criteria (most of them only including relatively healthy elderly patients).[22] In a study of two clinical trials among patients aged 70-80 years, 64% showed grade 4 neutropenia and 15% grade 3 or 4 thrombocytopenia.[23]. We found a rather high proportion of elderly patients who developed not only haematological but also non-haematological toxicity (60-75%) and this was the reason for early termination of chemotherapy in 24%. In cisplatin-etoposide-based studies great differences in fatal toxicities were found once the sub-populations above 70 years were analysed: Yuen et al [24] showed 10% fatal toxicities, while Schild et al. [25] found these toxicities in 6%. It should be noticed that many side-effects can be managed better nowadays by additional interventions, better supportive care and a good hospital referral system in case of acute toxicity.[26] Our study has shown that those aged 80-84 or 85 or older suffered from toxicity less often as compared to those aged 75-79. This probably reflects an even stricter selection for aggressive treatment for the very elderly. Among those younger than 80, the treating physician excludes patients who are too frail to undergo aggressive treatment. In contrast, the treating physician probably only selects the very fit patients for aggressive treatment among those aged 80 or older.

A previous clinical study has shown that significantly lower doses were delivered to patients aged 70-80 as compared to younger patients, and only 69% of elderly were able to complete the full treatment, which is comparable to our study.[23] It seems that more modest levels of toxicity led to dose reductions among elderly patients compared to younger patients, perhaps due to a greater reluctance on the part of both the physician and the older patient to risk or accept severe grade 3 or 4 toxic effects.[17]

Once the reduction in efficacy in case of adapted chemotherapeutic regimens is taken into account,[27] one can argue that in the elderly the benefit gained by few patients is paid for by a large group of patients who will not achieve the benefits. We found that toxicity was higher among those with serious co-morbidity at cancer diagnosis and those with poor performance status. Others also underlined the association between severe toxicity and, independent from each other, PS, depressive symptoms and IADL-dependency.[5] It has to be studied which of the many parameters are most predictive for toxicity.[28]

Response rates, Recurrence and Prognosis

Previous publications have reported that 75-80% of patients with limited SCLC (all ages) have a complete or partial response to chemotherapy.[16, 23] In our study of patients aged 75 or older, the response rate for those with limited disease receiving chemotherapy was comparable (78%). Siu and colleagues have shown that complete response rates were comparable in patients younger and older than 70, despite the fact that total dose of chemotherapy was significantly lower in the elderly.[23]

As expected, survival of limited stage SCLC decreased with increasing age. This was also found in previous studies.[3, 13, 16] The poorer prognosis among the eldest might be explained by several factors: an increased risk of mortality due to comorbid conditions,

death due to complications of treatment, or death of cancer due to less aggressive treatment.[3, 29, 30] The group of lung cancer patients mainly consists of (former) smokers. This means that they suffer much more from smoking-related comorbidity such as COPD or cardiovascular diseases as compared to the general population of the same age.[31] This may induce a higher probability of dying. However, because SCLC is a very lethal disease anyhow, most of these patients die of SCLC, before they become at risk of dying of a comorbid condition.[9] In our study we have shown that almost all patients died of lung cancer, irrespective of pre-existing co-morbidity.

Less aggressive treatment could lead to a lower response rate and a higher recurrence rate among elderly. In our study the prognostic effect of age became somewhat smaller after adjustment for treatment, but remained significant. In contrast, some previous studies have shown that prognosis for elderly patients with limited disease SCLC was not worse compared to younger patients after adjustment for differences in treatment modality and comorbidity.[12, 32, 33] However, these studies compared age 70+ with age <70 or had a median age in the elderly group that was below 74 years, whereas we have evaluated 5-year age groups within age group 75+.

We have shown that patients who received chemotherapy had a favourable prognosis compared to those receiving only BSC, even after adjustment for differences in age, co-morbidity and PS. This was expected, because this is an observational study in which generally only fit elderly were selected for aggressive treatment. Nowadays, the use of better supportive care may facilitate the application of full dose chemotherapy for SCLC in elderly patients. Thoracic radiation in combination with chemotherapy has been reported to moderately improve survival for patients with limited SCLC. However, the effect should be accurately evaluated in elderly patients, because relevant toxicity in the elderly has only

been investigated in a few studies.[34, 35] In our study we have found that the addition of radiotherapy to chemotherapy resulted in a slightly higher toxicity rate, but also an improved survival of elderly patients, even after adjustment for age, co-morbidity and PS. The impact of toxicities on quality-of-life (especially maintaining independence) is just as important for elderly cancer patients as the prolongation of life. A proper selection for chemotherapy and radiotherapy is therefore important, because toxicity rates were high, especially for those with severe pre-existent co-morbidity or poor PS. There is an urgent need for predictive models for toxicity that can be easily used in everyday clinical practice. As SCLC is a very chemotherapy and radiotherapy sensitive tumour, rapid responses with symptomatic improvement, are often seen with chemotherapy. This means that (a few, even dose adapted cycles of) chemotherapy can also be offered to patients with a poor performance status (especially if poor performance status is mainly due to the symptoms of cancer), since a rapid amelioration of the patient's symptoms and general condition can be expected together with an improved quality-of-life and survival.[26, 36]

This study gives a rather unique insight into everyday practice, motives for treatment choices and adaptations, toxicity and outcome in unselected elderly SCLC patients. However, we should keep in mind that this is a retrospective observational study in which there was selection for treatment. Furthermore, not all characteristics could be retrieved from the medical records. Performance status, for example, was missing in almost 40%. Therefore, these results should be validated in prospective studies for elderly patients with SCLC. In addition, we unfortunately were not able to evaluate the influence of treatment on quality-of-life, and were therefore not able to give insight into the benefits and harm.

In conclusion, a substantial part of elderly patients with SCLC did not receive the standard treatment, over 50% of those who were selected for chemotherapy could not complete the

full treatment and toxicity rate was high, especially among those with severe co-morbidity or poor PS. However, treatment was an independent prognostic factor, besides age and PS. Prospective studies are needed for giving insight into the risks and benefits of treatment. Patient characteristics that are predictive for severe toxicity that leads to a poor quality-of-life or even death should be identified. This would enable the treating physician to better select patients for aggressive treatment.

Acknowledgments

The work on this research was performed within the framework of GeriOnNe (Geriatric Oncology in the Netherlands). We thank the registrars of the cancer registries of the comprehensive cancer centres South, Limburg, East, Stedendriehoek Twente, Middle Netherlands and Leiden for their dedicated data collection.

Funding

The work on this research was performed within the framework of the project 'Treatment and outcome for cancer patients aged 75 or older: a national population-based study' (Dutch Cancer Society Grant IKZ 2007-3865).

Figure 1 Treatment of limited SCLC according to age. BSC=Best Supportive Care

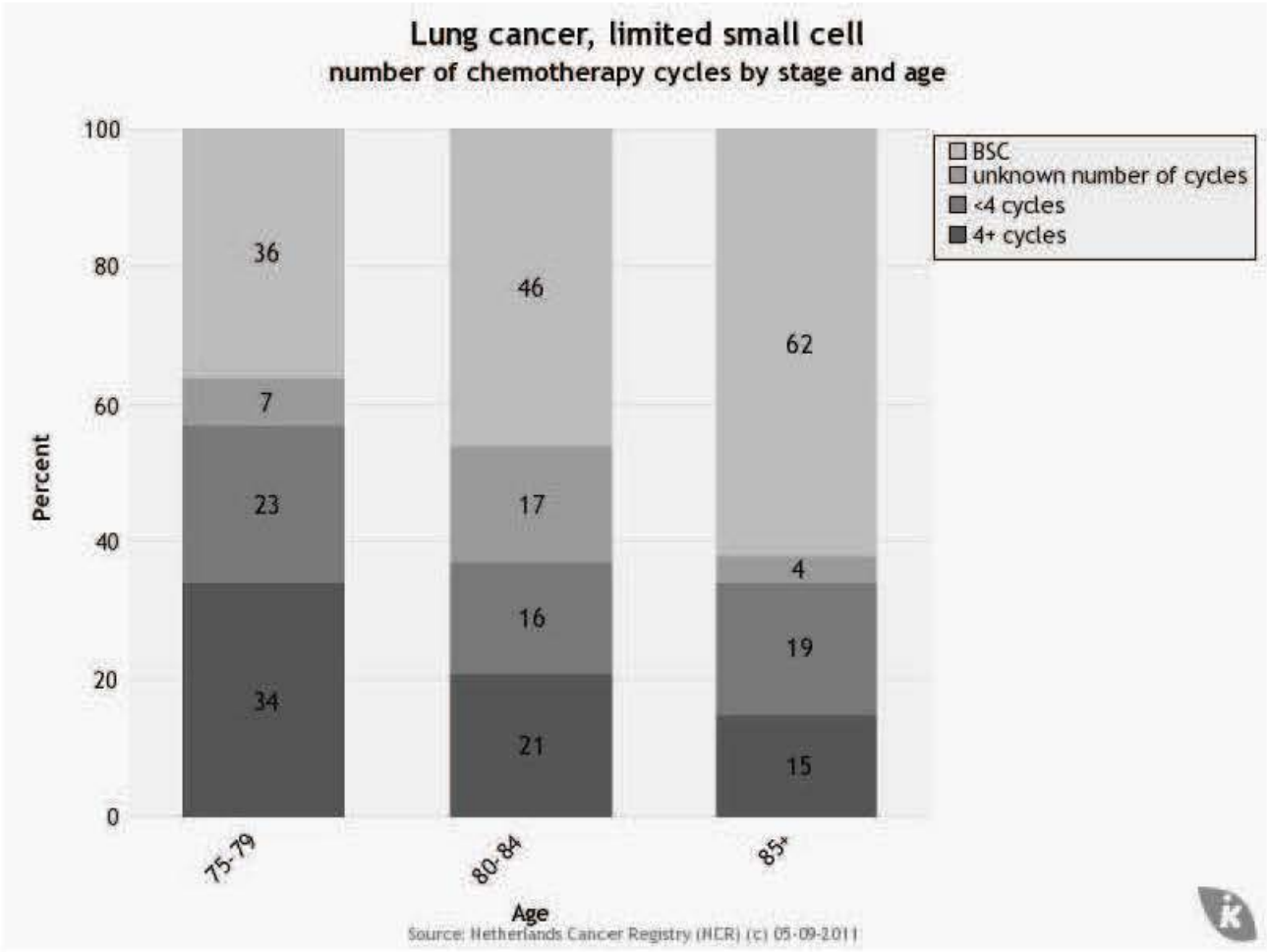
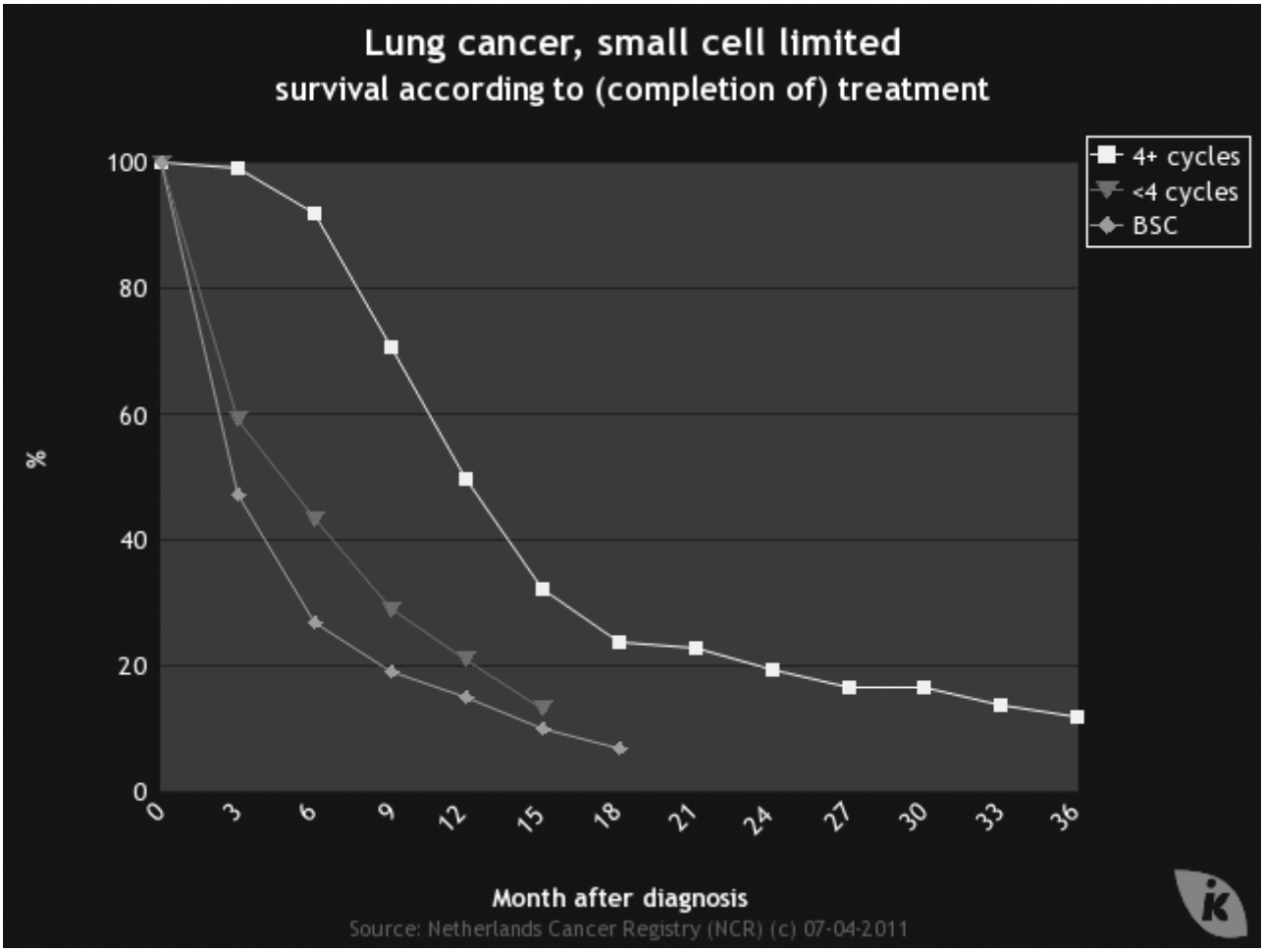


Figure 2 Crude survival of limited SCLC age 75+, according to completion of chemotherapy. BSC=Best Supportive Care



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Chapter 2.6

The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: a population-based study

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Published, Gynecologic Oncology 2005;97:104-109

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Abstract

Objective: With the rising mean age more patients will have one or more other serious diseases at the time of diagnosis of ovarian cancer (co-morbidity). In this study the independent effects of age and co-morbidity on the application of treatment guidelines and prognosis were evaluated.

Methods: All patients with epithelial ovarian cancer diagnosed between 1995 and 2001 in the southern part of the Netherlands (N=1116) were included.

Results: The prevalence of co-morbidity increased from 34% of the age group <70 to 63% of the older age group. Eighty-three percent of the patients with FIGO stage II or III younger than 70 years underwent the advised treatment (combination of surgery and chemotherapy) compared to only 45% of the patients aged 70 or older. In a multivariable analysis age, FIGO stage, presence of co-morbidity, and year of diagnosis seemed to be independent predictors of receiving the advised treatment.

In multivariable analyses age 70+ (HR=1.3, 95%Cl=1.03-1.7) and the use of both surgery and chemotherapy (HR=0.4, 95%Cl=0.3-0.6, reference is only surgery) were independent prognostic factors for overall survival.

Conclusions: Even in the absence of co-morbidity standard combination therapy was prescribed significantly less often for elderly patients with FIGO II or III ovarian cancer. Age and combined treatment of surgery and platinum-based chemotherapy were independent prognostic factors. Co-morbidity did not seem to have a prognostic effect.

Introduction

Ovarian cancer remains the leading gynecological cause of death in the Western world. In the Netherlands nearly 1300 new cases of ovarian carcinoma are diagnosed and nearly 1000 women die of this disease annually [1]. This is, among others, related to the fact that most patients (70%) present with metastatic disease. The incidence of ovarian cancer increases with age, the highest incidence occurring during the 7^{th} and 8^{th} decades of life [2]. Elderly women with ovarian cancer are more likely to present with advanced stage disease [2-4]. The optimal management of patients with advanced ovarian cancer still includes aggressive cytoreductive surgery (debulking) combined with platinum-based chemotherapy [5]. Several studies have indicated age as an independent prognostic factor, with a worse prognosis for older women [3]. Others, however, have found that age is not an independent prognostic factor [6]. These conflicting data could be related to the heterogeneity of the women studied and the different compositions of the age groups. The worse prognosis for elderly women may also be related to the higher risk of dying from co-morbid conditions or the fact that standard treatment guidelines are applied less frequently [2, 3, 7, 8]. Reasons for this are, besides the choice of the patient herself after counseling, co-morbidity and the idea that these women may not tolerate extensive surgery and chemotherapy as well as younger patients.

The purpose of this population-based study was to evaluate the independent effects of age and co-morbidity on the application of treatment modalities and prognosis for unselected ovarian cancer patients.

Patients and methods

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area of 2.3 million inhabitants. Within this region 15 non-academic hospitals are situated of which two are gynaecologic oncologic centers. Since 1993 serious co-morbidity with prognostic impact has also been recorded for all patients, according to a slightly modified version of the Charlson index (table 1)[9]. The data were extracted from the medical records by trained registrars. Previous admissions, letters from and to other specialists, the medical history and preoperative screening were used as sources. Co-morbidity was defined as diseases that were present at the time of cancer diagnosis.

Patients with ovarian cancer diagnosed between 1995 and 2001 (N=1116) were included. Patients with cancer diagnosed at autopsy (N=14) were excluded. Tumor stage was defined according to the FIGO staging system, preferably based on histological information after surgery [10]. Patients with FIGO stage II and III were further analyzed, because treatment guidelines for these stages are uniform (combination of surgery and chemotherapy). Treatment is classified as surgery in combination with chemotherapy (current guidelines for fit patients), chemotherapy alone, surgery alone, and other (metastasis -directed therapy, radiation therapy, hormonal therapy, and therapy not otherwise specified), none, and unknown. In all hospitals a multidisciplinary team was responsible for the treatment of the patients when treatment was initiated. However, involvement of a gynaecologic oncologist both in the general management and/or primary surgery was not structural and has changed during the time-interval studied. The independent influence of age, stage, co-morbidity, and hospital on adequate treatment of FIGO stage II and III ovarian cancer patients was evaluated by means of logistic regression analysis.

Vital status was available up to January 1st 2004. In addition to passive follow-up via the hospitals, this information was also obtained from the municipal registries in the area of the Eindhoven Cancer Registry and the Central Bureau for Genealogy. The latter is an institution that collects data on all deceased Dutch citizens via the civil municipal registries. In this way, information on patients who had moved outside the registry area was also obtained. The estimated proportion of patients lost-to-follow-up due to death outside the Netherlands was less than 0.2%. Of 1116 patients with ovarian cancer 469 (42%) were still alive and 647 (58%) were dead at the end of the study.

Overall 3-year survival rates were computed. The number of patients at risk was too small to compute 5-year survival rates. Survival time was defined as the time from diagnosis to death or the end of the study (on 1 January 2004). The log-rank test was performed to evaluate significant differences between survival curves in univariable analyses. A multivariable Cox regression model was built for evaluation of the independent prognostic effects. The independent prognostic effects of age, stage of disease and co-morbidity were first estimated using a model without treatment modality. Then treatment modalities were included in the model in order to investigate whether the prognostic effects of age and co-morbidity could be fully explained by inadequate treatment. With respect to co-morbidity, the prognostic effects of both the number of comorbid conditions and the specific diseases were evaluated. The prognostic impact of combinations of diseases could not be evaluated because of the small number of patients in each subgroup.

Results

The general characteristics of the patients are shown in table 2. Patients aged 70 or older presented less often with stage I ($p<0.05$). The elderly received surgery with adjuvant chemotherapy significantly less often and chemotherapy alone or no treatment more often. The prevalence of concomitant diseases clearly increased with age. The proportion of patients with one comorbid condition was 25% of the younger age group and 36% of the older age group. These proportions were 9% and 27% for two or more comorbid conditions. The most frequent comorbid conditions among patients aged 70 years or older were cardiovascular diseases (30%), hypertension (29%) and previous malignancies (17%).

Treatment modality

The percentage patients aged 70 or older with FIGO stage II and III treated according to the current guidelines increased from 25% in 1995 to about 60% since 1999 (table 3). Eighty-three percent of the patients younger than 70 years received the recommended treatment (combination of surgery and chemotherapy); 86% of those without co-morbidity and 78% of those with at least one comorbid condition (table 4). In contrast, only 45% of the patients aged 70 or older received the recommended treatment (58% of those without co-morbidity and only 38% of the patients with co-morbidity; $p=0.005$).

In multivariable analysis age, FIGO stage, presence of co-morbidity, and year of diagnosis seemed to be independent predictors of receiving treatment as advised (surgery + chemotherapy) (table 5). The odds ratio of undergoing surgery with adjuvant chemotherapy for patients aged 70 years or older was 7 times lower than that for those younger than 70. Furthermore, patients diagnosed in 2001 were 3.5 times more likely to undergo surgery plus adjuvant chemotherapy than those diagnosed in 1995 (95%Cl=1.66-7.71). Patients with one

or more comorbid conditions were 1.1 times less likely to be treated with adjuvant chemotherapy than patients without co-morbidity (95%Cl=0.78-0.93). The proportion undergoing surgery with adjuvant chemotherapy did not differ significantly between hospitals, after adjustment for age, stage, year of diagnosis and co-morbidity (results not shown).

Survival

Three-year overall survival was significantly worse for patients aged 70 or older (22%, compared to 51% for younger patients). For patients younger than 70 stage of disease, treatment modality, and period of diagnosis were prognostic factors for overall survival (table 6, univariable analyses). For those aged 70 or older stage, treatment modality and co-morbidity were prognostic factors.

In multivariable analyses age and treatment modality were independent prognostic factors (table 6, multivariable analyses). After adjustment for age, stage and co-morbidity, the risk of dying within 3 years for patients who underwent surgery with adjuvant chemotherapy was only half that of patients who underwent surgery alone.

Without co-morbidity 3-year overall survival was 58% for patients younger than 70 years (FIGO II or III) who underwent the recommended treatment and 33% for those who did not undergo the recommended treatment (figure 1). For patients aged 70 or older (FIGO II or III) without co-morbidity 3-year overall survival was 49% for those who underwent the recommended treatment and only 16% for those who did not undergo standard treatment. With co-morbidity 3-year overall survival was 52% for the younger group (FIGO II or III) who underwent the recommended treatment and 30% for those who did not undergo the recommended treatment (figure 1). In the elderly group with co-morbidity 3-year overall

survival was 40% for those who underwent the recommended treatment and only 4% for the patients who did not undergo standard treatment.

Discussion

Age-specific variations in the treatment of and prognosis for women with ovarian cancer were examined in this retrospective population-based study. We found that women aged 70 years or older with FIGO stage II or III ovarian carcinoma often did not receive the recommended treatment, being a combination of surgery and chemotherapy. Only 45% of the elderly women received the combination of surgery and chemotherapy compared to 83% of their younger counterparts. Even in the absence of co-morbidity the combination therapy was prescribed significantly less often for elderly women. Our data showed that age was an independent prognostic factor for survival. Co-morbidity did not seem to have an impact on survival. Using the combination of surgery and platinum-based chemotherapy appeared to be the most important independent prognostic factor for survival in the elderly. It is remarkable that in a few years time one can recognize a significant time trend towards increased use of combination therapy among the elderly. Despite the time trend effect still a large number of elderly women does not receive combination therapy, even when co-morbidity is absent. Both the patient's and the doctor's preference (including the participation of gynaecologic oncologists) might play a major role in the explanation of this time-related phenomenon. We had no further information on this topic. The importance of patient refusal to undergo adjuvant therapy is underlined in a recent study on adjuvant therapy for colorectal cancer patients [11]. It would be interesting to investigate patient images of therapy modalities and to analyze the decision-making process in the elderly group.

Potentially functional impairments might have influenced the selection process. Previous reports suggest that both the presence of co-morbidity and a less favorable performance status could be reasons for the more conservative approach among elderly patients with ovarian cancer [3, 8]. These reports were based on a selection of data from several randomized controlled trials [3] or data from one general hospital [8]. Our study was performed with unselected patients, but allocation bias might have distorted the comparison of treatment efficacy. Unfortunately, in this retrospective study we did not have information on performance status.

In our study co-morbidity had only a minor effect on survival of ovarian carcinoma. Previous studies have shown that co-morbidity and functional impairments are independently associated with survival of cancer [12, 13]. One study concerned a heterogeneous group of different cancers, the other focussed on head and neck malignancies. Potential bias of survival rates due to functional impairments cannot be ruled out in our study. It has also been postulated that less extensive surgical procedures or less aggressive chemotherapy may influence the survival of elderly patients [3, 14]. In contrast, Bruchim et al. (2002) found that, when it was decided to perform surgery, the optimal debulking rates in both groups of patients were similar. Furthermore, Villella et al. (2002) have shown that, although older women are more likely to need dose reduction during chemotherapy, the treatment remains within the recommended standard dosage [15]. Our database did not provide detailed information about the type of surgery (adequate or inadequate debulking) or chemotherapy (type, dose-reduction, treatment delay). The survival rate for the group of elderly without co-morbidity was comparable to that of the younger group without co-morbidity if combination therapy was performed. These facts suggest that surgery and chemotherapy were adequate for the fit elderly.

Despite the superiority of combination therapy it remains unclear which factors are valid and appropriate to use to select patients for undergoing surgery or chemotherapy (co-morbidity, combination with functional impairments or social factors?). Although the hematological toxicity of some chemotherapeutic regimens increases with age [16, 17], there is some evidence that, in the case of paclitaxel/platinum-based chemotherapy, no excess severe hematological toxicity occurs in the elderly [18, 19]. Neuropathy remains a problem and may have a high impact on mobility, especially in elderly patients. Perceived toxicity might play a role in the reluctance to give chemotherapy. At present, our group is conducting a prospective study using a multidimensional geriatric evaluation of elderly women with ovarian cancer to determine which patients are too frail to undergo standard treatment.

We conclude that older women with ovarian cancer, even in the absence of co-morbidity, often do not receive the ideal combination of surgery and chemotherapy whereas this approach leads to a significant improvement in survival. It is encouraging that from 1995 to 2001 there appeared to be a tendency towards treatment according to the standard protocol, especially for the older age-group.

Table 1 *Classification of co-morbidity, according to a modified version of the list of Charlson et al. (1987)*

Chronic Obstructive Pulmonary Diseases (COPD)

Cardiovascular diseases

- myocardial infarction, cardiac decompensation, angina pectoris
- peripheral arterial disease, intermittent claudication, abdominal aneurysm

Cerebrovascular diseases (cerebrovascular accident, hemiplegia)

Other malignancies (except basal cell skin carcinoma)

Hypertension

Diabetes mellitus

Other:

- soft tissue diseases (Besnier Boeck disease, Wegener's disease, SLE (systemic lupus erythematosis))
- rheumatoid arthritis (only severe)
- kidney diseases (chronic glomerulonephritis, chronic pyelonephritis)
- bowel diseases (Crohn's disease, ulcerative colitis)
- liver diseases (cirrhosis, hepatitis)
- dementia
- chronic infections

Table 2 General characteristics of all ovarian (excluding borderline) cancer patients, diagnosed between 1995 and 2001 in the Eindhoven Cancer Registry area.

Characteristic	<70 yrs (n=737)		≥70 yrs (n=379)	
	n	(%)	n	(%)
FIGO stage				
1	270	(37)	73	(19)
2	62	(8)	15	(4)
3	292	(40)	195	(51)
4	87	(12)	54	(14)
Unknown	26	(4)	42	(11)
Treatment				
Surgery + chemotherapy	453	(61)	120	(32)
Surgery	208	(28)	109	(29)
Chemotherapy	41	(6)	47	(12)
Other[1]	3	(1)	7	(2)
None	21	(3)	90	(24)
Unknown	11	(2)	6	(2)
Co-morbidity, number				
0	423	(57)	111	(29)
1	184	(25)	136	(36)
2+	63	(9)	104	(27)
Unknown	67	(9)	28	(7)

Co-morbidity, type[2]		
Previous malignancies	72 (11)	59 (17)
Heart diseases	46 (7)	77 (22)
Vascular diseases	17 (3)	21 (8)
COPD	34 (5)	27 (8)
Diabetes	30 (4)	49 (14)
Hypertension	89 (13)	102 (29)
Other	28 (4)	36 (10)

[1] Other therapies include: metastatic disease directed therapy, radiation therapy, hormonal therapy, and therapy not otherwise specified
[2] More than one concomitant disease per patient possible

Table 3 *Time trend in treatment as advised for FIGO II or III ovarian cancer patients, 1995-2001.*

Year of diagnosis	**% surgery plus chemotherapy**	
	<70 yrs	**≥70 yrs**
1995	77	25
1996	68	20
1997	77	50
1998	92	32
1999	88	60
2000	87	53
2001	90	62

Table 4 *Treatment of ovarian cancer FIGO stage II and III, according to age and co-morbidity (1995-2001)*

	<70 yrs		≥70 yrs	
	No co-morbidity (n=205)	**Co-morbidity (n=125)**	**No co-morbidity (n=64)**	**Co-morbidity (n=134)**
Treatment	**n %**	**n %**	**n %**	**n %**
Surgery +chemotherapy	176 (86)	98 (78)	37 (58)	52 (39)
Surgery	13 (6)	10 (8)	10 (16)	27 (20)
Chemotherapy	13 (6)	10 (8)	9 (14)	21 (16)
Other/unknown	1 (1)	2 (2)	0 (0)	7 (5)
None	2 (1)	5 (4)	8 (13)	27 (20)

Table 5 *Relative chance (OR) of receiving recommended treatment (surgery + chemotherapy) for FIGO II or III ovarian cancer patients 1995-2001; logistic regression model including all listed variables.***

	OR[1]	95%CI[2]	p-value
Age			
< 70 years[3]	1.0		
≥ 70 years	0.14	0.07-0.21	<.0001
FIGO stage			
II[3]	1.0		
III	0.34	0.12-0.81	.006
Co-morbidity, number			
0[3]	1.0		
1	0.91	0.78-0.93	.04
Year of diagnosis			
1995[3]	1.0		
1996	0.68	0.32-1.35	.3
1997	2.03	1.09-3.70	.07
1998	1.97	0.90-3.95	.08
1999	3.22	1.40-7.29	.002
2000	2.32	1.04-5.31	.04
2001	3.53	1.66-7.71	.001

[1] Odds ratio

[2] 95% Confidence limits

[3] Reference category

** Adjusted for hospital of treatment

Table 6 Uni- and multivariable analyses for overall survival of FIGO II or III ovarian cancer, according to age (1995-2001).**

	Univariable				Multivariable		
	< 70 years		≥ 70 years				
	3 yr (%)	P	3 yr (%)	P	HR[3]	95%CI[4]	P
Age							
< 70 years[1]	51				1.0		
≥ 70 years			22	<.0001	1.3	1.03-1.7	.03
FIGO stage							
II[1]	70		52		1.0		
III	47	.0002	19	.001	1.9	0.9-2.8	.1
Treatment							
Surgery[1]	31		8		1.0		
Chemotherapy	28		3		0.9	0.6-1.3	.5
Surgery + chemotherapy	55		44		0.4	0.3-0.6	<.0001
Other/none	*	<.0001	4	<.0001	1.5	0.9-3.1	.07
Period of diagnosis							
1995-1998	43		16		1.0		
1999-2001	59	.004	26	.06	0.9	0.7-1.1	.2
Co-morbidity, number							
0[1]	54		33		1.0		
1 or more	50	.4	17	.02	1.2	0.9-1.5	.2
Co-morbidity, type[2]							
Previous malignancies	49	.9	*		1.1	0.7-1.5	.8
Cardiovascular diseases	*		36	.6	1.1	0.6-1.7	.8
COPD	78	.6	*		0.8	0.5-2.0	.7
Diabetes	57	.9	*		1.3	0.8-2.4	.4
Hypertension	43	.08	13	.2	1.3	0.9-1.8	.2

[1] Reference category

[2] No co-morbidity as reference, one concomitant disease per patient

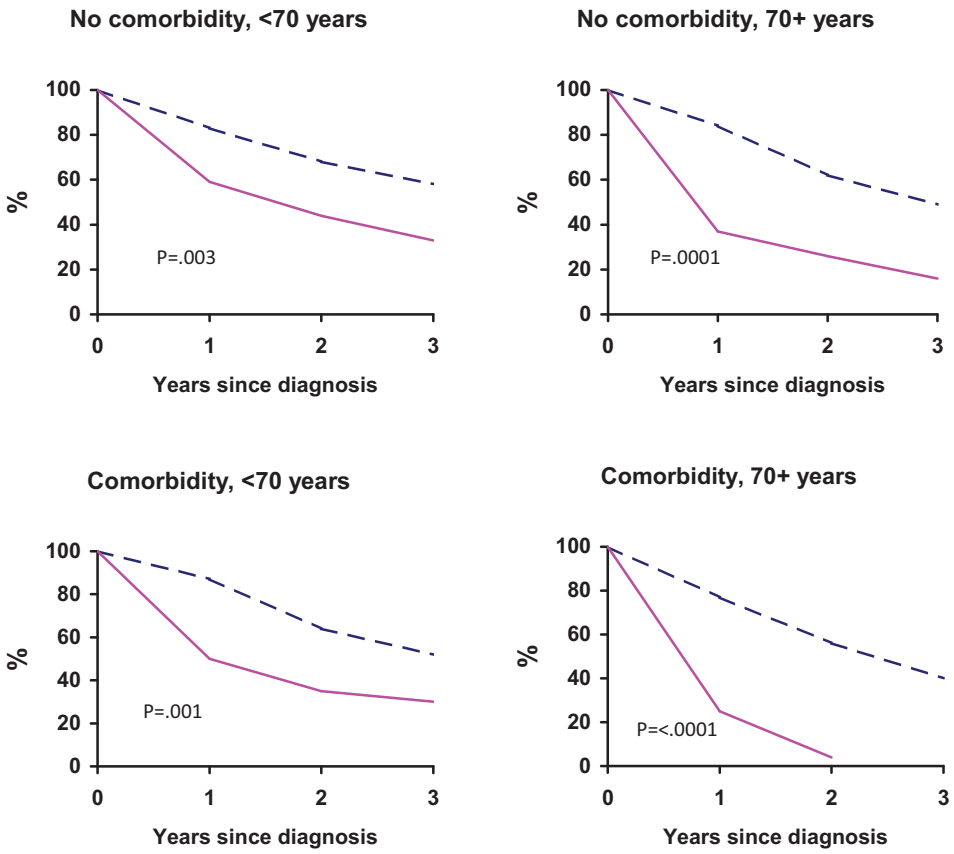
[3] Hazard Ratio

[4] 95% Confidence limits

*Not sufficient numbers to complete analyses

**Adjusted for hospital of treatment

Figure 1 *Univariable analyses for 3-year overall survival (%) of FIGO II or III ovarian cancer , according to age and co-morbidity.*



Legend for figure 1:

_ _ _ Recommended treatment	——— Other treatment

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Chapter 3

Geriatric assessment in oncology

Chapter 3.1

Comprehensive Geriatric Assessment (CGA) and its clinical impact in oncology

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Published, European Journal of Cancer 2007;43:2161-69

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Abstract

Comprehensive Geriatric Assessment (CGA) is a process that consists of a multidimensional data-search and a process of analyzing and linking patient characteristics creating an individualized intervention-plan, carried out by a multidisciplinary team. In general, the positive health care effects of CGA are established, but in oncology both CGA and the presence of geriatric syndromes still have to be implemented to tailor oncological therapies to the needs of elderly cancer patients. In this paper the conceptualisation of geriatric syndromes, their relationship to CGA and results of clinical studies using CGA in oncology are summarized. Geriatric syndromes are associated with increased vulnerability and refer to highly prevalent, mostly single symptom states (falls, incontinence, cognitive impairment, dizziness, immobility or syncope). Multifactorial analysis is common in geriatric syndromes and forms part of the theoretical foundation for using CGA.

In oncology patients, we reviewed the value of CGA on the following end-points: recognition of health problems, tolerance to chemotherapy and survival. Most studies performed CGA to identify prognostic factors and did not include an intervention. The ability of CGA to detect relevant health problems in an elderly population is reported consistently but no randomized studies are available. CGA should explore the pre-treatment presence of (in)dependence in Instrumental Activities of Daily Living (IADL), poor or moderately poor quality of life, depressive symptoms and cognitive decline, and thereby may help to predict survival. However, if scored by the Charlson's comorbidity-index, comorbidities are not convincingly related to survival. The few studies that included a CGA-linked intervention show inconsistent results with regard to survival but compared with usual care quality of life is improved in the surviving period. Functional performance scores and dependency at home appeared to be independent predictive factors for toxicity, similar to depressive symptoms and polypharmacy. Overall, CGA

implements/collects information additional to chronological age and Performance Score. So far in oncology, there are no prognostic validation studies reported using geriatric syndromes or information based on CGA in its decision making strategies.

Introduction

Health care for older people is becoming increasingly important in industrialised nations. As the population ages, there is an emerging need to develop a means to characterize the 'functional age' of older patients in order to tailor treatment decisions based on factors other than chronological age and to develop interventions to optimize cancer treatment. Comprehensive geriatric assessment (CGA) is one of the procedures designed to improve the health of this population.[1] CGA is defined as a multidisciplinary evaluation in which the multiple problems of older people are uncovered, described and if possible explained, and in which the resources and strengths of the person are catalogued and a coordinated plan is developed to focus interventions on the person's problems.[2] Usually CGA starts with a multidimensional search for relevant medical, functional, mental, social parameters of older individuals. Often nutrition and drug-use are explicitly assessed as well. Secondly an analysis of this information by a geriatrician and subsequently by a multidisciplinary team led by this geriatrician, leads to individualized goals and an integrated intervention-plan. The effects of implementing a CGA-based approach has been evaluated in a number of controlled studies, conducted in clinical and outpatient settings, as well as among community dwelling patients.[3] Positive effects of CGA are (among others) prevention of functional decline, unplanned (re)hospitalisations and nursing home admissions. Compared to usual care CGA detects a greater number of health problems.[4] Its impact on mortality is more robust for inpatients than

for community-dwelling elderly.[5,6] Key issue on the effectiveness of CGA concerns population characteristics of the elderly to whom CGA is addressed. Patients should neither be terminally ill or too frail nor too fit. Patients who benefit most are classified as “frail” or “having geriatric syndromes”. Another essential issue for the effectiveness of CGA compared to usual care is the presence of control or follow-up by the intervention team.[3-i]

In oncology there is increasing interest in assessment techniques for elderly cancer patients, both to determine the most feasible cancer treatment as well as to create an integrated intervention plan to deal with the multiple health problems that coexist in many elderly cancer patients. Both geriatric syndromes and CGA are used to tailor oncological therapies to the needs of elderly patients.

In this article we focus first on the conceptualization of geriatric syndromes secondly studies with CGA or CGA-like interventions in oncology are reviewed.

Geriatric syndromes

Geriatric syndromes play an important role in medicine of older patients such as clinical practice, teaching, research and management.[ii] Some authors state that presence of geriatric syndromes is important in the decision-making process, especially in deciding whether a life-prolonging oncological treatment should be offered to a patient.[iii] However validation studies regarding the prognostic value of geriatric syndromes are lacking in decision making strategies within oncological care.

What does a syndrome mean to clinicians and how do we use the word syndrome in medicine in contrast to a disease (e.g. E. Coli cystitis)? Commonly the term syndrome is defined as a nosological entity constituted out of signs, symptoms and manifestations clarified in medical techniques. A syndrome often refers to a (partly) uncertain pathological entity; in contrast a

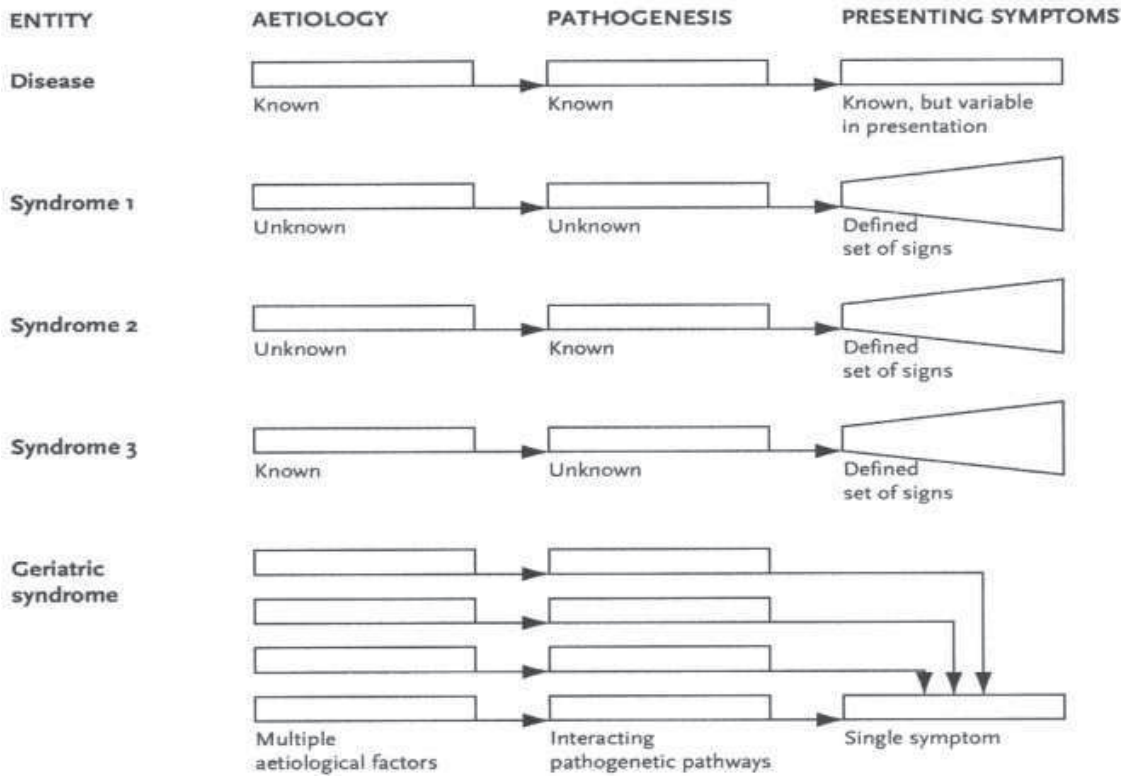
disease refers to a clinical entity, well defined in its pathogenesis and aetiology. Three types of clinical syndromes are described in figure 1. In the first type combinations of symptoms and signs are grouped together without evidence of aetiology or pathogenesis (e.g. chronic fatigue syndrome). In the second type symptoms and signs are grouped only with only evidence of aetiology (e.g. Marfan's syndrome). In the last type there is only evidence of pathogenesis but without a known aetiology (e.g. Cushing's syndrome).[7] In contrast a geriatric syndrome refers to highly prevalent, mostly single symptom states caused by accumulated impairments in multiple systems. In a recent review pressure sores, incontinence, delirium, falls and functional decline, turned out to be evidence based geriatric syndromes, while the multifactorial aetiology of other geriatric problems (e.g. cognitive impairment, dizziness, and syncope) still remains to be studied. In case of a geriatric syndrome, there is no single pathogenetic pathway which causes the symptom(s). The leading symptoms are linked to a number of diseases or aetiological factors, often concerning multiple organs. There is also an overlap in aetiological factors in different geriatric syndromes and often patients suffer from more than one geriatric syndrome (Figure 1). Diagnostic workups of geriatric syndromes consist of a search of disease(s) and a multiple risk factor assessment.

Clinical studies on geriatric syndromes as delirium, urinary incontinence, falls, dizziness and syncope provide evidence for the effectiveness of performing CGA as a multifactorial analysis if a multi-targeted intervention-plan forms part of it.[8-10]

On theoretical grounds the presence of geriatric syndromes can be used in oncology to recognise the need for multifactorial analysis and incorporate this analysis in oncological workups or clinical pathways. The occurrence of geriatric syndromes could be a banner for increased vulnerability in elderly patients e.g. heralding an increased incidence of adverse events, or even a reduced response rate or decreased survival. In cancer care high prevalences

of geriatric syndromes are reported in a population with prostate, breast and colorectal cancer receiving home care.[11] Outside oncology there is overt evidence geriatric syndromes are associated with increased vulnerability and adverse events.[12,13]

Fig 1 Differentiating clinical syndromes



CGA, multidimensional assessment techniques and their impact

As mentioned in the introduction, CGA consists of four key-features: a multidisciplinary team, a multidimensional data-search, a process of analysing and linking patient characteristics together and the creation of an individualized intervention-plan. The value of CGA in oncology can be appraised by using different and heterogeneous endpoints: survival, functional decline, hospitalisations or nursing home admissions, number of unrecognised health problems,

tolerance to or toxicity of oncological treatment, quality of life, etc. We conducted a review on the endpoints survival, toxicity and recognition of health problems. The review was based on a systematic search in Pubmed using the following Medical Subject Headings (MeSH) terms: 'geriatric assessment' and the free text search terms: 'geriatric care', 'multidimensional assessment', each combined with MeSH-terms: cancer, oncology or carcinoma. Reports presented at annual American Society Clinical Oncology-meetings concerning CGA were reviewed. Only clinical trials, meta-analyses and randomised controlled trials published before March 1st 2007 were included in our review.

Studies were grouped according to the endpoints mentioned above, special attention was drawn on CGA key-features. Furthermore, we discriminated between studies only conducting a multi-dimensional data-search and studies which also incorporated a multidisciplinary intervention-plan.

CGA and unrecognised health problems

A pilot study in elderly early breast cancer patients (mean age 79 yrs) showed that a high number of new health problems was detected, on average 1.5 new medical problem per patient required an intervention. Information delivered by CGA influenced oncological treatment directly in about one third of the patients. Pharmacological, nutritional, mental and social issues were highly prevalent and relevant in this study.[14] Their interventions lead to an improvement in quality of life. A prospective study on CGA (mean age 72 yrs) emphasized that even in case of a good Eastern Conference Oncology Group-Performance Score (PS) almost ten percent had ADL limitations, more than one third had IADL-limitations and 13% had 2 or more comorbidities.[15] A recent retrospective study reported (mean age 74 yrs) on an interdisciplinary

model of care in an Oncology-Acute Care for Elders unit.[16] Patients underwent a CGA focused on geriatric syndromes: Dependence on ADL and IADL was common; 29% had cognitive impairment of whom 36% was not documented in the medical records during hospitalisation and the majority of the cases this was not known before hospitalisation. Furthermore, restricted diets were present in 38% of the patients with weight loss. A French study showed in a somewhat older population (median age 78 yrs) that, although the majority (83%) had a Karnofsky-score above 60, many health problems were uncovered by CGA: only 44% of this group was fully ADL-independent and 13% IADL-independent; cognitive disorders and depressive symptoms were present in almost half of the patients; malnutrition, polypharmacy and dangerous drug-interactions were common.[17] All studies had an open design and led to an in-depth analysis of the clinical impact of CGA in oncology. Conclusions were almost identical, advocating the value of CGA to detect relevant health issues in older cancer patients. Unfortunately, no randomized study on this topic has been published.

CGA and survival

Our search revealed seven studies reporting on CGA and its impact on survival (table 1). The age of the study populations was young in geriatric terms with a mean age between: 72 to 75 years. Five studies were designed to detect prognostic factors on survival by using CGA as a multidimensional data-search.[18-25]

Two studies [22, 23] were phase II pharmacological studies with small numbers of patients. One study found that ADL-dependency was associated with a shorter progression free survival compared to those with ADL-independency. The second (not mentioned in table 1) ended prematurely because of high toxicity and a statistical analysis could not be performed. A study

[21] on older patients with different cancer types showed that an increased risk of death appeared in case of ADL-dependency (Hazard Ratio 2.0, CI 1.3-2.9) and IADL-dependency (HR 1.5, CI 1.1-2.0). In chemotherapeutically treated advanced lung cancer patients IADL-dependency and moderate/worse quality of life at baseline were independently associated with the risk of death.[24] Age, ADL-dependency and comorbidity were not associated with an altered risk of dying in this population with overall a very limited life expectancy.[24] In advanced ovarian cancer patients, an increased mortality risk was found when depressive symptoms occurred before treatment with chemotherapy. [iv] Only this study reported explicitly on cognitive impairment and cognitive deficits were not related to a significantly decreased survival.

Two other studies focused on a direct comparison between usual care and CGA, in which CGA also included an intervention-plan.[v] [vi] In a prospective study comparing geriatric care to usual care a posthoc analysis was done in the group of patients with malignancies.[27] No significant differences were found in survival or hospital costs. With regard to quality of life, inpatients on the geriatric unit showed a better performance on pain, emotional and mental limitations and ADL-functioning at 6 months, whereas the outpatients performed better on mental limitations. After 1 year only the effect on pain sustained. A larger randomised controlled trial on newly diagnosed cancer patients with solid tumours showed an increased mortality in the usual care group (HR 2.0, CI 1.3-3.1).[26] This effect was only established in the group with advanced cancer stages. In the intervention-group (including a large number of advanced cancer stages) quality of life remained comparable to patients with early stages. It should be taken into account that CGA was conducted in the postoperative period and specialised home visits were structurally applied.

Overall CGA reveals information that is relevant to predict survival in cancer patients, the

results are consistent in highlighting the impact of IADL-dependency and depressive symptoms on survival. Evidence for improving survival by performing CGA is less clear. Unfortunately there are only few studies in oncology including intervention-plans in their study-design. Both studies that included an intervention plan showed benefits on quality of life in their intervention-groups. On the survival endpoint, no robust conclusions can be drawn, although the one study primarily designed to study elderly cancer patients gave positive results. This study incorporated a follow-up to their recommendations and, as stated earlier, this is in line with positive results in studies on CGA outside oncology.

Comparison with studies on CGA in general health care reveals some major differences: Firstly, age in above-mentioned study populations is substantially younger than in other studies on CGA. The oldest old (age above 80 year) are poorly requested. Secondly, the functional status of newly diagnosed cancer patients seems to be comparable to an age-cohort that is ten years younger. [vii] This fact may diminish the potential effect of CGA that primarily focuses on more or less dependent or frail patients. Furthermore, it is remarkable that cognitive impairment was not associated with an increased mortality. However, cognitive decline is mentioned as one of the important elements in geriatric syndromes.[29] In general medicine functional measures, including cognitive impairment, predicted 90-day and 2-year mortality in a group of hospitalized elderly patients.[30] We can only speculate about this striking difference. Referral bias to an oncology department may occur, and in patients with cognitive impairment physicians may show a diminished tendency to perform diagnostic procedures to establish the diagnosis cancer. Overall study-data from intervention studies remain scarce, so the value of CGA in oncology on the endpoints “survival/mortality” needs to be addressed in a prospective fashion before conclusions can be made. Special attention needs to be drawn to interventions made within the CGA-procedure.

Table 1 – Endpoint: Mortality/survival

Author	Population, department + setting	Study-design + intervention	Results: geriatric factors as effect modifiers	Comment
Zagonel et al. 2002[21]	Oncology department N = 252 Mean age 72 yr, range 65-92 yrs	Prospective observational study Identifying the prognostic role on survival of ADL and IADL dependency Follow up unknown	Increased risk of death in ADL-dependency (HR 2.0, CI 1.3-2.9) and IADL-dependency (HR 1.5, CI 1.1–2.0)	- IADL and ADL scores were dichotomized - results were irrespective of Performance Status or type of cancer
McCorkle et al. 2000[26]	Surgical oncological academic department N = 375 Age: 60-92 yr early stage: N = 255 advanced stage N=120	RCT Postoperative CGA with consecutive home visits Mean follow up 24 months	No benefit on survival in early stage group. Benefit in advanced stage group, risk of death doubles: 2.0 (1.3-3.1) in usual care group vs intervention group	- home care was delivered by advanced practice nurses. - quality of life remained in surviving intervention-group
Rao et al. 2005[27]	Veterans Administration Medical Center N = 99 Mean age 74, range nknown	Post hoc analysis in a subset of a randomized 2 × 2 factorial trial. Geriatric inpatient unit, outpatient clinic versus non-geriatric in- and outpatient services, Follow up 1 yr	No difference on mortality	- strictly defined frailty characteristics, - no difference in hospital costs - geriatric care improved quality of life, only the effect on pain sustained after 1 yr
Del Mastro et al. 2005[22]	Medical Oncology department, Women >= 70 yrs with stage III and IV breast cancer N = 48 Mean age 74 yr, range 70-87 yrs	Phase II study to evaluate activity and toxicity of weekly paclitaxel. Post hoc factor analysis within pre-treatment CGA (comorbidity, functional status, mental health, age)	At least one inability in the ADL-scale was associated with a lower probability of response ($p = 0.009$) and a shorter progression free survival ($p = 0.04$) Charlson ADL- and IADL scales: not predictive on activity or toxicity	- 63% Charlson score = 0 - 26% one ADL-dependency - no report on the impact of incomplete cytotoxic regimens - mean overall survival 36 months, mean progression free survival 9.7 months
Maione et al. 2005[24]	Multicenter, oncology department Stage IIIB or IV non-small-cell lung cancer, PS ⩽ 2 N = 566 Median age 74 yrs, range 70–84 yrs	Preplanned analysis within MILES-study, a phase III study with randomization to vinorelbine, gemcitabine or both; to identify prognostic role of baseline levels of comorbidity, functional status and QoL measured by CGA	Increased risk of death in - Performance Score 2: $p = 0.06$ (HR 1.2–1.9) - worse IADL-score: $p = 0.04$ (HR 1.0–1.7) - intermediate + worse QoL score: $p = 0.003$ (HR 1.3–2.4)	- age, ADL-score and Charlson score did not correlate with an increased risk of death - short life expectancy due to advanced lung cancer may cover up factors which may be relevant to survival in case of a longer life expectancy
Tredan et al. 2007[25]	Oncology department Advanced ovarian cancer FIGO III/IV N = 155 Age > 70 yr Mean age 75 yr, range 70–90 yrs	Retrospective observational study to identify prognostic factors using CGA Carboplatin-cyclophosphamide or carboplatin/paclitaxel Follow-up 30 months	Performance Status was not a significant predictor of mortality ($p = 0.06$), depressive symptoms at baseline were highly significant ($p < 0.001$)	- CP-group had at baseline better prognostic factors; high toxicity due to paclitaxel - Part of the study population was reported before[26]: also polypharmacy (>6 drugs per day) was predictive on survival ($p = 0.04$)

CGA and tolerance to chemotherapy

A major topic in geriatric oncology is the question as to whether CGA can predict risks and benefits of chemotherapy in a heterogeneous elderly population in a pre-treatment phase. Selecting fit elderly to receive standard treatment is the goals of most clinicians. Other goals may be to achieve a well structured and individualized risk assessment, to inform and advice to a patients health problems including the most feasible cancer treatment. Selecting the unfit elderly e.g. for adjusted chemotherapeutical regimes or supportive care can be other objectives if CGA is a relevant information source predicting tolerance to chemotherapy.

Our literature search revealed five studies that evaluated the value of CGA to predict tolerance to chemotherapy (table 2). Two studies were phase II studies with limited numbers of patients. [22,23] A prospective study to identify prognostic factors using CGA showed that both depression at baseline and dependence were significant predictors for toxicity in advanced ovarian cancer patients treated with carboplatin-cyclophosphamide. [31] This study was retrospectively extended with a group of patients treated with carboplatin/paclitaxel. In this non-randomized cohort no predictive factors were found for occurence of side effects. [25] Authors suggest that the failure to determine predictive factors might be due to the high toxicity of paclitaxel, especially since pre-treatment patient characteristics in the paclitaxel group were somewhat better compared to the cyclophosphamide group. An American study used a multidimensional assessment to predict toxicity in an elderly group with diverse cancers. The index on published toxicity (MAX2), higher diastolic blood pressure, bone marrow invasion and lactate dehydrogenase were predictors for toxicity. The Charlson index on comorbidity proved not to be a good predictor. [32] Also in the other studies neither the Charlson index nor the most prevalent comorbidities were predictive of tolerance for chemotherapeuty. [22-31] Comorbidity itself or an accumulation of comorbidities gives no additional information unless severity of comorbid conditions is taken into account.

PS and dependency at home were independent predictive factors for toxicity. As expected, statistical analysis showed no predictive strength in studies where the prevalence of high grade PS or dependency was low. We found no study in which an intervention was performed that ameliorated relevant items and then reviewed the effects.

A surplus value of CGA in detecting relevant factors on toxicity lies probably in exploring dependency, emotional status and polypharmacy. This is in line with studies that focused on one of these items separately: Blower stressed the importance of co-medication in cancer

treatment in the elderly and its consequence for toxicity. [34] Jatoi found no prediction of toxicity using the PS in elderly lung cancer patients while an activity-score predicted toxicity very well. [35] Chen underlined the association between severe toxicity and, independent from each other, PS, depressive symptoms and IADL dependency. [36] Studies on different chemotherapeutical regimens stress the importance of cognitive decline as an adverse effect due to chemotherapy. Also high prevalences of pre-existing cognitive impairment are reported. [37]If substantial cognitive deficits occur, these may affect self-management capacities, life expectancy and interfere with cancer treatment. In our search only two studies analysed the relation between cognitive malfunctioning and severe toxicity. Although the prevalence of cognitive impairment was between 8 and 18%, cognitive impairment was no predictor for toxicity. [25 31] To our knowledge no studies are available primarily studying the association between cognitive impairment and overall tolerance to chemotherapy.

Table 2 – Endpoint: toxicity to chemotherapy

Author	Population + setting, department	Study-design + intervention	Results: geriatric factors as effect modifiers	Comment
Freyer et al. 2005[30]	Advanced ovarian cancer FIGO III/IV, age > 70 yr N = 83 Median age 76 yr, range 70–90 yrs Oncology department	Open multicenter prospective study to identify prognostic factors using CGA Carboplatin- cyclo-phosphamide	- depression at baseline $p = 0{,}006$ - dependence $p = 0.04$ - Performance Score $\geqslant 2$ $p = 0.03$	- 72% received six cycles with no S-toxicity and no tumor progression - few geriatric conditions in study population - dependence dichotomized
Tredan et al. 2007[25] (Freyer 2005 extended)	Advanced ovarian cancer FIGO III/IV, Age > 70 yr N = 155 Mean age 75 yr, range 70–90 yrs Oncology department	Retrospective observational study to identify prognostic factors using CGA Carboplatin-/cyclophosphamide or carboplatin/paclitaxel	No predictive factors in paclitaxel group	- CP-group had at baseline better prognostic factors; high toxicity due to paclitaxel
Extermann et al. 2002[31]	Diverse cancers and chemotherapies N = 60 mean age 75 yr, range 70–87 yrs Tertiary cancer centre	Open prospective pilot study on predictors of tolerance to chemo-therapy Using a multidimensional assessment	Higher diastolic blood pressure, MAX2, lactate dehydrogenase, marrow invasion related to toxicity ($p < 0.1$); Charlson -index did not predict toxicity	- baseline functional, mental and mental status were not reported in relation to toxicity - 47% of the patients showed grade 4 hematological or grade3/4 non-hematological toxicity
Del Mastro et al. 2005[22]	Women $\geqslant$ 70 yr with stage III and IV breast cancer N = 48 Mean age 74 yr, range 70–87 yrs Oncology department	Phase II study to evaluate activity and toxicity of weekly paclitaxel. Post hoc factor analysis within pre-treatment CGA (comorbidity, functional status, mental health, age)	Charlson-index, ADL- and IADL scales were not predictive on toxicity	- 63% Charlson score = 0 - 26% one ADL-dependency - no report on the impact of incomplete cytotoxic regimens - mean overall survival 36 months, mean progression free survival 9.7 months
Freyer et al. 2004[23]	Women with hormonal-resistant metastatic breast cancer, age > 70 years, Performance Status 0–2 N = 26, mean age and range unknown Oncology department	Open multicentre phase II study with Idarubicin. Geriatric assessment to identify factors predicting tolerance	No statistical analysis could be performed. Multi-dimensional geriatric assessment seemed not to be indicative to poor outcomes	- premature ending of the study because of high toxicity and lack of efficacy

Clinical impact and future directions

CGA seems highly valuable in describing populations of elderly cancer patients in trials e.g. to determine whether results can be translated to the heterogeneous population of elderly patients. Data concerning CGA and its ability to detect relevant health problems in elderly cancer patients are consistent and promote the application of CGA in everyday practice. The high prevalence of geriatric syndromes in oncology underlines its importance. CGA is also promising in revealing domains associated with high incidence of adverse effects when

chemotherapy is considered. Information is obtained additional to chronological age and the use of the Performance Score. Emotional, cognitive function, functional dependency and polypharmacy are the most relevant domains to explore. With regard to survival CGA also uncovers relevant items. Especially IADL-dependency, moderate quality of life and depressive symptoms at baseline are relevant for survival. Data on comorbidities explored by CGA (and collected by Charlson's index) and ADL-dependency are not however convincingly related to survival. Although CGA convincingly reveals extra information, its definite place in cancer medicine has not been elucidated yet.

Our search showed that most studies in geriatric oncology have focused on identifying prognostic factors detected by CGA and they did not include an intervention in their design. The few studies that included an intervention showed an improvement in quality of life measures. Lack of interventions-studies limits our conclusions about the surplus value of CGA in oncology. Clinicians should be cautious to make an analogy with studies on CGA in general health care especially because age and functional status differ substantially between study-populations. Therefore, studies with an intervention strategy and including older cancer patients and especially 'the oldest old' cancer patients should be encouraged. Prognostic validation studies using geriatric syndromes or information added by CGA in decision making in oncology are lacking. If detection of health problems and risks are indeed the only objectives, the multiple health domains which are explored by CGA can be integrated into oncology practice. This working method reduces CGA to a multidimensional screening on pretreatment risks, incorporating the multiple screening tools used in CGA in oncology. It only leads to an individualized treatment plan if the process is structurally implemented in elderly cancer patients. Implementing screening tools in clinical pathways can be an option and has been advocated to establish beneficial effects in multidisciplinary teams. [38]

To put CGA into everyday clinical practice some practical issues should be resolved. For example should clinicians only evaluate the patient's characteristics as fit or no fit for oncological treatment, and thus dichotomize the relevant parameters to apply them in clinical practice? Among others Freyer did so on dependency defining every assistance living at home as a "dependency state".[31] Quantifying or dichotomizing each parameter in decision rules may be an option but require a great number of prognostic validation studies. Cut off points will probably differ significantly between each malignant disease, stages and every cytotoxic regimen. Furthermore, patients may act differently on several domains, sometimes via interacting pathways, sometimes via independent pathways. For the present a qualitative use of data revealed by CGA is more valid in clinical practice, and reflects the lack of evidence.

A geriatric oncology taskforce stated that a two step approach is an alternative to deliver CGA to older cancer patients.[39] The first step should be a screening process on every older cancer patient to select the vulnerable patients who will benefit most of CGA. The second step is the actual performance of CGA in those who have highest chances to benefit. This two step approach is less time and manpower-consuming than addressing CGA to every older cancer patient. Many screening instruments refer to vulnerability, in geriatrics known as 'frailty'. Frailty is associated with a high incidence of adverse health outcomes: increased dependency, death, hospitalisation and nursing home admission. Some authors use the term frailty-concept or frailty-syndrome.[40] Definitions of frailty have been proposed but as yet there is no formal consensus. Definitions agree that a combination of factors influences peoples physiologic state to the extent that its reserve is largely reduced. Subsequent exposure to minimal stresses may be sufficient to lead to the adverse outcomes.[41] At present the annotation 'syndrome' is premature: signs, symptoms cannot unequivocally be grouped together, neither can frailty be defined as a single symptom state. Many factors are proposed as predictors of frailty, especially

markers on neuromuscular function, cognition and inflammatory activity seem relevant. Several indexes of frailty have been constructed to use in clinical care and community dwelling elderly. The clinical criteria by Fried[42], the Edmonton Frailty Scale[43], Groningen Frailty Indicator [44] are examples of frailty indices. Also the Vulnerable Elders' Survey-13 (assesses self-reported health, functional capacity and physical status) can be seen as a frailty screening tool. Preliminary findings suggest that these screening tools select adequately the fit from the frail elderly. [45,46] In screening situations the negative predictive value of frailty indices is probably the most important aspect since it leads directly to the proposal of standard therapy to fit elderly. A two-step approach stresses the necessity to determine which interventions are made based on CGA and influence treatment or cancer decision making. Clinical studies are required to assess suitability and benefits implementing frailty-scales with subsequent full-CGA in identified frail patients. The present data suggest that interdisciplinary working methods between oncology and geriatric teams are promising. Also physicians should be aware that the optimal interdisciplinary design has not been determined in detail. [47]

Conclusion

Geriatric syndromes, as assessed by Comprehensive Geriatric Assessment (CGA), act as effect modifiers for the outcome of oncological treatment, with regard to quality of life and chemotherapeutic drug toxicity, though the effect on survival is insufficiently studied. The introduction of CGA in routine oncology is probably most appropriate in a step wise procedure. First all elderly should be screened for frailty. The screening tool should be very effective in identifying fit patients in order to prevent undertreatment in this group. Next the frail elderly should receive multidisciplinary geriatric assessment, and finally oncological treatment should

be adapted to the presence of one or more geriatric syndromes. Cost-effectiveness studies need to be conducted to optimize CGA in oncology, but the increasing necessity of tailor made oncology in the heterogeneous elderly population now already warrants the application of basic geriatric screening and assessment procedures.

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Chapter 3.2

Predictive value of geriatric assessment techniques, clinical judgment and performance status for feasibility of chemotherapy and survival in elderly patients with epithelial ovarian carcinoma (FIGO IIB-IV)

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Introduction

The peak incidence of ovarian cancer is in the seventh decade of life and about 40% of the patients is over 70 years old.[1-3] Standard treatment in advanced epithelial ovarian cancer consists of a staging laparotomy with aggressive cytoreductive surgery, aiming at removing all tumor deposits, followed by platinum-based chemotherapy.[4] Chemotherapy with platinum-paclitaxel appeared to be feasible and tolerable in (selected) elderly patients enrolled in phase III studies or treated in tertiairy care centers.[5-7] Population-based reports showed that both increasing age and comorbidity lead to less utilization of combination therapy in patients with ovarian cancer FIGO stage II and III.[8, 9] Relative 5-year survival differed significantly between 45% in patients < 70 years and 25% in patients ≥ 70 years.[8] Undertreatment is suggested, as elderly patients without any comorbidity do not receive standard treatment. [8, 10, 11] However, others emphasized that high complication rates among elderly who received chemotherapy may reflect overtreatment and, therefore, a search for less radical treatment strategies is needed.[12] Patient characteristics as increasing age, comorbid conditions and dependency on functional status may be the underlying motive for less aggressive treatment or non-inclusion into trials.[5, 13]

To qualify and quantify the heterogeneity in populations of elderly cancer patients, Comprehensive Geriatric Assessment (CGA) is recommended as it identifies strengths and weaknesses in individual patients.[14] In oncology, studies on CGA mainly focus on identification of unrecognized health problems and factors that influence complication rates or survival.[15] Although CGA is promising in revealing relevant health problems in elderly cancer patients, prospective studies on oncological decision making in patients with ovarian cancer, comparing clinical judgment to geriatric assessments techniques are lacking. Therefore, we developed a prospective study to describe the correlation between GA and clinical judgment, as well as the association between different methods to classify

frailty and course of disease during cancer treatment, not only in terms of survival and completion rate of chemotherapy, but also in terms of dependency.

Patients and methods

Patients were recruited from 6 general hospitals in the southern part of the Netherlands. The study population consisted of women ≥ 70 years of age with histologically or cytologically proven primary ovarian cancer, FIGO stage IIB-IV, not being treated previously. Other inclusion criteria were adequate bone marrow, hepatic, cardiac and renal functions. Exclusion criteria were performance status[16] (PS) >2, prior treatment with cytostatic agents or radiotherapy, estimated life expectancy of less than 3 months or concomitant other cancer (except basal or squamous cell carcinoma of the skin). Patients with a prior cancer were excluded, unless this cancer had been cured with surgery and the patient had a disease-free interval of 5 years. Oncologists had the intention to treat patients with six cycles of chemotherapy (see below). Study approval was obtained from the medical ethical committee and filed in the national registry (CCMO-nr P03.1456 L) Written informed consent was obtained from all patients.

Patients were both referred to a medical oncologist (MO) and geriatrician; at the time of judgment both physicians were unknown of each other's assessments and no decision to administeror reject chemotherapy was made before this moment. Multidimensional assessment consisted of using regular geriatric assessment (GA) techniques: comorbidity was evaluated according to Charlson et al.[17]; functional status by Activities in Daily Living (ADL) according to Barthel and Instrumental Activities in Daily Living (IADL) according to Lawtons and Brody's scale[18, 19]; cognition was examined by Mini-Mental State Examination (MMSE).[20] Besides a performance score according to Eastern Cooperative Oncology Group Performance Status (PS), also a Timed-up-and-go test (TUG) were performed.[21] TUG times proof to classify risk for falls and mortality in elderly.[22-24] Furthermore, 95% confidence interval for TUG in healthy elderly (70-90 year old) has been determined.[25]

Patients were stratified as “fit for chemotherapy” (MO-Fit) and “unfit for chemotherapy” (MO-Unfit) according to clinical assessment (this is called “clinical judgment”) by the patient’s medical oncologist. Patients were qualified as ”geriatric assessment-unfit for chemotherapy” (GA-Unfit) when at least one of the following clinimetrical scores applied: score on Charlson’s Comorbidity Index (CCI) was >3, IADL-score was <12, ADL-score was <18 or score on MMSE was <24. Patients who did not fulfill GA-Unfit criteria were classified as “geriatric assessment-fit for chemotherapy” (GA-Fit). Results on TUG were dichotomized in scores of 12 seconds and less and scores above 12 seconds. Preferred chemotherapy was 3-weekly Paclitaxel (175 mg/m^2) and Carboplatin (AUC5), with a regimen of six cycles. Adjustment of dose or limited chemotherapy to one of the agents was at choice of the medical oncologist and accepted within the study-protocol, unless the intention to treat the patient with six cycles of chemotherapy was firm at the start of chemotherapy. The intention was to maintain hemoglobin level at≥ 7.4 mmol/L, either with an erythropoietin or transfusion therapy; every patient received prophylactic granulocyte colony stimulating factor.

Geriatric assessment and follow-up of patients was performed after three and six cycles of chemotherapy and every 3 months afterwards until 1 year after start of chemotherapy. If interval-cytoreductive surgery took place, assessment was performed in the period after interval surgery and before the fourth cycle of chemotherapy. These follow-up assessments were done for giving insight into changes in the extent of dependency, physical performance and comorbidity after initial treatment. Scores on ADL and IADL were categorized into two groups with “stable or improved” or “decreased” scores (based upon ADL and IADL-scales lower scores reflected increased dependency). A significant decrease in scores on IADL-Lawton scale was defined as a decrease of 3 points or more compared to the initial assessment; on the ADL-Barthel scale a significant decrease was defined as 2 points or more. All toxicities encountered during the study were evaluated according to the Common Toxicity Criteria Scale (CTC).

Statistical analysis: Completion of chemotherapy (defined as administration of six cycles of chemotherapy) was formulated as primary endpoint. Associations between this endpoint and the

variables for classifying frailty (GA-vitality, performance scores and TUG) were evaluated. Furthermore, the associations between these variables and both overall survival and incidence of toxicity were evaluated. Assuming that GA-status reflects frailty, positive and negative predictive values were computed for GA and PS, and GA and TUG. We used chi-square tests to compare univariate associations between both outcomes (completion of chemotherapy and toxicity) and variables of vitality (GA-unfit/GA-fit, performance scores and TUG scores). Level of significance was fixed at 0.1. Survival rates were computed. The logrank test was performed to evaluate differences between survival curves in univariable analyses.

Results

Patient characteristics and completion of chemotherapy

Thirty eight patients were included. Two patients had incomplete geriatric assessment before administration of chemotherapy and were excluded from the analyses. Characteristics of the remaining 36 patients in the study population are summarized in table 1. Thirteen patients were evaluated as GA-Unfit and only 3 patients were evaluated MO-Unfit on the base of clinical judgment by the medical oncologist (all within the group GA-Unfit and all 3 obviously did not receive 6 cycles of chemotherapy). Mean age was significantly higher in the GA-Unfit group (79 years) compared to the GA-fit group (75 years).

Charlson's co-morbidity index (CCI) scores before start of chemotherapy: 28 (77%) had CCI-score 0-1 (this group included 15 patients with PS 0-1, 12 with PS 2, 1 patient was annotated with PS<3; 20 patients within CCI group 0-1 were GA-Fit and 8 patients GA-Unfit), 6 (17%) patients had a CCI-score 2 and 2 patients (6%) CCI-scores >2. As a consequence, CCI-scores attributed in only 2 patients to the classification GA-Unfit.

About 60% of all patients could complete at least 6 cycles of chemotherapy. Completion of chemotherapy according to GA-Fit/Unfit, Performance status (PS) and Timed-up-and-Go scores (TUG) is shown in table 2. Although the number of patients in this study was small, all three variables (GA-

Unfit, PS 2 and TUG > 12 seconds) were significantly associated with incomplete chemotherapy regimens. Eleven out of 33 patients (33%) who were evaluated “fit for chemotherapy” by clinical judgment (MO-fit) did not complete the treatment regimen. When evaluating patients by PS, GA and TUG (applying strict cut-off points within these measurements), four out of 22 patients (18%) who were classified as PS 0-1 (=fit) did not complete chemotherapy and 6 out of 23 classified as GA-Fit (23%) or 6 out of 22 classified as TUG ≤12 seconds (27 %). Despite a classification as frail, conceptualized by CGA-unfit, PS-2 or TUG >12 seconds, respectively 5 (43%), 5 (36%) and 3 (27%) were able to complete at least 6 cycles.

Table 1: Patient characteristics according to GA-status, stage, surgery performed and regimen of chemotherapy.

	Total	GA-Fit	GA-Unfit
Mean age (range)	77 (70-85)	75 (70-83)*	79 (72-85)
Number of patients	36	23	13
Tumor stage IIc	5	3	2
IIIc	23	14	9
IV	8	6	2
Cytoreductive surgery[+] Yes	26	19	7
No	10	4	6
Combination chemotherapy (both taxane and carboplatin)	28	20	8
Mono chemotherapy	8	3	5

[+] Cytoreductive surgery performed before chemotherapy or after 3 cycles of chemotherapy

*p<0.05 for age, comparing GA-Fit versus GA-Unfit

Table 2: Completion of chemotherapy according to GA-status, performance score, MO-fit and Timed Up-and-Go score.

	< 6 cycles	≥ 6 cycles	Total	
GA-Fit	6 (23%)	17 (77%)	23	
GA-Unfit	8 (57%)	5 (43%)	14	P=0.04
Total	14 (39%)	22 (61%)	36	
PS 0-1	4 (20%)	16 (80%)	22	
PS 2	9 (64%)	5 (36%)	14	P=0.03
Total*	13 (38%)	21 (62%)	34	
TUG ≤ 12 (seconds)	6 (27%)	16 (73%)	22	
TUG > 12 (seconds)	8 (73%)	3 (27%)	11	P=0.01
Total**	14 (42%)	19 (58%)	33	
MO-fit #	11 (33%)	22 (67%)	33	

* The exact, initial performance score was unknown in two patients, not included in analysis
** Initial TUG times were not reported in three patients not included in analysis
# Feasibility of patients initially assessed "fit" by medical oncologist (MO) to receive 6 cycles of chemotherapy

The association between GA-Unfit/Fit on the one hand, and performance status (0-1 versus 2) and TUG (≤12 versus >12 seconds) on the other hand, are listed in table 3. Assuming that GA-unfit reflects frailty, the positive predictive value of PS 2/0-1 for frailty was 0.43, negative predictive value is 0.70; with regard to TUG ≤12/>12 seconds positive predictive value is 0.73 and negative predictive value is

0.86. 3 out of 6 patients who were classified as GA-Unfit and PS 0-1, had MMSE scores less than 24 points; 2 out of 6 patients with PS 2 had MMSE-scores under 24 points. All patients with PS 2 had ADL-scores of 19 and 20, reflecting that these patients were (almost) independent on ADL. Assuming that GA-unfit reflects frailty, positive predictive value of PS 2/0-1 for frailty is 0.43, negative predictive value is 0.70; with regard to TUG ≤12/>12 seconds positive predictive value is 0.73 and negative predictive value is 0.86.

Table 3: Association of GA-status and Performance status/TUG.

	PS 0-1	PS 2	TUG ≤ 12 (sec)	TUG > 12 (sec)
GA-Fit	14 (64%)	8 (36%)	19 (86%)	3 (14%)
GA-Unfit	6 (50%)	6 (50%)	3 (27%)	8 (73%)

Survival

10 (28%) patients had died within 1 year and 22 (61%) within 2 years. Figure 1 shows overall survival curves dichotomized as GA-Fit versus GA-Unfit (figure 1a), TUG > 12 versus ≤ 12 seconds (figure 1b) and PS 0-1 versus 2 (figure 1c). GA-Unfit, TUG time over 12 seconds and PS 2 were all significantly associated with decreased overall survival. 46% of patients classified as GA-Unfit were alive after one year and 28% after two years, versus 86% and 52% respectively in the GA-fit group. Overall survival at one year in the group with TUG-time > 12 seconds group was 47% compared to 87% in the group with TUG-time ≤ 12 seconds, 2-year survival rates in these groups were 23% and 52% respectively. 1-year survival rate among patients with PS 0-1 was 87% versus 58% in the PS 2 group, 2-year survival was respectively 55% and 27%.

In figure 2 survival is shown according to the number of cycles received: 100% of patients who received at least 6 cycles were alive after one year, in contrast to 37% of patients who received less than 6 cycles. After 2 years these proportions were 62% and 18%, respectively.

Figure 1a: Overall survival according to GA-status. Log-rank p=0.02

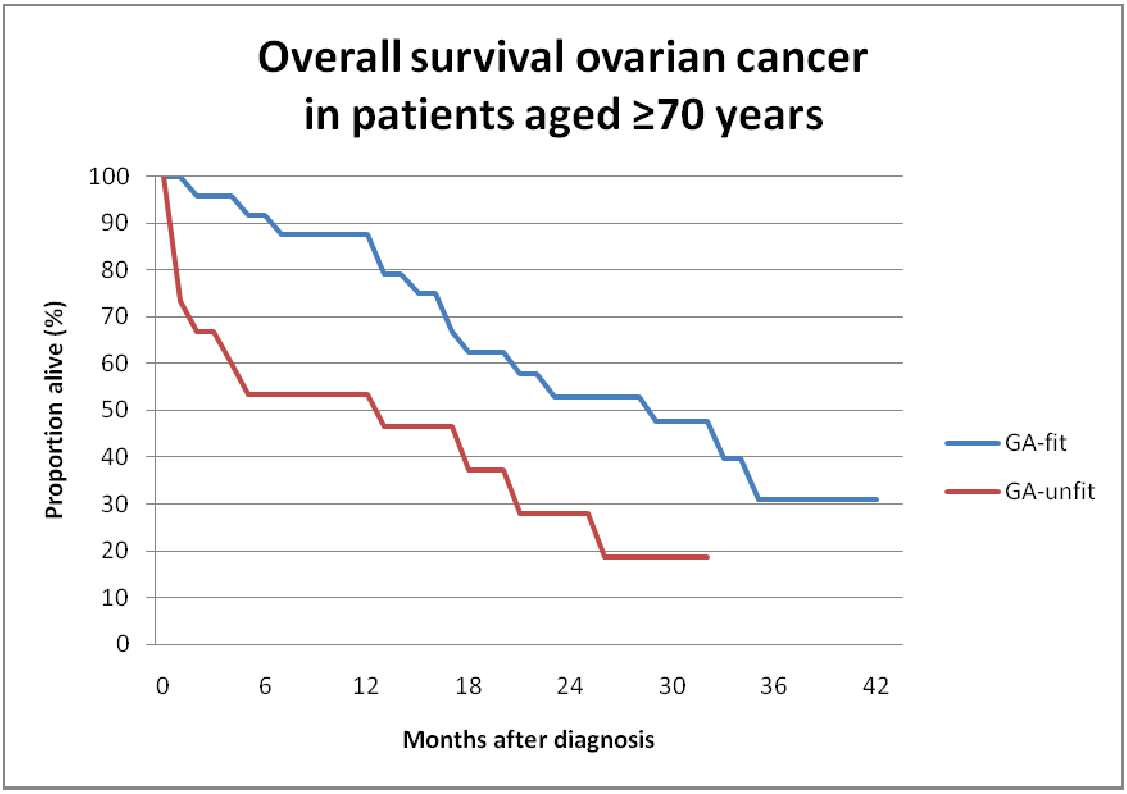


Figure 1b: Overall survival according to Timed-Up-and-Go results. Log-rank p=0.02

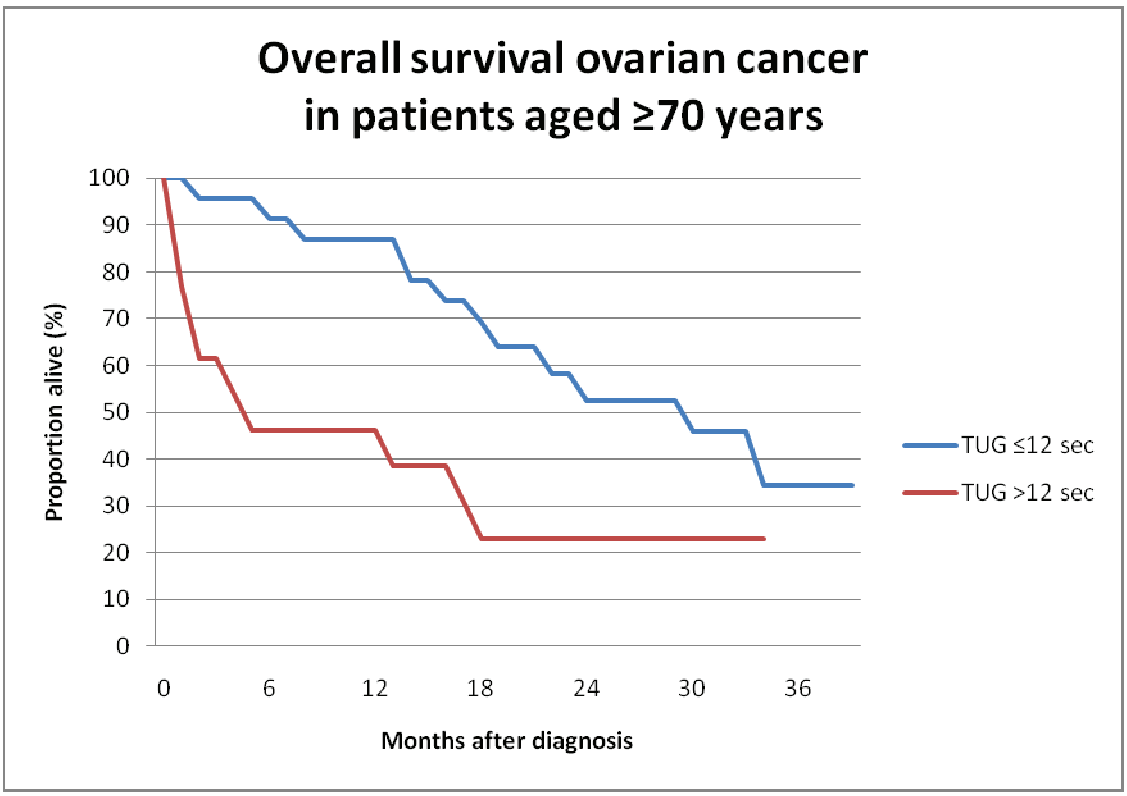


Figure 1c: Overall survival according to performance score 0-1 versus 2. Log-rank 0.01

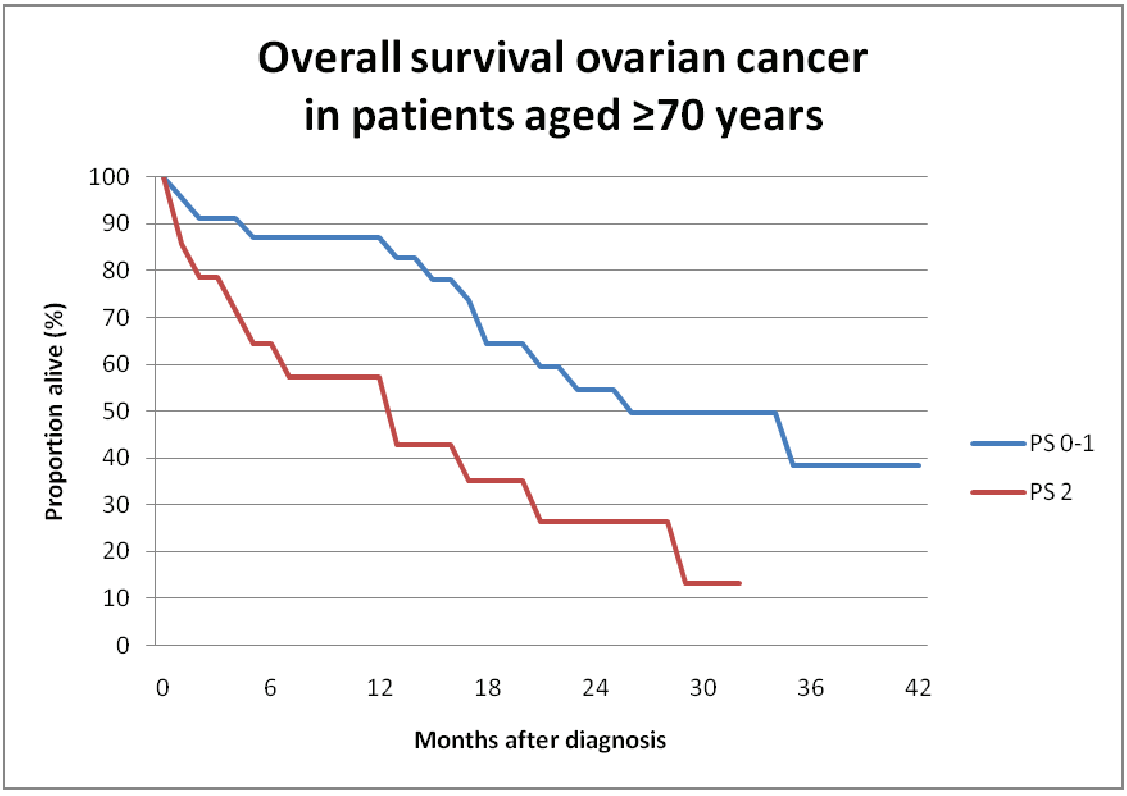
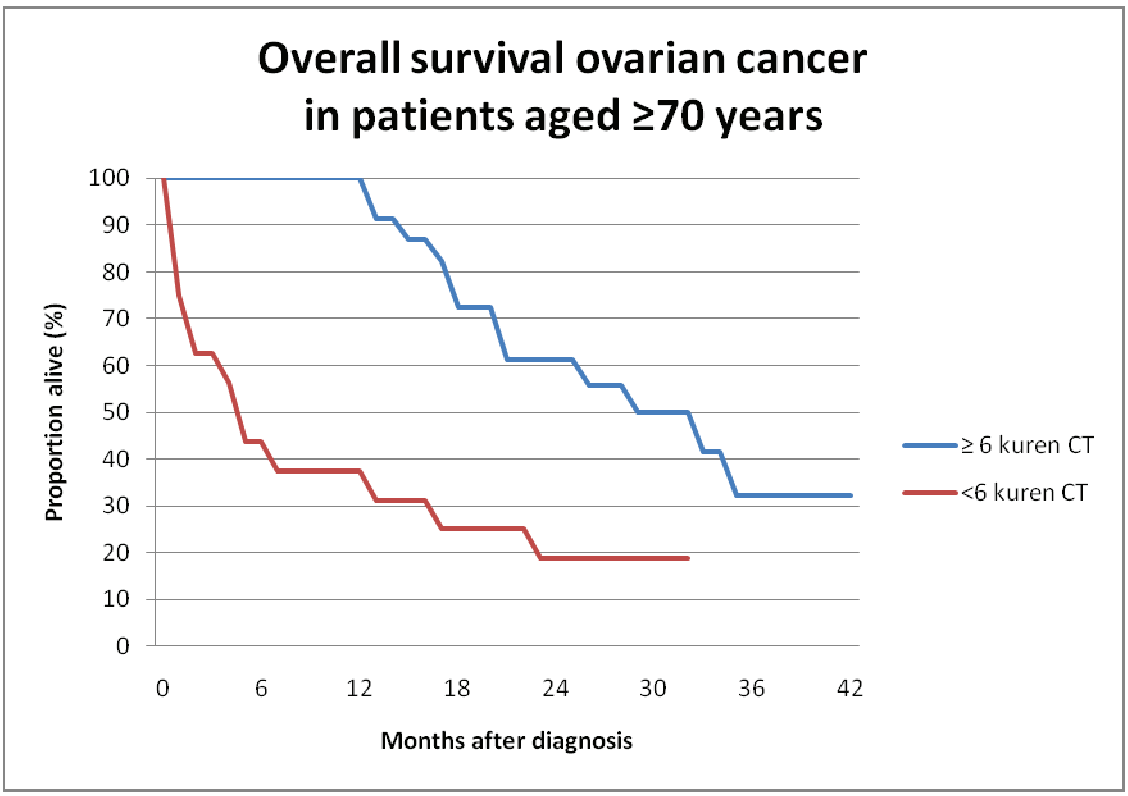


Figure 2: Overall survival according to number of cycles received. Log-rank p=0.001



ADL and IADL-functioning after 1 year of follow up.

18 (50%) patients had a stable or improved ADL-status after 1 year, 8 (22%) patients had declined on ADL-functioning, and 10 (28%) had died within 1 year. IADL-status was stabilized or improved after 1 year in 16 (47%) patients and 8 (24%) patients became more dependent on IADL. Table 5 shows course of functional status according to GA-status. 2 out of 3 patients who were classified as GA-Fit had a stable or improved functioning on ADL or IADL after 1 year (22% showed declined on ADL, 14% had died). In contrast, 1 out of 4 patients within the GA-unfit category had stable or improved ADL or IADL functioning, while 1 out of 4 declined on functional status and 50% had died after 1 year.

Table5: Course of functional status after 1 year follow up according to GA-status.

	ADL-stable	ADL-declined	IADL-stable	IADL-declined	Died within 1 year
GA-Fit (at baseline)*	15 (65%)	5 (22%)	13 (62%)	5 (24%)	3 (14%)
GA-Unfit (at baseline)	3 (23%)	3 (23%)	3 (23%)	3 (23%)	7 (54%)

*On two patients no IADL-scores were available at 1 year
ADL stable = scores at highest 1 point less compared to initial score before chemotherapy
ADL declined = scores declined 2 points or more on ADL-scale
IADL stable = scores at highest 2 points less compared to initial score before chemotherapy
IADL declined = scores declined 3 points or more on IADL-scale

Discussion

This prospective observational pilot-study underlines additional value of performance score and geriatric assessment techniques (GA-fit, TUG) to predict completion of chemotherapy compared to clinical judgment by medical oncologists. PS, TUG-scores and GA-Fit/Unfit (a predefined, multidimensional construct based upon pre-treatment deficits on ADL, IADL, cognition and a comorbidity index) were all associated with failure to complete chemotherapy and survival. Patients who were evaluated GA-fit had a good chance (65%) to have stable or improved ADL or IADL functioning after 1 year. In contrast, only a minority (23%) among patients in the GA-Unfit group did not decline on ADL or IADL functional status within the next year and 50% of patients in the GA-Unfit group had died within 1 year.

In clinical trials on ovarian cancer there is concern about the representativeness of elderly patients and data gathered by geriatric assessment techniques are advocated to describe patient populations.[13] Improper selection of older patients, leading to both under- and overtreatment, is assumed to be the result of inadequate assessment of patients' general health status, as traditional measures for evaluating oncology patients are not well adapted to older patients.[26 27-31] The results of our pilot study nuance this point of view: use of assessment techniques (with administration of a strict cut-off point in PS, GA and TUG) can improve the selection process (the positive and negative

predictive values for TUG being somewhat higher than for PS when GA is used as a golden standard). However, the improvement seems modest as the proportion of patients who could not complete at least 6 cycles of chemotherapy decreases from 33% by clinical judgment to 20% at most by using these assessments. Moreover PS, a common oncological assessment technique for functional status, predicted completion of chemotherapy even somewhat better than GA. The patient group with TUG-scores > 12 seconds, had the lowest proportion of patients, who completed chemotherapy despite "being frail" (compared to PS 2 and GA-unfit). This statement is clinically relevant as completion of chemotherapy is strongly associated with survival.

All patients with PS 2 had none or minimal dependency on ADL before start of chemotherapy. GA-status was primarily affected by cognitive functioning, ADL and IADL functioning, as comorbidity only determined GA-status in 2 patients. The positive and negative predictive values were higher for TUG as compared to PS (GA as golden standard). Others also showed that results on physical performance test were associated with functional limitations and these tests were better tools to assess functional status in elderly cancer patients than Karnofsky Performance Scale or PS.[3132] Alternatively, physical performance measures may reflect the broader spectrum of physical reserves, whereas the performance on ADL and IADL principally introduces a ceiling in its measuring in case a specific task is fully (un)impaired. Physical performance measures (handgrip strength, Timed-Up-and-Go test, Physical Performance Test) have previously been shown to predict survival and recovery in geriatric patient populations.[33-35] In a study on platinum-based chemotherapy among lung cancer patients, increasing TUG-scores were also associated with increased mortality.[36] In our study, impairment on ADL, IADL and physical functioning were all associated with early termination of chemotherapy. Unfortunately, most prospective studies on pretreatment patient characteristics in elderly cancer patients focus on toxicity and only hypothesize on the role of these characteristics in the decision making processes.[37-39, 39, 40] As completion of chemotherapy is a major criterion to achieve the benefits of chemotherapy, we emphasize that both completion of chemotherapy and toxicity are relevant endpoints.

In recent years, few studies studied the impact of comprehensive geriatric assessment (CGA) or geriatric consultation services on oncological decision making processes. The proportion of patients in which CGA led to changes in chemotherapy, varied from 21% to 49%.[41-43] Non-oncological interventions were proposed in 72-76% of the patients.[43, 44] In a single center study on patients with digestive cancers, a data-search on multiple domains was combined with clinical judgment by a gastro-enterologist. This combination led to adaptations of oncological treatment (not restricted to chemotherapy) in 47% of the patients, a subsequent CGA consultation led to additional interventions (in 72% of the patients) but did not influence the oncological strategy.[44] We are aware that we put things to extremes in our study, as we evaluated clinical judgment by the oncologist on the one hand and several clinimetrical assessment techniques (PS, GA-status and TUG) with a predefined cut-off point but without any clinical reasoning on the other hand (i.e. a woman who had lost one or two lower extremities after a trauma may show high scores on TUG but is probably not considered vulnerable).

Our study also gives in depth information about the course of functional status within 1 year after treatment started. The observation that the majority of patients (65%) who were evaluated as non-frail by GA, showed stable or improved functional status after 1 year is clinically relevant. This information can guide patients and physicians, in their decision on benefits and drawbacks of chemotherapy and is additional to information on survival and toxicities.

Limitations to our study are clear: we report on a small number of patients and are aware that not all eligible patients out of the participating hospitals were included. Unfortunately, threepatients declared to participate but refused to sign a written consent and could thus not be included. Due to the small number of patients we could not conduct multivariable analysis. Also early discontinuation of chemotherapy due to progressive disease or platinum resistance was not taken into account. However, others reported that among elderly above 70 years old, these reasons for discontinuation were only observed in a small minority of cases (2% of patients treated with chemotherapy), whereas discontinuation by patients' withdrawal or toxicity was more frequently reported (10% and 19%,

respectively).[5] Furthermore, comprehensive geriatric assessment (CGA) is a defined process that contains more domains than our study did include, for instance neither interventions, nor depression and malnutrition were part of our operationalisation of GA-Fit/Unfit.(CGA-richtlijn Orde 2011) Especially depressive mood may be relevant to evaluate in elderly patients with chemotherapeutically treated ovarian cancer, as it is associated with an increased risk for toxicities and decreased survival.[40, 45]

In conclusion, all assessment techniques studied (PS, TUG and GA-status), gave additional information on completion of chemotherapy and survival in elderly women with ovarian cancer compared to clinical judgment by the medical oncologist. Also GA-status predicted patients' functional status after 1 year to an acceptable extent. Further research is needed, both on the positioning of physical performance measures in oncology decision making and on the preferred implementation of (comprehensive) geriatric assessment techniques into oncology decision making.

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Chapter 4

Outline and general discussion

The studies described in this thesis investigated heterogeneity among elderly cancer patients and its influence on treatment and outcome. Especially age and comorbidity were studied as parameters responsible for heterogeneity among elderly cancer patients. Gender and performance score at diagnosis were also taken into account in a few studies. A variety of patient groups and treatment modalities were evaluated:

- surgery for patients with stage I-III colon cancer,
  stage I-III rectal cancer,
  stage I-III breast cancer,
  stage I-II non-small-cell lung cancer
- surgery in combination with radiotherapy for patients with stage I-III rectal cancer
- surgery in combination with chemotherapy in ovarian cancer
- chemotherapy in small-cell lung cancer.

Most studies in this thesis were based on population-based data. As the elderly population is heterogeneous concerning many health status parameters[1], we additionally conducted a review that described the clinical impact of comprehensive geriatric assessment (CGA) on treatment and outcome in elderly cancer patients. In general, CGA includes a multidimensional data-search and a process of analyzing and linking patient characteristics to create an individualized intervention plan . In a small prospective study we implemented CGA to judge feasibility of chemotherapy for unselected patients with epithelial ovarian cancer aged 70 years and older. In this chapter the main findings are discussed in relation to (recent) literature.

Main findings and comparison with literature

1a. Colorectal cancer (stage I-III): surgical treatment and complications in relation to comorbidity and age.

Almost all patients with colon or rectal cancer stage I-III underwent surgery regardless of age or comorbidity at time of cancer diagnosis.(Chapter 2.1) Surgery seems inevitable in these patients to treat and prevent intestinal obstruction. Furthermore, it often (immediately) relieves cancer-related symptoms. Resection rates in our study remained high despite concomitant disease(s): 99 % of patients with colon cancer and two comorbid conditions and 95 % of patients with rectal cancer and

co-existent comorbidity underwent surgery. A population-based audit in the UK also showed high resection rates (92-96% of patients with locally resectable tumours underwent surgery, no adjustment for age).[2] Few studies have assessed the effect of comorbidity on the management of patients at population level. In a review study the rate of no operation differed among age groups: 6% among patients 65-74 years old to 21% in those over 85 years old.[3] Differences were thought to be age-related but in this review the effect of comorbidity on resection rates could not be determined. A recent French population-based study showed substantially lower resections rates (76% among patients <75 years and 66% among patients ≥75 years) and comorbidity influenced selection for surgery only among younger patients.[4] Other, unknown factors than concomitant disease(s) seemed highly relevant for withholding surgery in French elderly. The French study merely included patients who had surgery with curative intent. Our study included all patients who had undergone staging procedures. As resection rates are barely affecteded by selection of relatively fit elderly, these group of patients is very appropriate to study the influence of age and comorbidity on major surgical procedures and postoperative complications.

In our study, postoperative mortality rates (within 30-days) in colorectal cancer patients were significantly higher in older patients (Chapter 2.1), increasing from 2-3% among patients aged 50-64 years to 13-19% among patients aged 80 years and older. In a review on colorectal surgery (emergency and elective surgery), 3 % postoperative mortality in the age group below 65 years, 8.6 % in the 75-84 year age group and 19.4 % among patients over 84 years old were reported.[3] Our population-based results are in line with these results. However, data included in the review were obtained 15 to 30 years ago. Implementation of pre-operative radiotherapy and total mesorectal excision (TME)-technique did not lead to reduction of 6-month mortality rates (15 to 18%) in patients over 75 years diagnosed between 1990 and 2002.[5] Despite surgical progress, 30-day and 6-months postoperative mortality rates remained high, suggesting that non-surgical issues (i.e. comorbidity, functional status, sarcopenia,malnutrition) are key-issues. These issues can not always be taken into account for decision-making for surgery, as surgery is often inevitable in colorectal cancer patients. Therefore, trials with interventions concerning additional pre-operative preparation or postoperative non-surgical care are needed.

Additionally, we evaluated among patients with mobile (pT2-T3) rectal cancer the association between age and comorbidity on the one hand and treatment-related complications on the other hand using ACE-27, an index on severity of comorbidity. (Chapter 2.3) Increasing age was not associated with an increased postoperative complication rate among patients aged 75 years and older. In a multivariable logistic regression analysis severe comorbidity and pre-operative radiotherapy were, among others, associated with higher complications rates. The post-operative complication rate and 30-day mortality were increased in case of presence of severe comorbidity

compared to patients without comorbidity (respectively 58% and 10% versus 43% and 3%). COPD, diabetes and cerebrovascular disease led to significantly increased postoperative complication (59-62%) and 30-day mortality rates (11-14 %). Our group earlier showed that both age and comorbidity were associated with higher complication rates among surgically treated patients with rectal cancer.[6] Other studies also have shown that concomitant diseases were significantly associated with postoperative complications after surgery for rectal cancer, mainly among patients aged 70 years or older.[3, 7, 8]

The Colorectal Collaborative Group underlined the increased incidence of postoperative respiratory problems in the elderly after colorectal surgery (5% of patients younger than 65 years, increasing to 15% in the 85+ year age group), low rates for cardiovascular events (1% of patients younger than 65 years, 4% in the 85+ group), but did not relate complications to pre-surgical comorbidity.[3]

In a Dutch population-based study, especially COPD predicted surgical complications (73% versus 46% among patients without COPD) after surgery for rectal cancer, and pneumonia among patients with colon cancer (18% versus 2% in non-COPD patients).[9]

In chapter 2.3 we described that COPD was not only associated with systemic complications and postoperative death but also with local problems after rectal cancer surgery (21 % of elderly with COPD developed pelvic abcesses or anastomotic leakage). The impact of COPD on postoperative complications, both local and systemic, seems a consistent finding. A more than 3-fold increased risk on local infections occurred with corticosteroid use.[10] In a review on non-cancer, abdominal surgery and concurrent use of steroids led to an increase of both postoperative complications and infectious complications.[11] The question arises whether the benefit of presurgical corticosteroid use on pulmonary disease is essentially nullified by drawbacks on local infection control or anastomosis related problems. Underlying pathofysiological processes of the COPD or steroid-effect (hypoxygenated tissue, insufficient immune response with a (subsequent) lack of signs and symptoms?) require clarification.

1b. Colorectal cancer: survival in relation to comorbidity and age

Age > 65 years, comorbidity and specific comorbid conditions as COPD or cardiovascular disease were independent (after adjustment for stage, gender and histology) prognostic factors for survival after surgery for colon cancer and rectal cancer, stage I-III. (Chapter 2.1) Diabetes was associated with decreased overall survival after colon surgery. Several mechanisms may explain the impact of comorbidity on overall survival: increased risk of death due to the concomitant disease itself, inferior treatment of the comorbid condition after cancer diagnosis, inferior anti-cancer treatment or a

higher rate of tumour-related complications with subsequent mortality.
Other population-based studies also demonstrated a negative effect of comorbidity on survival.[6, 12-18]

None of these studies, including our study, took the effects of dependence on (instrumental) activities of daily living or geriatric syndromes on survival into account. A recent population-based study among elderly patients with colorectal cancer showed that functional limitations and geriatric syndromes at time of cancer diagnosis were associated with early death in contrast to comorbidity.[19] It was postulated that comorbidity was not associated with decreased survival as long as functional limitations or geriatric syndromes were absent. Also, dependency and geriatric syndromes may guide clinicians to favor less aggressive treatments, although consequences on survival in colorectal cancer are unclear.

2a. Short-course pre-operative radiotherapy in rectal carcinoma (T2-T3, N0-2,M0): influence of age, gender and comorbidity on chance of receiving radiotherapy and development of complications.
Chapter 2.2 describes factors that influence the use of pre-operative radiotherapy (5x5Gy) for patients with mobile rectal cancer. Both among young and older patients the presence of multiple co-morbid conditions (Odds ratio (OR) 0.4 and 0.3 respectively) was associated with withholding pre-operative radiotherapy. Diabetes was associated with a significantly decreased use of radiotherapy (OR = 0.5) among elderly patients. High age (80 years or older) significantly lowered receipt of radiotherapy (OR = 0.5), whereas men received radiotherapy more often than women (OR=2.0).
In general, factors that predicted life expectancy were also associated with the decision to withhold preoperative radiotherapy, with the exception that women received radiotherapy less frequently compared to men, although they survived longer. Non-utilization of radiotherapy in rectal cancer with increased age and female sex was also reported in Australian and US population-based studies.[20, 21] In a German multicenter trial in rectal cancer, the odds of receiving radiotherapy was also almost twice as high in men as in women.[22] In our study male gender was also associated with a significantly higher complication rate. In literature, data on gender disparities show a better posttraumatic immune competence in women, clinically relevant in case of abdominal or rectal cancer surgery.[23-25] Others concluded that female anatomy favours TME-technique and subsequent survival.[26] Unless refusal by patients, we cannot find a rationale for underuse of radiotherapy in women.
Within our study we sent out a questionnaire to gain insight into the surgeon's decision to propose pre-operative radiotherapy to patients or not. Size and localization of rectal carcinoma predominantly determined the decision to refer for radiotherapy (less referrals in case of more proximal tumours, which are treated more frequently with low anterior surgery). Within the

decision-making process, comorbidity and age were considered less important factors. Half of the respondents mentioned that actual presence of two or more concomitant diseases or age above 80 years influenced their decision to propose radiotherapy. Unfortunately we did not include gender in the questionnaire.

Besides male gender and severe comorbidity, pre-operative radiotherapy was associated with higher postoperative complication rates in our study.(Chapter 2.3) A recent review on postoperative complications following surgery for rectal cancer showed a local infection rate of 7%, a 30-day mortality of 2% and an anastomotic leakage rate of 11%.[27] In our study, including non-selected patients aged 75 years or older, showed higher complication rates, especially in the group that received radiotherapy: local infection in 14% versus 7% in the non-irradiated group, anastomotic leakage/intrapelvic abcess in 16% versus 10%; Nevertheless, 30-day mortality rate was equal (8%) in both groups. The review included mainly trials and cohort-studies, and only few population-based data. Pre-operative radiotherapy was not related to anastomotic leakage rate or 30-day mortality. Maybe selection of fit patients is underlying at the differences, otherwise factors on quality of care may be responsible for the different results between the review and our study. The results in the review are comparable to ours among elderly without comorbidity.

The discrepancy between data gathered from trials and cohort studies on the one hand and population-based data in elderly patients on the other hand is striking and underlines the importance of including patient characteristics to benchmark surgical results and complications rates.

2b. Short-course pre-operative radiotherapy in rectal carcinoma (T2-T3, N0-2,M0): influence of age and comorbid conditions on prevention of local recurrent disease.

In chapter 2.2 we showed that overall survival among patients with rectal carcinoma decreased with age (3 –year survival was 50% among patients over 80 years old, 72% in the age group 70-79 years) and especially patients with two concomitant diseases or COPD showed low survival rates (respectively, 48% and 39% after 3 years). As the main objective of short course (5x5Gy), pre-operative radiotherapy is to decrease the risk of local recurrent disease, mostly within 3 years, one can argue that the time to benefit from radiotherapy may be too short for a substantial proportion of elderly patients. In chapter 2.3 local recurrence rates among patients ≥ 75 years old were compared, between those who received pre-operative radiotherapy and those who received surgery alone. Local recurrence rate was 2% in the group with pre-operative radiotherapy versus 6% in the group with surgery alone. In patients without radiotherapy and alive after 1 year, the recurrence rate was 8%. In multivariable analysis the Hazard Ratio(HR) for recurrent disease was 0.2 for radiotherapy versus no radiotherapy. Thus, regardless the drawbacks of pre-operative radiotherapy in rectal

cancer, prevention of local recurrent disease is also achieved among elderly with high prevalence rates of concomitant diseases. Therefore, withholding radiotherapy seems justified when patients do not accept its disadvantages or the increased 'number-needed-to-treat' that may change the inconvenience/benefit ratio for individual patients. Withholding pre-operative radiotherapy seems also justified when the estimated survival of an individual patient seems less than two years. If the latter is the case one can argue that alternative (=besides surgery) treatment options are preferred, for instance a combination of external beam radiotherapy and brachytherapy.[28-30]
Point of interest in our study (chapter 2.3) are also the low local recurrence rates both in the irradiated (2%) and the non-irradiated group (6%). In literature, recurrence rates of 11-17% are reported in patients without pre-operative radiotherapy and 4-6% in pre-operatively irradiated patients, which is also depending on the circumferential resection margins achieved.[31-33] Low recurrence rates in our study may be the result of high quality TME-surgery, but other explanations should also be taken into account: local recurrences may remain asymptomatic in our elderly patient group, growth rate of residual tumour may be decreased at high age or recurrent disease is not always recorded in clinical records (for instance as a general practitioner solely treats a patient).

3. Non-small-cell lung cancer (NSCLC) and its surgical treatment in relation to age and comorbidity.
In contrast to colorectal cancer, surgery for elderly patients with stage I-II NSCLC is performed in a more selected group as patients are older: 88% of patients in age group 50-64 years underwent surgery, compared to 67% of patients aged 65-79 years and 15% of patients over 80 years. (chapter 2.1) Resection rates were lower when COPD, diabetes or cardiovascular disease were present. Older patients (with comorbidity) received more often radiotherapy instead of surgery. These data are in line with other studies.[34-37] Probably surgery in elderly lung cancer patients is considered a high risk intervention, leading to a choice for less aggressive, alternative treatments. Radiofrequency ablation in stage I-II NSCLC is an alternative treatment to surgery with comparable survival in non-randomized studies on elderly patients.[38, 39] Especially among patients with COPD stereotactic ablative radiotherapy is advocated nowadays and potentially superior to best supportive care.[40, 41]
Nevertheless in selected “old but very fit” octogenerians outcome of surgery is reported comparable to younger age groups.[42-44] Probably strict selection criteria are used, as less postoperative mortality and comparable length of hospital stay are reported in the aged versus younger groups.[45]
Comorbidity, measured by Charlson’s co-morbidity scores (3 to 4), was highly predictive for major complications.[43] In our study 50 % of patients between 50 and 80 years developed postoperative complications, although postoperative mortality rate was only 3 to 5% in this age group. This rate is comparable to British and Norwegian studies.[45, 46] In the southern region of the Netherlands, 25% of

patients aged over 80 years and diagnosed between 1995 and 2004, died postoperatively (chapter 2.1). In logistic regression analyses the risk of developing postoperative complications was not significantly related to any specific comorbid disease present at time of diagnosis.

4. Breast cancer and its surgical treatment in relation to age and comorbidity

Among patients with stage I–III breast cancer younger than 80 years, 99% underwent surgery, compared with 81% of those aged 80 or older.(Chapter 2.1) Among patients undergoing surgery, the application of breast conserving surgery decreased from 60% of those aged 50–64 years to 23% of patients aged 80 years or older. For those aged 65 years or older, the resection rate appeared to be lower when comorbidity was present, especially in case of cardiovascular diseases or diabetes. Axillary dissection for those undergoing breast conserving surgery and adjuvant radiotherapy also decreased in presence of comorbidity. With the restriction that we analyzed patients with known stage of cancer (see paragraph 1a), these trends are comparable with other studies.[47, 48]

Remarkable is a recent US study that showed an increase in breast conserving surgery in patients over 80 years old and also reported a 2.6 increased risk of dying from breast cancer in patients over 90 years compared to patients aged 67-70 years old.[49]

Complications after surgery for breast cancer (low risk surgery) did not increase by age, comorbid condition or type of surgery (Chapter 2.1). This is comparable to other studies.[50, 51] Even in the oldest old (80+ years) predominantly minor postoperative complications (16%) were present in our study. A recent German, observational study reported no mortality but 20 % postoperative complications in patients ≥80 years old (qualified as “minor”, half of them being wound problems and obesity being the only independent factor predicting complications).[52]

5a. Surgery combined with chemotherapy in ovarian cancer (FIGO stage II-III): Influence of age and comorbidity on receiving treatment.

Optimal management of patients with advanced ovarian cancer includes aggressive cytoreductive surgery combined with platinum-based chemotherapy.[53] In chapter 2.6 we described the effects of age and co-morbidity on the adherence to treatment guidelines and prognosis in women with ovarian cancer (FIGO stage II en III). In multivariable analyses, age, presence of comorbidity, FIGO-stage and year of diagnosis were independent predictors of receiving combination therapy. In time, the proportion of patients over 70 years old who were treated with both surgery and chemotherapy doubled to about 60%.

Furthermore, in our study 89% of patients younger than 70 years and 61% of those over 70 years old underwent surgery. Among patients < 70 years, chemotherapy use ranged from 92% in patients

without comorbidity to 86% in those with concomitant disease. Among patients aged ≥ 70 years, this proportion decreased from 72% in patients without comorbidity to 54% in those with comorbidity. Compared to our results, a higher proportion of elderly women received surgery in US multicenter and population-based studies (more than 80% of patients up to 80 years old received chemotherapy, with a rapid decline to 43% in patients at higher ages).[54, 55] Comorbidity did not affect the probability of undergoing surgery, combination therapy, likelihood of treatment adjustment or grade 3-4 toxicities. Age was associated with a higher incidence of these toxicities only in women over 80 years old who received combination therapy.[54] In our study complication rates were not available. Other retrospective studies (community-based and single center data) reported no increase of hematological toxicity or postoperative complications with increasing age.[56-58] It is worth mentioning that these authors explicitly qualified their study populations as `fit`. A German trial showed that toxicity rate was equal among elderly and younger patients, except for febrile neutropenia (5% versus <1%).[59] Delayed initiation and early discontinuation were common in elderly treated with chemotherapy and associated with early mortality.[60] A recent, prospective study showed a significant increase of chemotherapy induced toxicity in patients aged over 70 years and treated with carboplatin-paclitaxel (6% febrile neutropenia and 36% grade 2-3 neuropathy).[61] Reduced doses of both carboplatin and paclitaxel led to significantly less toxicity and delays in treatment schedules, while no difference in progression-free or overall survival was observed.[62] The above mentioned studies focussed on patients aged 70 years and over, but included primarily patients up to 75 or 80 years. A single center study among patients over 80 years old showed higher toxicity and discontinuation rates (73% developed grade 3-4 toxicity, only 51% completed at least 6 cycles).[63]
In chapter 3.2, we showed that 40% of the patients did not complete chemotherapy in our prospective pilot study on women aged 70 years and over. Non-completion of chemotherapy was associated with the results of assessments on vulnerability. A high proportion (77%) of patients who were qualified as frail, died or showed a decline on functional status within one year (compared to 35% in the non-frail group). Nevertheless, at least a quarter of the patients who were qualified as "vulnerable or frail" did complete the full treatment. Both our results and those of other studies underline the complexity in decision making with respect to chemotherapy in elderly women with ovarian cancer. To non-frail patients treatment should be offered in accordance with the guidelines. Frail patients should be informed explicitly on additional risks they face and adapted doses are suitable in these patients. Unfortunately, no assessments are available that predict the lack of treatment benefits at an individual level.

5b. Surgery and adjuvant chemotherapy in ovarian cancer (FIGO stage II-III): influence of age, chemotherapy and comorbidity on survival.

In our study in patients diagnosed between 1995 and 2001, 3-year overall survival was worse for patients aged 70 or older (22%, compared to 51% for younger patients, chapter 2.6). For patients over 70 years old without co-morbidity, 3-year overall survival was 49% for those who underwent standard treatment (cytoreductive surgery and platinum-based chemotherapy) and only 16% for those who did not. Age over 70 years old was an independent prognostic factor in our study (compared to age < 70 years). A recent study on advanced ovarian cancer showed that 3-year survival rates declined with age: from 47% in patients aged 70-74, to 32%in patients ≥80).[64] Median survival for patients over 80 years old varies greatly depending on the study (19 -36 months).[54, 63-65] After adjustment for age, stage and comorbidity, the risk of dying within 3 years was double in our study for patients who underwent surgery alone compared to patients who underwent surgery and chemotherapy. An American multicenter study concluded that in patients aged 70 years and older survival primarily depended on undergoing surgery and was not associated with comorbidity, age or different regimens/components of chemotherapy. Principally, survival is determined by the extent to which resection is achieved and residual disease remains.[64, 66] Residual disease affects survival even more in patients over 80 years old compared to younger age groups.[64] Therefore, selection bias may have contributed to (the size of) the beneficial effect of combination therapy versus surgery alone in our study. We took age and comorbidity into account, but were not able to adjust for other variables as nutritional, functional or social-economic status. Prior studies stated that dependency on functional status led to a more conservative approach on patients with ovarian cancer.[67, 68] Comorbidity did not predict survival, probably related to the fact that ovarian cancer (with or without therapeutic interventions) is a lethal disease; likewise, in a population-based study, comorbidity was also not associated with survival among patients with small cell lung cancer (limited disease, chapter 2.5).

Retrospective single center studies showed that elderly, even octo- and nonagenerians, can tolerate cytoreductive surgery in ovarian cancer at the cost of minimal postoperative morbidity.[60, 69, 70] Limited 30-day mortality (5-10%) was reported in patients over 80 years old, both in US and Dutch population-based studies.[71, 72] A hospital based study (80% had performance score <2, 87% had concomitant diseases) revealed that drawbacks among patients over 80 years old were not limited to 30 days postoperatively, as 60-day mortality rate after surgery was 20% and only 40% of the women was discharged directly from hospital to home.[63]

Interpreting our data and literature, some recommendations can be made for clinical practice: until the age of 80 years, combination therapy should be offered to women with ovarian cancer (FIGO stage II-III), unless women are qualified as “frail”. In patients over 80 years old optimal cytoreductive

surgery remains the cornerstone of therapy but chemotherapy should be restricted to the fit patients and reductions of initial doses are probably justified in this age group.

6. Chemotherapy in elderly patients with small-cell lung cancer (limited disease): influence of increasing age and comorbidity on tumour-related treatment, its toxicity and outcome.

In chapter 2.4 we described patient characteristics that were associated with withholding chemotherapy in patients over 75 years old. Increasing age led to changes in treatment policies: use of chemoradiation decreased from 23% in patients aged 75-79 years to zero in those aged ≥ 85 years. Women received chemoradiation less frequently compared to men (12% versus 22%), while the proportion of patients who received only chemotherapy remained stable at 40%. Most common motives for not receiving chemotherapy were refusal by the patient or family (29%) and a combination of high age, comorbidity and poor PS (30%). Other studies underlined a decreased acceptance of toxic chemotherapy in elderly patients if survival was expected to be less than 6 months.[73, 74] Also, non-utilization of anti-cancer therapy following multidisciplinary meeting was associated with the preferences of elderly patients.[37]

Although only relatively fit elderly were selected for chemotherapy or combined chemoradiation, 70% of them needed adaptations of these regimen and about 40% received fewer cycles of chemotherapy than planned. Adaptations were not associated with age or PS but rather with the presence of comorbidity. However, the number of cycles received was not associated with comorbidity. Previous studies have also reported less aggressive treatment in patients over 70 years old (dose reductions, less frequent use of chemotherapy or radiotherapy).[75-79]

To put the low proportion of patients receiving chemotherapy as well as the high prevalence of toxicities and outcome into perspective, we conducted an additional population-based study, also on elderly (≥ 75 year) with limited SCLC. (Chapter 2.5) With the rise of age significantly less patients received at least 4 cycles, from 34% of patients aged 75-79 to 15% of those aged 80 years or older; also patients with PS 3-4 less often received at least 4 cycles (5%). In a post-hoc analysis among patients priorly included in trials, 69% of the patients (aged 70-80 years) were able to complete pre-planned chemotherapy.[80]

In our study hematological toxicity (24%) and early death (19%) were the most common motives for discontinuation of chemotherapy. Grade 3 or 4 toxicity developed in 69% of the patients but decreased with age (from 81% in the age-group 75-79 to 56% in those aged 85 and older). This probably reflects a more strict selection in the very elderly. Previous studies reported inconsistent findings on toxicity levels for elderly patients with SCLC.[79, 81-83] We argue that selection, partly due to non-identical eligibility criteria in trials, induces variability on incidence rates for toxicities.

Median survival of all patients was 7 months but became 12 months for those who completed at least 4 cycles. For those who did not complete at least 4 cycles or did not receive chemotherapy at all, median survival times were 4 and 3 months respectively. Besides number of cycles actually received, age and performance score independently determined survival. Eventually 92% of all patients died of lung cancer. One should keep in mind that SCLC can be very sensitive to chemotherapy or radiotherapy. Relevant amelioration of symptoms or even of the general condition are described after (a few cycles of) chemotherapy.[84, 85]

It seems that in elderly with small-cell lung cancer (limited disease) the benefit gained by few patients is paid for by a large group of patients who will not achieve the benefits. As the prevalence of toxicities decreased in patients older than 80 years, a more stringent selection of vital patients might have brought disadvantages more into balance. We postulate that in case of combination of highly toxic therapy and lethal disease, physicians should select more closely on the remaining strengths of patients. A search for the brisk or vigorous elderly may be more suitable than to rely on signs of frailty. Of course, longitudinal research is needed to create a clinically useful operationalization of "brisk elderly", also taking into account improvements by innovating health care.

7. Comprehensive Geriatric Assessment (CGA) in oncology

In our review on comprehensive geriatric assessment we concluded that, in oncology, CGA was predominantly used to identify prognostic factors on survival and tolerability of anti-cancer treatments.(chapter 3.1) This contrasts to the key-features of CGA in general medicine, in which a search for relevant information on medical, mental, functional, social and pharmacological domains, is combined with an analysis of this information by a geriatrician-led, multidisciplinary team that subsequently individualizes goals and an integrated intervention-plan is implemented. Despite the limitation that CGA in oncology often does not include all of these key-features, CGA seems valuable to describe older cancer populations in studies, i.e. to determine whether results can be translated to the heterogeneous group of elderly patients. Furthermore, information obtained by CGA seems, additional to chronological age and performance score to estimate risks on adverse effects of anti-cancer treatment. Functional dependency, cognitive and emotional functioning and polypharmacy appeared the most relevant domains to explore in relation to tolerability of chemotherapy. Limitations on IADL-functioning and depressive symptoms at time of diagnosis were most consistently found to be predictive with regard to survival. Recently, US and Canadian multicenter studies emphasized that especially failure on multiple domains was associated with poor treatment tolerance and decreased survival.[86-88] Despite these data, the lack of intervention-studies limits

conclusions about the value of CGA in oncology.(chapter 3.1)

After our review was published in 2007, several prospective studies have reported on geriatric assessment techniques in the oncology setting. In these studies limitations in ADL or IADL led to an increased risk of non-completion of chemotherapy in patients with a variety of cancer types.[89, 90] Also malnutrition, impaired cognition, dependency on ADL and failure on multiple domains were shown to predict early termination of chemotherapy in groups of patients with solid tumours.[90-92] Severe comorbidity and, again limitations on IADL, were CGA-components that were most predictive for survival in malignant lymphoma.[93] In thoracic surgery, mainly among patients with lung cancer, CGA revealed information on ADL and cognition that was highly predictive for postoperative complications.

Based upon CGA, including parameters as functional status, concomitant disease(s), mental status, malnutrition, age and presence of geriatric syndromes, a selection to frail and non-frail patients can be made.[94-96] In the frail group, response and survival after chemotherapy was decreased compared to the non-frail group.[94, 95]

In patients needing oncological surgery a CGA-based categorization into frail and fit patients predicted postoperative complications (76% in the frail group versus 46% in the fit group) in patients with colorectal cancer.[96] Furthermore, severe complications were almost seven-fold increased in the frail group (2% versus 13%). Recent studies have shown that the proportion of patients in whom changes in chemotherapy were made based upon CGA, varied from 21% to 49%.[90, 97, 98] Furthermore, unidentified medical problems were present in about 70% of the patients.[86, 92]

Special attention is needed for the way CGA is implemented into oncological care: a `mini-CGA´ with basic information on multiple domains led to adaptation of treatment regimens in 47% of the patients with gastro-intestinal or lung cancer, and a subsequent full CGA did not lead to further adaptations.[92] Others reported that the surplus value of CGA in elderly cancer patients was more prominent in those patients for whom the oncologist could not instantly decide upon. (83% adaptations versus 4% in other cases).[86]

In our pilot-study on geriatric assessment prior to chemotherapy in elderly patients with ovarian cancer, we dichotomized patients into a fit and unfit group according geriatric assessment(GA) scores.(Chapter 3.2) GA-Unfit, based upon pre-treatment deficits on ADL, IADL, cognition and a comorbidity index, was associated with failure to complete chemotherapy, early mortality and ongoing functional decline. Also, performance score(PS) =2 and results on a physical performance measure (Timed Up-and-Go test= TUG) were associated with early discontinuation of chemotherapy and decreased survival. In our study, positive and negative predictive values were higher for TUG than for PS when GA was used as golden standard. Previous studies found no correlation between PS and scores on comorbidity indices.[99, 100] Reports on the correlation between (I)ADL and PS showed

divergent results.[99-101] In our study, all patients with PS 2 were independent or almost independent on ADL and only a few were classified `GA-unfit´ based upon their comorbidity. Maybe our study-group was more homogeneous and this might have influenced the differentiating capacity of geriatric assessment techniques. Physical performance tests seem sensitive tools to measure mild functional decline without the ceiling-effect inherent to ADL- and IADL-tasks.[102] Others emphasized the predictive capacity of these tests for mortality and their potential role to determine which patients need a full CGA.[103-106] To our knowledge the role of physical performance tests to select brisk elderly patients for interventions with substantial risk, has not yet been studied.

The question arises whether a search for data on multiple domains, focused on patient characteristics as ADL-, IADL-dependency, nutritional status, cognitive and psychological functioning and medication use, is sufficient determining "automatically and upfront" an individualized oncological treatment plan. It is clear that CGA reveals information on multiple domains, relevant to estimate individual risks on early mortality and treatment tolerance both in medical as in surgical oncology. CGA enables physicians to qualify oncological patients as frail based upon their characteristics.

Going back to the introduction of this thesis and the determination of "frailty" by its consequences made up by Ferucci et al.[107] CGA in oncology indeed predicts an increased risk on negative health outcomes and on harmful side-effects or complications, when interventions are employed. A third denominator of frailty: "dangerous fluctuation of a patients health status when a minor medical condition occurs" is to our knowledge not studied in oncology. One should also keep in mind that the concept of "frailty or vulnerability" is not a panacea for answering the difficult questions of diagnosing and treating elderly cancer patients with high rates of comorbid conditions. Thus, Hippocrates' rule: `first, do not harm…', remains the mainstay of every clinical judgment and decision. Originally, operationalizations on frailty were made up in studies among community dwelling elderly and no specific diseases were evaluated.[108-110]

In oncology, concepts of frailty or markers of frailty are introduced within the process of clinical decision making, sometimes concerning a specific type of cancer.[107, 111-113] Also, frailty indices i.e. the Groningen Frailty Indicator and the Vulnerable Elderly Survey-13, were introduced (the issue of validation of these indices and their potential role as prescreening tool was not addressed within the studies in this thesis).[114, 115] Yet, it is unclear how to apply frailty markers using evidence-based cut-off points in clinical decision making. Can we create a universal cut-off point in frailty tests? Theoretically, both the characteristics of specific type or stage of a cancer and the interventions are numerous. As interventions may differ from a minimal noxe to a life-threatening intervention, one can hardly expect that a uniform cut-off point will emerge. Nevertheless, these issues have to be studied.

The implementation of CGA or one of its elements into oncological care and decision-making is not evident. A task force of the International Society of Geriatric Oncology on CGA put a two-step approach forward.[116] Two different ways of implementation can be distinguished: the first focuses on a prescreening step for vulnerability before treatment or invasive staging.[117, 118] Physical performance measures and frailty indices can be used as prescreening tools. As no vulnerable patient should be missed by this working method, negative predictive value of these tools need to be sufficient. If a patients scores `positive´ on the prescreening tool, then a full CGA is performed. The second way of implementation aims at gathering basic information on multiple relevant domains (ADL, IADL, nutrition, cognition, emotional functioning, social support, mobility, foregoing delirium and medication use) in every elderly cancer patient. This step can be performed as a nurse-led module in clinical paths.[119] Examples of this working method are “Mini CGA”, “Minimum Data Set” and “Geriatric Navigator”. [92, 120, 121] If case complexity is present (i.e. multiple domains are affected, or geriatric syndromes are present) then a full CGA is employed. The usefulness of both approaches needs to be assessed and should then lead to new working methods or hybrid forms in between these methods. The question arises whether we have to stage the aging process, the burden of comorbidity, impairments and frailty characteristics of every senior regardless the type of cancer and intended intervention?

Future perspectives.

Literature on cancer treatment in the elderly is dominated by reports on equal outcomes in studies that compare (relatively) fit elderly with younger patients on the one hand and a search for frailty markers to properly select elderly patients for oncological therapies in every day practice. Both issues require a continuing scientific interest. From a clinical point of view, it is expected that points of interest will be directed at the various types of cancer and interventions. Also the impact of specific combinations of comorbid conditions and their controllability should be subject of study. As patient preferences seem to change with age – roughly, elderly patients accept less toxicity for an (un)known benefit or expect a greater benefit for a known effort- studies that include patient preferences are valuable. Especially, if standard therapies are highly toxic or not frequently administered in elderly patient groups, patient preferences may guide to alternatives that indeed are administered and benefit elderly cancer patients.

Eventually, it would not be sufficient to describe patient characteristics within the heterogeneous group of elderly patients, nor to have adequate selection techniques. Studies should also focus on interventions that can alter the outcomes (decreased toxicity or complications, functional outcome or survival) of a specific treatment. For example, high 6-months mortality rates after surgery for rectal cancer and ovarian cancer in the elderly demand for new initiatives on pre-, per- and postoperative care. Reflection is also needed on the appreciation of mortality (by patients) as a valid endpoint to assess preferred treatment strategies, also functional outcomes and palliative techniques may be endpoints that motive innovation.

Furthermore, in case of high rates of non-completion of planned therapy and high incidence of complications, a search for the vulnerable elderly cancer patient may not be appropriate, because most of them are relatively fit (i.e. in case of small-cell lung cancer). In these situations a search for the brisk or vigorous elderly may be more suitable than a search for frail elderly. Likewise frail, these terms have a multidimensional meaning, including quick, bold, courageous, firm, alert and bustling features. Obviously, also brisk features need to be operationalized and studied in clinical practice.

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Chapter 5

Summary/samenvatting

Dankwoord

Curriculum vitae

Other publications by the author related to this thesis

Chapter 5: Summary

Heterogeneity within groups of cancer patients is usually described in terms of dissemination and histo-pathological data. In general, health status of elderly patients is determined by both patho-physiological processes and many other patient characteristics (i.e. concomitant diseases, functional and mental status, need for social support, nutritional status, polypharmacy). Also, these characteristics are often affected to a more variable extent compared to groups of younger patients. As a consequence, heterogeneity in health status is increased in groups of elderly cancer patients compared to younger groups. Clinical studies and trials often use eligibility criteria that contrast with patient characteristics as seen in everyday practice, and their results are often attributed to "fit" elderly. Therefore, studies that reach the "real life" spectrum of fit and frail elderly are needed to determine the impact of patient characteristics and age per se on cancer care utilization and outcomes of cancer care (survival, complications). Cancer registries are known to have reliable population-based data on diagnosis of cancer, received treatment(s) and a number of patients characteristics and outcome(s). Therefore, population-based studies can give a unique "real life" insight into the heterogeneity of both patient groups and treatment choices or outcome(s) of cancer therapies. To weigh out morbidity, patients characteristics and preferences, comprehensive geriatric assessment (CGA) is advocated to assist in choosing a realistic and individualized intervention plan. A review on studies that administered CGA into oncological care is part of this thesis. Furthermore a prospective pilot-study is described that evaluated the additional value of geriatric assessment techniques in patients with ovarian cancer.
The aims and main conclusions of the studies, that were included in this thesis, are summarized below.

Chapter 2 describes population-based studies on the effects of multi-morbidity, gender and age at time of cancer diagnosis in relation to treatment choice, complications/toxicities and survival in elderly patients with colorectal, (small-cell and non-small-cell) lung, breast and ovarian cancer.
When surgery is inevitable for prevention of life-threatening/life-limiting complications, relief of symptoms and/or cure, as in colorectal cancer, surgery is applied regardless of age

or comorbidity. Among these `unselected' surgically treated patients, both comorbidity and increasing age are associated with decreased survival and increased postoperative mortality and complication rates. **(chapter 2.1)** When alternative anti-cancer strategies are available or surgery is regarded as high risk-surgery, both age and comorbidity are associated with lower resection rates (as in stage I-II non-small cell lung cancer or among patients over 80 years old with stage I-III breast cancer) or with adaptations in surgical interventions (among patients aged 65-79 year with stage I-III breast cancer).

In **chapter 2.2** we describe the effects of age and comorbidity on utilization of pre-operative radiotherapy (5x5Gy) and survival in patients with mobile rectal cancer. Withholding radiotherapy depended on age only in patients aged 70 years and older. In general, factors that predicted life expectancy were also associated with the decision to withhold preoperative radiotherapy, with the exception that women received radiotherapy less frequently compared to men, although they survived longer. With regard to survival in patients over 70 years old, the most relevant patient characteristics were higher age, male gender, COPD and presence of at least 2 concomitant diseases.

Chapter 2.3 describes the dilemmas in elderly patients (≥ 75 years) with rectal cancer (pT2-T3) who are either treated with short course, pre-operative radiotherapy or just with surgery alone. Compared to prior studies, our population-based data on elderly patients revealed low local recurrence rates, both in irradiated (2%) and non-irradiated patients (6%). Severe comorbidity, COPD, diabetes mellitus and cerebrovascular disease were associated with high postoperative complication rates (60%) and a 4-fold increase in 30-day mortality rates (10-14%). Postoperative complications developed more frequently in irradiated patients but 30-day mortality rates were equal in the irradiated and non-irradiated patient groups. Comorbidity predicted 5-year survival, but pre-operative radiotherapy did not. However, comorbidity and its influence on survival did not neutralize the preventive effect of pre-operative radiotherapy on local recurrences. As we found low recurrence rates, our results even increase the clinical dilemma to administer radiotherapy or not. Both the estimation of life-expectancy and risk of complications in the individual patient and a discussion on patient preferences, seems the most plausible way to deal with this dilemma.

In **chapter 2.4 and 2.5**, we evaluated which patient characteristerics were associated with adherence to treatment guidelines, motives for non-adherence, completion of therapy and

survival in elderly patients (≥ 75 year) with small-cell lung cancer (SCLC). The proportion of patients who received chemoradiation was lower among the elderly, while the proportion of patients who received chemotherapy alone did not differ between age groups (at 40%). Most common motives for not receiving chemotherapy were refusal by the patient or family (29%) and a combination of high age, comorbidity and poor performance score (30%). A substantial proportion of patients (40%) received fewer cycles than planned. In patients with limited SCLC, the number of cycles received was associated with age but not with comorbidity. Grade 3 or 4 toxicity developed in 69% of the patients but decreased with age, probably reflecting a more stringent selection for chemotherapy in the very elderly. Finally, median survival of the patients who received less than 4 cycles chemotherapy was about equal to patients who received best supportive care (4 versus 3 months). Nevertheless, completion of chemotherapy was associated with an increased median survival (12 months). Considering these results, we argue that a selection focusing on the "brisk" elderly may be helpful to bring benefits and disadvantages more into balance.
In chapter 2.6we ascertained in time an increased use of combination therapy (combination of cytoreductive surgery and chemotherapy) in women ≥ 70 years with ovarian cancer (FIGO stage II-III). Age above 70 years and comorbidity were predictors of non-adherence to treatment guidelines. Patients over 70 years without concomitant disease had a 3-year survival rate of 49%, once they received standard treatment (versus 16% if this treatment was omitted).
Our population-based studies underlined the importance of patient characteristics on treatment choices, complications and outcomes in elderly cancer patients, although the influence of patient characteristics varies according to type of cancer and intervention.

In general medicine, Comprehensive Geriatric Assessment (CGA) is viewed as an appropriate tool to analyze elderly patients and develop a coordinated and individualized treatment plan in elderly patients. In 2007, our review on the impact of CGA in oncology **(chapter 3.1)** showed that CGA was predominantly studied to identify prognostic factors on survival and tolerability of treatment. This limitation contrasts to the use of CGA in geriatric medicine as individualized goal setting and interventions are inherent components of CGA. Although in oncology previously unknown health problems were identified by CGA in a majority of patients, interventions upon these problems were only scarcely studied. Nevertheless, additional to chronological age and performance score, information obtained by CGA seems to estimate survival and risks on adverse effects of anti-cancer treatment. Despite these data, the lack of intervention-studies limited conclusions about the value of CGA in oncology. Additionally, a small pilot study on geriatric

assessment techniques (GA) and their prediction of non-completion of chemotherapy and early mortality, was accomplished in elderly patients with ovarian cancer.**(Chapter 3.2)** As geriatric assessment techniques qualified patients "unfit" (based upon deficits on ADL, IADL, cognition and a comorbidity index), this qualification was associated with failure to complete chemotherapy, early mortality and ongoing functional decline. Also, performance score and results on a physical performance measure (Timed Up-and-Go test=TUG) were associated with early discontinuation of chemotherapy and decreased survival. In our study, positive and negative predictive values were higher for TUG than for performance score when GA was used as golden standard. The results are only indicative on the additional value of these techniques, performance score and a physical performance measure to the usual clinical judgment. They did not give a crystal clear evidence which measure is superior. Since our review **(chapter 3.1)** was published, several recent studies have confirmed the ability of CGA to guide oncological decision making (discussed in chapter 4). Collection of information on standard domains (functional status, concomitant diseases, mental status, social support, malnutrition and medication use) seems essential to give guidance at the level of an individual patient, but cut-off points are still not defined for many treatment groups.

Patient characteristics are thus relevant and helpful to describe heterogeneity in groups of elderly cancer patients, to compare study results and to interpret results for daily clinical care.
The extent to which age and comorbidity influence the choice for treatments vary across types of cancer and interventions. If alternative treatments are available or high risk interventions do not lead to (immediate) relief of symptoms, both comorbidity and increasing age lead to less administration of standard treatment.
Comorbidity and increasing age usually lead to higher complication-rates in case of oncological therapies. These associations do not hold, in case of low-risk interventions (surgery on breast cancer) or in case high-risk interventions are accompanied by a stringent selection of patients before the intervention takes place (surgery on non-small cell lung cancer). Overall survival is, amongst other factors, determined by age and comorbidity. This is also applied in patients with lethal tumours (small-cell lung cancer), although almost all of these patients will die because of these tumours. Among others (i.e. mental and nutritional status), increasing age, functional dependency and (severity) of concomitant diseases are important parameters to estimate the benefits that can be achieved by oncological treatments, risks for early death and tolerability in individual patients. Geriatric assessment techniques seem practical instruments to clarify heterogeneity in elderly cancer patients, but cut-off points for predicting risks and benefits of treatment still need to be defined.

Samenvatting

Heterogeniteit in groepen van kankerpatiënten wordt gewoonlijk beschreven aan de hand van tumorkenmerken (histo-pathologische kenmerken van de tumor en de uitgebreidheid van het tumorproces). In het algemeen wordt de gezondheidstatus van kankerpatiënten niet alleen bepaald door de aanwezige tumorkenmerken maar ook door eventuele aanwezigheid van bijkomende ziekten (comorbiditeit), functionele beperkingen, inadequate voedingsstatus, stoornissen in het geestelijk functioneren en de behoefte aan professionele zorg. Deze beperkingen komen bij oudere patiënten vaker voor in vergelijking met jongere patiëntgroepen en worden in dit proefschrift, naast factoren als onder meer leeftijd, geslacht en sociale status, aangeduid als patiëntkenmerken. Klinische en experimentele studies hanteren gewoonlijk criteria waardoor vooral vitale ouderen deelnemen en de resultaten logischerwijs ook vooral toepasbaar zijn op de groep vitale ouderen. In de alledaagse praktijk is sprake van een grote variëteit aan patiënten, van fit tot kwetsbaar. Bestudering van de alledaagse praktijk is mogelijk middels data beschikbaar vanuit de kankerregistraties. Deze registraties beschikken over betrouwbare gegevens met betrekking tot de diagnose en stadiering van kwaadaardige tumoren, de ontvangen oncologische behandeling, overleving van patiënten, eventueel opgetreden complicaties en enkele van de bovengenoemde patiëntkenmerken. Op deze manier is het mogelijk, om regio-gewijs of nationaal, data te verzamelen die de gehele populatie van patiënten ('population-based') met een specifieke kanker behelzen en niet alleen een selectie van relatief vitale patiënten. In dit proefschrift wordt nagegaan in hoeverre verschillen in patiëntkenmerken als leeftijd, bijkomende ziekten of geslacht de keuze voor oncologische therapie bepalen. Tevens wordt nagegaan in hoeverre overleving, complicaties of recidief-groei van tumoren geassocieerd zijn met deze patiëntkenmerken en/of de gekozen behandelmethode(n).

In **hoofdstuk 2** zijn een zestal population-based studies beschreven naar de effecten van bijkomende ziekten (leidend tot multi-morbiditeit), geslacht en leeftijd ten tijde van de diagnosestelling van diverse typen kanker op de keuze van behandeling, complicaties bij behandeling, recidief tumorgroei en overleving. **Hoofdstuk 2.1** laat zien dat in geval van dikke darmkanker en endeldarmkanker chirurgisch ingrijpen vrijwel steeds plaatsvindt, ongeacht bijkomende ziekte of hoge leeftijd. Kennelijk is curatie en behandeling of preventie van ernstige symptomen/complicaties zodanig van belang dat als het ware “ongeselecteerd” tot chirurgisch ingrijpen wordt overgegaan. Bij deze ingrepen zijn zowel hogere leeftijd als de aanwezigheid van bijkomende ziekten geassocieerd met lagere overlevingspercentages, toegenomen postoperatieve mortaliteit en een hoger percentage complicaties. Als alternatieve behandelmogelijkheden aanwezig zijn (naast chirurgie) of er sprake is

van zeer risicovolle chirurgie dan leiden hogere leeftijd en aanwezigheid van comorbiditeit tot lagere resectie-percentages. Dit is het geval bij patiënten met niet-kleincellig longcarcinoom stadium I-II en bij patiënten ouder dan 80 jaar die met stadium I-III borstkanker gediagnosticeerd zijn. Bij patiënten tussen 65 en 79 jaar oud met stadium I-III borstkanker wordt echter minder vaak borstsparende operatie toegepast en vaker mastectomie in vergelijking met jongeren of patiënten zonder bijkomende ziekte.

In **hoofdstuk 2.2** werd het gebruik van pre-operatieve radiotherapie (5x5Gy) en de overleving van patiënten beschreven in geval van endeldarmkanker (stadium T2 -T3, M0). Doel van deze radiotherapie is de kans op ontwikkeling van een locaal recidief te verlagen. Dit recidief treedt meestal op binnen 1 tot 3 jaar na chirurgisch ingrijpen. Verminderde toepassing van pre-operatieve radiotherapie wordt alleen gezien in de patiëntengroep die ouder is dan 70 jaar. Zo daalt het gebruik van pre-operatieve radiotherapie van 87% onder patiënten tussen 60 en 69 jaar oud naar 65% onder 80-plussers. In zijn algemeenheid blijken patientkenmerken die geassocieerd zijn met een lagere overleving (hogere leeftijd, diabetes mellitus, aanwezigheid van 2 of meer bijkomende ziekten), ook geassocieerd met verminderd gebruik van pre-operatieve radiotherapie. Uitzonderingen op deze 'regel' zijn er ook: patiënten met COPD hebben weliswaar een hoger risico op overlijden, maar ontvangen niet minder vaak radiotherapie. Verder ontvangen mannen vaker radiotherapie dan vrouwen, maar blijken juist mannen meer kans te hebben om vroegtijdig te overlijden. Op basis van onze data kunnen we niet vaststellen of dit verschil een gevolg is van patiënt-voorkeuren of dat radiotherapie selectief wordt aangeboden op basis van geslacht. Radiotherapie wordt ook minder toegepast bij patiënten met meer proximaal gelegen tumoren. Een enquete onder oncologisch chirurgen liet zien dat zij radiotherapie voor deze subgroep minder van belang achten.

In **hoofdstuk 2.3** werden de voor- en nadelen van pre-operatieve radiotherapie bij patiënten met endeldarmkanker (T2-T3, N0-2,M0) van 75 jaar of ouder beschreven middels vergelijking van twee aselect verworven groepen die ofwel pre-operatief radiotherapie dan wel alleen chirurgische therapie ontvingen. In de groep met radiotherapie traden postoperatieve complicaties significant vaker op (58% versus 42%). Ook naadlekkage en intrapelviene abcessen (16% vs 10%), wondinfecties (14% vs 7%) kwamen significant vaker voor in patiënten die bestraald werden. De 30-dagen mortaliteit was in beide groepen gelijk (8%). Re-operatie binnen 6 maanden na primaire resectie kwam vaker voor in de bestraalde groep, maar dit verschil bleek niet significant (19% vs 14%, p=0.09). Uiteindelijk doel van de pre-operatieve radiotherapie, preventie van locaal tumor-recidief, werd wel bereikt: in de bestraalde groep ontwikkelde 2% van de patiënten dit recidief, in de niet-bestraalde groep 6%. Preventie van locaal recidiverende tumor wordt weliswaar ook in de hoge leeftijdscategorieën bereikt, maar de incidentie van een recidief is lager en ‘number-needed-to-treat’ blijkt hoger dan in eerdere literatuur vermeld. In de onderzoekspopulatie (zowel bestraalde als niet-

bestraalde patiënten) werden de effecten van bijkomende ziekten op postoperatieve complicaties en 30-dagen mortaliteit geanalyseerd. In de groep zonder comorbiditeit had 43% postoperatieve complicaties en 3% overleed binnen 30 dagen; deze percentage stegen significant bij patiënten met ernstige comorbiditeit (respectievelijk tot 58% en 10%), COPD (59% en 12%), diabetes mellitus (60% en 11%) of cerebrovasculaire ziekte (62% en 14%). Onze resultaten vergroten het klinische dilemma om al dan niet pre-operatief radiotherapie in te zetten bij 75-plussers met endeldarmkanker. Duiding op niveau van de individuele patiënt van diens levensverwachting en risico's op complicaties (op basis van bijkomende ziekten) én een discussie over de voorkeuren van de individuele patiënt, lijkt de meest passende werkwijze om met dit dilemma om te gaan.

In de **hoofdstukken 2.4 en 2.5** werd onderzocht in hoeverre bij ouderen (≥ 75 jaar) met een kleincellig longcarcinoom patiëntkenmerken geassocieerd waren met adherentie aan behandelrichtlijnen, afronding van chemotherapeutische behandeling, toxiciteit en overleving. In geval van 'limited disease' nam het gebruik van chemoradiatie af van 23% in de leeftijdsgroep 75-79 jarigen tot 0% bij 85-plussers, het percentage patiënten dat louter chemotherapie ontving bleef stabiel (40%) over de leeftijdsgroepen. Vrouwen, patiënten met bijkomende ziekten of hogere Performance Score (PS, oncologische maat voor vitaliteit) ontvingen minder vaak chemoradiatie. Belangrijkste reden om af te zien van chemotherapie waren de keuze van de patiënt zelf (29%) of een combinatie van hoge leeftijd, comorbiditeit en matige PS (31%). Van de patiënten die chemotherapie ontvingen, ontwikkelde 69% graad 3 of 4 toxiciteit. Deze toxiciteit nam af van 81% in de groep 75-79 jarigen tot 56% bij 85-plussers. Waarschijnlijk wijst dit verschil op een meer stringente selectie voor chemotherapie naarmate patiënten ouder zijn. 34% van de patiënten van 75-79 jaar en 15% van de 80-plussers ontving 4 of meer cycli chemotherapie; ook patiënten met PS score 3-4 bleken in vergelijking met PS score 0-2 minder vaak 4 cylci te (kunnen) ontvangen (34% vs 5%). Chemotherapeutische behandeling met minstens 4 cycli, leeftijd en PS score bleken onafhankelijke variabelen voor overleving. Mediane overleving van hen die minstens 4 cycli ontvingen was 11.5 maanden, voor patiënten die minder cycli of geen chemotherapie ontvingen was de mediane overleving respectievelijk 4 en 3 maanden. Chemotherapie en chemoradiatie blijven ook na correctie voor verschillen in leeftijd, comorbiditeit en PS significant bepalend voor overleving. Globaal gezien wordt de belasting (chemotherapie en bijbehorende toxiciteit) voor velen, slechts gevolgd door profijt voor enkelen. Dit overwegend lijkt selectie, niet zo zeer gericht op kwetsbare maar op ferme ouderen, een mogelijkheid om voor- en nadelen van behandeling meer in balans te brengen.

In **hoofdstuk 2.6** werd het gebruik van standaardtherapie (combinatie van platinum-houdende chemotherapie en cytoreductieve chirurgie) bij vrouwen met ovariumcarcinoom (FIGO stadium II-III) onderzocht in een population-based studie. De prevalentie van comorbiditeit was 34% in de groep

patiënten jonger dan 70 jaar, vergeleken met 63% bij ouderen (≥ 70 jaar). In een multivariate analyse bleken leeftijd, FIGO-stadium, jaar van diagnose en de aanwezigheid van comorbiditeit onafhankelijke factoren voor toepassing van de standaardtherapie. Een trend in de tijd tot meer frequente toepassing van standaardtherapie bij ouderen was aanwezig. Leeftijd en toepassen van standaardtherapie bleken onafhankelijke variabelen voor overleving, in tegenstelling tot comorbiditeit.

Hoofdstuk 3.1 beschrijft een review-studie naar gebruik van het Comprehensive Geriatric Assessment (CGA) in de oncologie. CGA bleek in de oncologie vooral gebruikt te worden om prognostische factoren met betrekking tot overleving en tolerantie van behandeling te identificeren. Deze informatie was additioneel aan gebruik van biologische leeftijd en PS. Beperkingen in algemeen dagelijkse levensverrichtingen (ADL) en instrumentele activiteiten van het dagelijkse leven (IADL) en depressieve gevoelens waren het meest consistent geassocieerd met toegenomen toxiciteit ten gevolge van chemotherapie. Comorbiditeit, gemeten aan hand van Charlson's comorbiditeitsindex bleek geen voorspeller van toxiciteit. Met betrekking tot overleving waren IADL-beperkingen en depressieve gevoelens meest consistent geassocieerd met lagere overleving. CGA leidde tot identificatie van voorheen onbekende gezondheidsproblemen. Vrijwel geen oncologische studie met betrekking tot CGA heeft de impact van een geïndividualiseerd interventie-plan op tolerantie van behandeling of overleving bestudeerd. De beschikbare studies laten vooral een effect op de kwaliteit van leven zien. Na publicatie van de review-studie hebben enkele recente studies (bediscussieerd in hoofdstuk 4) het vermogen van CGA bevestigd om oncologische besluitvorming te onderbouwen. Informatie van patiënten op een aantal standaard domeinen (ADL, IADL, bijkomende ziekten, mentale status, ondervoeding, medicatie-gebruik en sociale ondersteuning) zijn essentieel om richting te geven aan behandelbesluiten op het niveau van de individuele, oudere oncologische patiënt.

In **hoofdstuk 3.2** werd een prospectieve pilot-studie beschreven, waarin vrouwen met een ovariumcarcinoom (≥ 70 jaar, FIGO stadium IIB-IV)) op basis van geriatrische klinimetrie als 'fit' of 'niet-fit' werden aangeduid. Zowel de PS score (0-1 versus 2) als de kwalificatie fit/niet-fit bleken voorspellend voor afronding van chemotherapie en voor overleving. Bovendien bleek de aanduiding 'fit' ook voorspellend voor functioneren: 65% van deze patiënten functioneerde na 1 jaar gelijk of zelfs beter met betrekking tot ADL of IADL, terwijl dit voor de als 'niet-fit' aangeduide patiënten 23% was.

Patiëntkenmerken zijn **aldus** relevant om de heterogeniteit te beschrijven in groepen van oudere kankerpatiënten, onderlinge studie-resultaten te vergelijken en deze resultaten voor de dagelijkse

klinische zorg te kunnen duiden.

De mate waarin leeftijd en bijkomende ziekte(n) de keuze voor een behandeling beïnvloeden verschilt naar gelang het type kanker en interventie. Zowel aanwezigheid van bijkomende ziekte als hogere leeftijd leiden tot minder frequente toepassing van de standaardbehandeling als er alternatieve behandelmogelijkheden beschikbaar zijn of hoog-risico interventies geen (onmiddellijke) verlichting van symptomen opleveren.

Comorbiditeit en hogere leeftijd leiden bij oncologische behandelingen gewoonlijk tot hogere complicatie-percentages. Dit is niet het geval in geval van laag-risico behandelingen (chirurgie bij borstkanker) en evenmin bij hoog-risico behandelingen waarbij een zeer stringente selectie vooraf plaats vindt (chirurgie bij niet-kleincellige longkanker). Ruwe overleving wordt eveneens bepaald door leeftijd en comorbiditeit. Dit geldt ook voor lethale tumoren (als kleincellige longkanker), zij het dat vrijwel alle patiënten als gevolg van de kanker zullen overlijden.

Naast patiëntkenmerken als leeftijd en comorbiditeit zijn, onder meer, functionele beperkingen, mentale status en voedingsstatus van belang om tolerantie en effecten van oncologische behandeling vooraf in te schatten en patiënten gericht te informeren. Geriatrische beoordelingstechnieken lijken praktische instrumenten om deze kenmerken te objectiveren en de heterogeniteit onder oudere kankerpatiënten te verhelderen. Afkappunten, verbonden aan deze metingen, zijn nog onduidelijk. Zo stricte grenswaarden gevalideerd kunnen worden, vergt dit in ieder geval prospectieve studies.

Dankwoord

Ogenschijnlijk leidt een promovendus een solitair bestaan dat uitmondt in een 'boekje'. De realiteit is echter dat geen promotie mogelijk is zonder helpende hand en zachte duw van velen.

Aan mijn promotor prof. dr. J.W.W. Coebergh. Beste Jan-Willem, we leerden elkaar kennen in discussies over het wel en wee van de gezondheidszorg en, later meer specifiek, de oncologische zorg voor ouderen. In discussies bleef je als epidemioloog een man van grote aantallen en trends, mij kritisch bevragend over maatschappelijke ontwikkelingen en vooral mijn eigen ontwikkeling. Het laatste resulteert uiteindelijk in dit proefschrift. Mijn bewondering hoe je je aandacht voor het “grote geheel” weet te combineren met inzicht in het micro-milieu van patiënten. Ik hoop overigens in de toekomst je mails in turbo-taal niet te moeten missen.

Aan mijn co-promotoren dr. M.L.G. Janssen-Heijnen en dr. V.E.P.P. Lemmens. Beste Maryska, met jou had ik het niet beter kunnen treffen. Jouw kritische attitude, betrouwbaarheid en respectvolle houding naar mij en eenieder met wie je werkt, heb ik zeer gewaardeerd. De snelheid waarmee je op mijn stukken reageerde, was ongekend. Samen met Jan-Willem dreef je me langzaam de promotie-fuik in, overigens zonder dat er een 'masterplan' aan vooraf ging. Onze voordrachten, nogal eens in de vorm van een duo-presentatie, vormden steeds een prettige mix van epidemiologische en klinische know how. Beste Valery, jij voegde op natuurlijke wijze in bij het begeleidingsteam. De gesprekken met jou vielen op door je open mind, zoekend naar alternatieve verklaringen en tegelijkertijd nieuwe onderzoeksideeën genererend. Dit alles was voor mij zeer stimulerend en smaakt naar meer.
Volgens mij liggen er nog heel wat uitdagingen die samen met jullie beiden uitgezocht kunnen worden. Ik stel voor dat we gewoon voortgaan met nieuwe projecten.

Mijn dank gaat uit naar velen die ik niet bij naam ken, maar die werkend bij het IKZ of andere kankerregistraties, nauwkeurig data verzamelden. Deze data vormen de betrouwbare basis waarop ik en vele anderen onderzoek kunnen verrichten. Bovendien biedt jullie dataverzameling de mogelijkheid om met de gegevens in de hand in gesprek te gaan met

behandelteams. Mijns inziens een uniek systeem dat zowel kwaliteit van zorg, onderwijs en research ondersteunt. Eigenlijk zouden ook andere terreinen van de gezondheidszorg een soortgelijk systeem moeten ontwikkelen.

Velen schreven mee aan artikelen. Ik ervoer steeds een positief-kritische houding bij de vele co-auteurs die aan de manuscripten meewerkten. Juist omdat we uit verschillende disciplines input leverden, leidde dit tot een succesvolle kruisbestuiving. Dus dr. Machteld Wymenga, prof. dr. Harry Groen, prof. dr. Caro Koning, dr. Ignace de Hingh, dr. Sabine Siesling, drs. Susan Cox, dr. Paul Nijhuis, dr. Hendrik Martijn, dr. Brigitte vander Bruggen, prof. dr. Roy Kruitwagen, dr. Saskia Houterman, dr. Hoo Goey en dr. Harm Rutten: een dertien-werf 'Merci'.

Aan dr. J. van den Eijnden-van Raaij, M. de Vries en R. Stege. Beste Janny, Maruscha en Rinske, jullie waren niet primair betrokken bij uitvoering van het wetenschappelijk onderzoek maar zorgden wel voor het focus en drive om blijvend aandacht te geven aan de problematiek van ouderen met kanker en hun tocht door de gezondheidszorg. Vanzelfsprekend mijn dank daarvoor.

De leden van de manuscript-commissie – prof. dr. J.F. Lange, prof. dr. M.G.M. Olde Rikkert en prof. dr. C.C.D. van der Rijt- dank ik hartelijk voor de inhoudelijke beoordeling van mijn manuscript en de gemaakte opmerkingen.

Mijn collega’s uit de vakgroep Geriatrie in het TweeSteden ziekenhuis Trudy Eerenberg, Cees Verschoor, Ralf Vingerhoets, Susan Cox en Audrey van Vught dank ik omdat zij (al lang) geconfronteerd worden met mijn neiging tot multi-tasking, zij geduldig zijn en we tezamen blijven investeren in een prettige, professionele collegialiteit. Multi-tasking heeft zo zijn voordelen maar, al benoem ik dat niet graag, ook zo zijn nadelen.

Last but not least, mijn thuishaven. Lieve Marjo, vanzelfsprekend bedank ik jou voor de ondersteuning die je gaf. Jij was altijd beschikbaar als klankbord en gaf me de ruimte. Michiel, Elise en Pauline: 'mijn computer' en de studeerkamer kunnen weer met jullie gedeeld worden, maar liever onderneem ik met jullie activiteiten buiten.

Curriculum Vitae

Huub Maas was born on October 18th 1962 in Terneuzen, a city he did not visit in the first 6 months of his life. In 1981 he graduated from gymnasium ß at Jansenius Scholen-gemeenschap in Hulst. Subsequently, he studied Medicine at the Radboud University Nijmegen. In the last year of this study, he focused on geriatric medicine. After obtaining his medical degree in 1988, he worked one year at the geriatric department of Psychiatric Center 'Het Groot Graffel' in Warnsveld. Eventually, he could start fulfilling his national service. In 1991 he started his residency in internal medicine at the Twenteborg Hospital (J. Wolthuis) in Almelo, in geriatric medicine at Vincent van Gogh Institute (G. Golüke-Willemse) in Venray and at the Rijnstate Hospital (dr. E. Bruijns) in Arnhem.

In 1996 he became a geriatrician and started working at the geriatric department of the TweeSteden Hospital in Tilburg and Waalwijk. To his satisfaction, clinical patient care is his main work. Since 1996 he is medical coordinator of the 'Geriatric Network' in Midden-Brabant. Furthermore, he contributed to the national guidelines on 'fall prevention' and 'Comprehensive Geriatric Assessment'.

Huub enjoys teaching medicine. He became a teacher in geriatric medicine (2001-), member of the Concilium Geriatricum (2003-), Centraal College Medisch Specialismen (2007-2010) and chairman of the medical training board at the TweeSteden Hospital (2006-). Since 2009 he is dean at this hospital.

Formerly, he was president of the Dutch Geriatrics Society (2003-2006) and committee member of the national steering committee on malnutrition (2003-2010).

Since 2005 he became more interested in geriatric oncology, participated in projects organized by the Comprehensive Cancer Center South in Eindhoven and became committee member of the GeriOnNe foundation.

Huub is married with Marjo van Kuijck and they enjoy their children Michiel, Elise and Pauline.

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