Chapter 13

Introduction
In this thesis, we addressed current treatment practices and decision making in elderly cancer patients as well as the consequences of these decisions for clinical outcome. In addition, we investigated the value of a comprehensive geriatric assessment in the decision-making process for these patients. In this final chapter, the results of these studies will be placed in a broader perspective and some issues and implications of these findings will be discussed, including some directions for future research.

Research in elderly cancer patients: clinical trials and observational cohort studies
If we want to know the optimal treatment for older cancer patients, we must design studies that specifically target these patients, as it is incorrect to assume that optimal treatment for a younger patient population will be just as suitable for the older group. However, designing clinical trials for elderly patients is complicated by multiple factors, including the heterogeneity of the population resulting in a great variability in the ability to tolerate treatment, as well as hesitance of older patients to participate in a trial, especially in case of randomization (Chapter 5). These factors may affect the accrual of elderly patients, or mean the patients that are included in clinical trials do not form a representative sample of the target population. Therefore, studies in real-life populations are needed to supplement trial data.

One option is to use observational cohorts as was done in this thesis, where we examined cohorts of patients with breast cancer, colon cancer and head and neck cancer, to address the issue of guideline adherence and differences in treatment choices between younger and older patients (Chapter 1-3 and 6-8). These have provided us with data on real-life clinical practice and in particular, on the reasons why certain treatment choices are made; these data could not have been obtained in a clinical trial format. However, as all these studies were done retrospectively, data on potentially relevant confounders such as the presence of geriatric syndromes or decreased functional capacity were not available. Since these data could also have influenced treatment choices or prognosis, it will be useful to repeat these studies prospectively, with incorporation of baseline data on frailty and geriatric syndromes. In fact, it could be argued that for any research in elderly cancer patients – irrespective of the chosen study design – reporting of geriatric baseline data is as important as the tumour-related data or other patient characteristics. Without these data, it is not possible to compare study results or extrapolate their findings to the individual patient.¹
Non-standard or sub-standard treatment: more than mere semantics
For decades, the issue of guideline adherence for the elderly was barely addressed in oncologic literature, as older age was a generally accepted contra-indication for cancer treatment. In the last decades of the twentieth century, cancer specialists came to realize that this automatic exclusion of older patients did not do them justice. In wake of studies demonstrating that standard cancer treatment could be given successfully to selected elderly, older patients not receiving standard care were stated to receive “substandard” or even “inappropriate” treatment. However, despite the obviously positive development that age itself is no longer considered to be a criterion on which to base decisions, it should be emphasized that for the elderly patient discordance with standard practice or guideline-recommended treatment does not automatically imply that treatment is suboptimal. As discussed in Chapters 1-4 and 6-8, valid reasons for deviation from guidelines exist. Furthermore, although there is general consensus that age should not be the primary reason for withholding treatment, it would be unfair to say that age does not matter at all. For instance, the process of ageing means that a person gradually loses some of his or her physiological reserves, influencing their treatment tolerance. In addition, much cancer treatment is aimed at preventing future cancer-related complications; as ageing limits the remaining life-expectancy of a patient, it may also limit the benefit of such treatment.

Using the terms “substandard treatment” or “undertreatment” to describe non-standard treatment suggests that any tailoring of treatment to the patient’s situation should be avoided. However, overtreatment of frail elderly patients may be as harmful as undertreatment. Therefore, tailor-made care should be the standard of care for older patients. The important questions that remain are what factors should guide such tailoring and how to reliably determine and balance potential benefit with potential harm.

Using geriatric concepts in oncology
With this in mind, cancer specialists are looking towards the concepts and methods of geriatric medicine. One such concept is frailty, which is a state of decreased physiological reserves, arising from cumulative decline across multiple physiological systems, resulting in a diminished resistance to stressors; it can be seen as the final common pathway of ageing. As both cancer and its treatment form significant stressors, which require patients to encroach on their reserves, the concept of frailty appears particularly relevant for older cancer patients. Another geriatric concept that has been adopted in oncology is the comprehensive geriatric assessment (CGA), which is a systematic appraisal of the health status of older individuals, focusing on somatic as well as psychosocial and functional domains; it is used to detect disabilities and geriatric conditions that potentially contribute to frailty.
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However, whereas geriatricians consider the CGA to be the entirety of their consultation with a patient, focusing on as many as twenty geriatric conditions,\textsuperscript{9,10} in geriatric oncology the term CGA is used to describe any procedure in which one or more screening tests for individual geriatric conditions is used. For example, the International Society of Geriatric Oncology, in their 2005 guidelines for the use of geriatric tools in the assessment of older cancer patients,\textsuperscript{11} states that a CGA should consist of a mini-mental state examination (MMSE), geriatric depression scale (GDS) and Katz activities of daily living (ADL) scale. In other studies that describe using a CGA for older cancer patients, this consisted of only one ADL or instrumental ADL scale.\textsuperscript{12} However, malnutrition, polypharmacy, addressed and unaddressed comorbidity and mobility disorders have also been demonstrated to be quite common in older cancer patients (Chapter 9 and 10) and deserve evaluation. Limiting a CGA to only a few geriatric conditions could mean that relevant frailty remains unrecognized, as it has been demonstrated that many geriatric conditions are easily missed if they are not specifically looked for.\textsuperscript{13} For example, one study comparing the physician’s assessment of a patient’s fitness for chemotherapy with the assessment as done by a CGA, revealed that 20% of patients deemed fit by their oncologist had more than three geriatric conditions.\textsuperscript{14}

These newly identified health issues could form the starting point for interventions aimed at optimizing quality of life, survival and treatment tolerance. Studies that incorporated a geriatric consultation into standard oncologic care for older cancer patients found that over 70% of patients subsequently receive at least one non-oncologic intervention.\textsuperscript{15-17} The effect of such interventions remains to be evaluated, as thus far only one study has addressed this issue. In this study by Rao et al. adding geriatric care to standard in-patient cancer care for 99 hospitalized elderly cancer patients resulted in a significant decrease in the amount of emotional limitations, social dysfunction and bodily pain that these patients experienced at three months; the effect on pain was still significant one year after hospital discharge.\textsuperscript{18} This aspect of CGA in cancer care certainly warrants further investigation.

Another purpose for which CGA could be used in geriatric oncology is to guide treatment decisions. Cancer treatment should be tailored to the estimated remaining life-expectancy, and as demonstrated in Chapter 10 and 11, frailty – defined by the presence of one or more geriatric conditions – is an independent predictor of survival, even after correcting for age, cancer type, stage and treatment choice. Interestingly, the presence of frailty seems to be more important than the individual geriatric conditions that cause the frailty, supporting the concept of frailty as a final common pathway of the ageing process. In addition to predicting survival, frailty also appears to be of value in predicting treatment tolerance, in particular toxicity of chemotherapy (Chapter 10 and 11), but these findings still require further confirmation. Despite this uncertainty, studies that have incorporated
CGA into standard cancer care demonstrate that knowledge of the presence of geriatric conditions resulted in an altered treatment plan in 21-49% of patients;\textsuperscript{15-17,19} these alterations consisted of temporary delays to optimize non-oncologic issues as well as both decreased and increased intensity of treatment, meaning that some patients actually were less frail than initially thought by the cancer specialist.

In summary, the value of CGA has been proven for identifying previously unrecognized health issues, which can guide treatment decisions and can also be used to implement multidisciplinary interventions to optimize a patient’s health status and quality of life. We therefore strongly urge all cancer specialists to incorporate a CGA into the standard assessment of all older cancer patients.

\textit{Frailty screening tools}

An important obstacle to incorporating the CGA into oncologic practice is the fact it is time consuming. This has understandably led cancer specialists to search for a short screening tool or checklist that could stratify patients as fit or unfit for treatment, rendering a full assessment unnecessary.\textsuperscript{20} An alternative approach is to use the tool to select patients for further assessment.\textsuperscript{21} However, currently available screening tools lack discriminative power and the prevalence of one or more geriatric conditions is so high that almost all older cancer patients will potentially benefit from further assessment (Chapter 12). As capturing the heterogeneity and nuances of the elderly cancer population in a few simple questions is unlikely to become a reality, future research should focus on other ways in which the full CGA with subsequent interventions could be incorporated into the cancer care process. Although this will be time consuming, it will be balanced out by the gains in terms of avoiding under- and overtreatment, preventing complications and adverse treatment outcomes as well as improving quality of life.

\textit{Patient preferences and decision making}

Another factor that could influence treatment decisions for older cancer patients is a patient’s personal preferences. In several studies included in this thesis (Chapter 1-4 and 8), patient preference was an important reason for non-adherence to treatment guidelines. In addition, patient’s refusal of trial participation was an important factor in the poor accrual for our clinical trial on chemotherapy for metastatic breast cancer (Chapter 5). It is possible that elderly patients truly do not want cancer treatment, and are unwilling to participate in trials. However, older patients tend to take a more passive role in the decision-making process,\textsuperscript{22} and because they are less likely to access alternative sources of information,\textsuperscript{23} their decisions will be greatly influenced by the information that he or she has been offered by the cancer specialist.\textsuperscript{24} In addition, studies have shown that the endorsement of a clinical trial by the treating physician greatly increases the likelihood
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of trial participation. Therefore, an interesting but as yet unanswered question is how much of what is stated to be the patient’s preference is actually a reflection of the physician’s preference.

Various studies have demonstrated that to the older patient, quality of life and maintaining functional independence are much more important than overall survival. However, these types of outcome measures are generally not included in clinical trials. In order for future studies to supply truly relevant information for the older patient, we highly recommend incorporating geriatric outcome measures, such as cognitive function and functional capacity, as well as quality-adjusted survival analyses like the TWiST, the Time Without Symptoms or Toxicity.

**Directions for future research and patient care**

Given the currently available data on the value of CGA in geriatric oncology, we believe that some form of geriatric assessment should be incorporated into standard cancer care for older patients. However, the precise role of the comprehensive geriatric assessment for both patient care and decision making needs to be determined. A further exploration of the ability of CGA to predict treatment tolerance is warranted; however, to avoid previous issues with heterogeneity in patient population and limited content of CGA, these studies should be conducted in single-tumour cohorts and include a broad range of geriatric conditions. Another important research question still to be addressed is whether implementing interventions aimed at the conditions identified by CGA can improve a patient’s ability to tolerate treatment, and in line with this, whether this will improve quality of life and/or survival.

As stated before, research that addresses older cancer patients should incorporate baseline frailty information. Given the heterogeneity of the elderly population, these data allow for comparison between studies and enable translation of outcomes to the individual patient. In addition, future studies in older cancer patients should focus not only on survival and somatic treatment complications, but also include relevant patient-centred outcome measures to allow weighing the benefits with the risks of a particular treatment for the individual patient.

*In conclusion,* for older cancer patients, tailor-made care should be the standard of care, striking the golden mean between undertreatment and overtreatment and fully taking into account the heterogeneity of this patient population. The comprehensive geriatric assessment will provide invaluable information about a patient’s overall health status, but its exact place within the decision-making process still remains to be defined.
References
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