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Introduction

Cancer has a major impact, both in terms of the number of people affected by it and the individual impact it has on patients with cancer and those close to them. Despite improving treatment outcomes, cancer is a major health problem with high morbidity and mortality rates worldwide; approximately one-third of the population will develop cancer in their lifetime^{1,2}. Advanced cancer indicates that cancer is diagnosed in or has progressed to a more serious, less treatable stage³. A term closely related to advanced cancer is “metastatic cancer”, which indicates that a malignancy has spread from the original tumor site to distant parts of the body⁴. Patients with advanced cancer can vary in disease stage, recurrence (primary diagnosis vs. recurred cancer), number and location of metastases, treatment intention (e.g., palliative care, curative care, end-of-life care), and prognosis⁵. Regardless of this variance, the use of the term “advanced cancer” can be used to classify individuals with comparable cancer experiences and psychosocial concerns. For the purposes of this thesis, patients with advanced cancer are considered those patients with distant metastases, and most probably, a poor prognosis for long-term survival. The exact number of patients living with advanced cancer is difficult to determine as cancer statistics often do not report on this parameter^{1,6}. However, of the 5,395,382 patients diagnosed with 7 common solid tumors (e.g. breast, cervical, colorectal, kidney, lung, prostate, and uterine cancer) in the United States registered by the National Cancer Database over an 8-year period (2000-2008) more than 773,000 patients with advanced cancer were identified. This indicates that nearly 1 in 7 patients with cancer will at some point in the disease trajectory face advanced disease⁷. Advanced cancer is often incurable and prognosis is frequently measured in months instead of years⁸. The average five-year survival rate for metastatic cancer is around 20%, with survival rates dropping even below 15% in the advanced stage of lung (4%) and colorectal cancer (12%)⁹⁻¹². Furthermore, due to the progressive course of the disease, these patients face a challenging disease experience.

The availability of new treatment regimens has increased median overall survival and prognosis of some diagnoses, with their potential efficacy being evaluated in randomized controlled trials (RCTs)¹³. The treatment of advanced cancer has become increasingly complex and refined as treatments have advanced over the past several decades¹⁴ due to improvements in imaging, surgical techniques, and systemic therapy^{10,15}. The treatment of patients with advanced cancer should be seen as a continuum of care in which determination of

individual treatment goals is important: prolongation of survival, cure, improving tumor-related symptoms, stopping tumor progression and/or maintaining quality of life (QOL)¹⁶.

Part I - Emotional problems of disease and treatment

The emotional burden of living with a diagnosis of advanced cancer and its treatment, fear of disease progression, and the stress imposed by living with the accompanying physical problems (described in detail below) can lead to psychosocial problems. These types of problems are frequently referred to as psychological distress, which has been defined as 'a multifactorial unpleasant emotional experience of psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis'¹⁷. Although the majority of patients with cancer have normal psychological functioning, symptoms of heightened distress are common. Self-reported psychological distress has been shown present in, on average, 40% of patients¹⁸. Patients with advanced disease seem to be even more susceptible to develop symptoms of psychological distress¹⁹. Psychological distress is an unfavorable outcome in itself. Furthermore, distressed patients are usually less satisfied with the care they receive and show lower rates of treatment adherence²⁰. Other studies have shown that psychological distress may cause worse quality of life (QOL) and may even negatively impact survival²¹⁻²⁴. A variety of psychological interventions have been found to be effective in decreasing symptoms of distress and improving QOL in patients with cancer²⁵⁻²⁷, among which are relaxation techniques, cognitive behavioral therapy, and problem-solving techniques.

Screening

Despite the impact of the psychosocial problems described above and the available treatment possibilities, patients have reported that these problems are not well addressed as part of their oncology care. It has been stated that clinicians underestimate psychosocial needs in a considerable number of patients, thereby leaving many patients in need for psychosocial care²⁸⁻³⁰. As a result, a number of major cancer organizations have recommended to routinely screen for psychosocial concerns and to subsequently offer treatment to those in

need, thereby integrating psychological care into standard oncology practice³¹. The use of screening instruments has been advocated to improve quality of care for psychological distress by endorsing earlier evaluation and timely management of psychological distress, which may lead to improved outcomes of psychological distress³²⁻³⁵. Screening tools have been found to be effective and feasible in identifying distress and psychosocial needs of patients³⁶⁻³⁹. Despite its intuitive appeal, true benefit of screening for psychological distress has not been demonstrated in previous studies^{40,41}. However, in earlier studies no specific triage algorithms were followed and no standardized referrals and treatment were offered^{42,43}. It has therefore been concluded that screening alone is not sufficient to impact patient outcomes; suggested is that for screening programs to be effective these should be designed to target and follow-up on patients' actual needs, in order to direct patients to appropriate psychosocial services⁴⁴⁻⁴⁸.

In this thesis, we aim to test whether an intervention combining screening and subsequent treatment, the TES program, would be effective in improving psychological distress in patients with metastatic colorectal cancer (mCRC). In the TES program, targeted selection (T), enhanced care (E) and referral to well-described effective interventions using a stepped care oriented approach (S) are combined to create optimal conditions to target psychological distress. Targeted selection (or triage) of patients involves administering and scoring of the screening instrument by someone other than the clinician, with only those with high scores offered a referral for treatment. Enhanced care requires that screening is followed-up with additional assessments, follow-up contacts and monitoring of the treatment process by adequately trained staff. In delivering treatment for psychological distress, the stepped care approach has been strongly advocated⁴⁹. Stepped care aims at an effective and efficient allocation of therapeutic resources; patients start with the least intensive treatment that is most likely to work, and only those patients insufficiently helped by the initial treatment receive more intensive and costly interventions. The steps included in our trial were: (1) watchful waiting; (2) a guided self-help program via the Internet or a booklet; (3) face-to-face problem solving treatment (PST) offered by a trained nurse; and (4) referral to specialized psychosocial services and/or psychotropic medication. As psychological distress often improves without active treatment, watchful waiting is a meaningful first step. The second step of the stepped care program was based on a problem solving treatment (PST) self-help program in which patients' self-management skills to solve problems are strengthened. PST has proven to be effective in treating psychological distress⁵⁰. Also the face-to-face counseling offered by trained nurses in the third step of

the stepped program was based on PST.

Chapter 2 and 3 of this thesis present the design and results of a cluster randomized study we conducted in patients with mCRC receiving first line systemic treatment, in which the effectiveness of the TES program on psychological distress was tested. Chapter 4 describes the evaluation of the cost-effectiveness of the TES program.

Predictors for use of psychosocial support services

During the execution of the TES study, we noticed that the majority of our study patients scoring above the cutoff for distress did not use active interventions to improve psychological distress. In total, about a quarter of patients entered the stepped care program: most patients chose for watchful waiting and only a minority of patients made use of subsequent active treatment steps. The low uptake of actual psychosocial care, despite a rather high rate of distressed patients, is consistent with findings in other recent studies showing low acceptance rates of interventions ranging from 3-10%^{22,51-53}. Empirical evidence is accumulating that an elevated level of distress does not equate the need of patients to make use of psychosocial support^{38,53,54}. Valid indicators for the need of psychological treatment are lacking⁵³. Therefore, we studied predictors for use of these psychosocial support services. Identification of predictors for use of psychosocial support may contribute to the understanding of the need for psychosocial support or treatment. We aimed to identify predictors that are widely available such as demographic, clinical, and psychosocial factors at baseline and clinical factors during treatment. The results of this study are presented in Chapter 5.

Part II – Physical consequences of disease and treatment

As patients' life expectancy is increased due to improved treatment options, they suffer more from the toxicities of systemic therapies and live longer with the possible negative consequences of their disease and treatment. Treatment protocols for patients with advanced cancer can last months or in some cases even years. Fatigue is the most frequently reported side-effect of advanced cancer and its treatment and is identified as causing the greatest interference with patients' daily activities⁵⁵. Pain is another common side effect that patients undergoing systemic treatment for cancer experience, resulting from the illness, its treatment, or co-occurring illnesses⁵⁶. Advanced disease can give rise to a range of additional symptoms such as cachexia, loss of

appetite, anemia, liver failure, biliary obstruction and impaired pulmonary function⁵⁷. Side effects depend on the type and dosage of drugs and the length of treatment. Some side effects are temporary (e.g., hair loss), while others such as neuropathy (i.e. numbness in the hands or feet) may persist after treatment. Targeted therapies have specific adverse effects of their own; the EGFR-specific antibodies used in patients with advanced colorectal cancer are associated with high-grade skin and nail toxicities that can involve pain and secondary infections⁵⁸. Antiangiogenic agents cause bleeding, arterial thromboembolic events, impaired wound healing, hypertension and proteinuria⁵⁹ and may additionally increase chemotherapy-induced adverse events (AEs) such as diarrhea, neutropenia and asthenia⁶⁰.

Quality of life

Besides psychosocial and emotional problems, the physical impairments and disabilities as well as fatigue and pain experienced by patients often interfere with patients' health-related QOL. Where patients with advanced cancer may not gain much benefit in terms of traditional endpoints such as survival or disease-free survival, maintaining their QOL is an important objective. Assessment of patients' QOL has been more and more accepted by clinicians to collect meaningful data about patients' treatment experience. Therefore, patient-reported QOL is increasingly reported as an endpoint in oncological RCTs⁶¹⁻⁶³. QOL covers patients' perceptions of physical, emotional, social, and cognitive functioning, disease symptoms and side effects of treatment⁶⁴, the ability to perform everyday activities that reflect physical, psychological, and social well-being; and patient satisfaction with levels of functioning and control of the disease⁶⁵. Clinicians are aware of the potential major impact of advanced cancer on many aspects of QOL⁶⁴ and can offer a range of interventions consisting of active management of pain, guidance in dietary intake, maintenance of physical activity with training programs, providing antiemetic drugs to prevent or reduce nausea and vomiting, and providing drugs such as growth factors to increase the white blood cell count⁶⁶⁻⁷⁰.

Adverse events

RCTs evaluating new treatment regimens report on adverse events (AEs) to evaluate patients' safety, improve clinicians' understanding of toxicity, and to assess risk-benefit ratios^{71,72}. An AE is described as 'any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to that medical

treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses⁷². Clinicians grade AEs using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) on a five-point ordinal scale, with higher numbers being worse, and grade 3 and 4 generally indicating a need for clinical action.

The current reporting of AEs in RCTs is primarily focused on high-grade AEs (grade 3-4) while the lower-grade AEs are not always incorporated⁷³. It is assumed that toxicity during treatment affects QOL, with more toxicity leading to worse QOL⁷⁴. With this assumption in mind, QOL outcomes are used in clinical decision making as they are supposed to inform about possible risks and benefits of new agents. However, a systematic evaluation of relation between treatment-related toxicity and QOL outcomes was not yet available. Therefore, we conducted a systematic review on how severe toxicity during palliative systemic treatment in patients with mCRC relates to global QOL in phase III RCTs. The results of this review are presented in Chapter 6.

It is of imperative importance that patients' QOL is taken into consideration when evaluating the benefit and potential clinical implementation of novel systemic therapies. Although a description of high-grade toxicities is important and relevant to determine drug tolerability, patients' QOL is also likely to be influenced by the cumulative effect of total experienced AEs, including the lower grade AEs (grade 1-2). In Chapter 7 and 8 we present two studies in which we aimed to gain more insight into the impact of cumulative toxicity scores on QOL in patients with mCRC and metastatic castrate-naïve prostate cancer, respectively.

Aims and outline of this thesis

The overall objective of this thesis is to improve overall well-being and QOL for patients with advanced cancer undergoing anticancer treatment by optimizing psychosocial support and symptom management. In particular, the first objective of the current thesis is to study the (cost-)effectiveness of a combined screening and treatment program in reducing psychological distress in patients with mCRC receiving first line systemic treatment. In addition, we aim to increase our understanding of the relatively low use of psychosocial support during first line treatment despite high rates of patients screened positive for psychological distress. Our second objective is to critically evaluate the clinical value of QOL and toxicity reporting in oncological RCTs.

In line with our aims, Chapter 2 and 3 describe the design and results of a cluster randomized clinical trial which we conducted to test the effectiveness of the TES program in reducing psychological distress in patients with mCRC receiving first line systemic treatment. Chapter 4 evaluates the cost-effectiveness analysis and cost-utility analysis of the trial. Chapter 5 describes which factors predict the use of psychosocial support services in patients with mCRC receiving first line systemic treatment. Chapter 6 contains a systematic review to assess whether treatment-related toxicity in recent RCTs in patients with mCRC receiving systemic treatment affects global QOL. Chapter 7 explores whether cumulative toxicity scores are predictive for QOL in patients with mCRC receiving first line treatment. Chapter 8 explores whether patient-reported toxicity may be more predictive for QOL than clinician-reported toxicity. Finally, Chapter 9 summarizes and discusses the main findings of the studies included in this thesis.

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