Daily clinical practice and patterns of care in upper gastrointestinal cancer treatment

Toxicity, quality of life and survival

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Chapter 1

General introduction and outline of the thesis
INTRODUCTION AND OUTLINE OF THE THESIS

Upper gastrointestinal (GI) cancers - esophageal, gastric and pancreatic cancer - have a dismal prognosis. Despite treatment with curative intent, randomized clinical trials report 5-year survival rates of only 47% in esophageal cancer, 36% in gastric cancer, and 21% in pancreatic cancer. In population-based series, 5-year survival rates of patients treated with curative intent are even lower and range from 19-25% in esophageal cancer, 20-31% in gastric cancer, and 11-16% in pancreatic cancer.

Besides the poor results of treatment, management of upper GI cancers is further complicated by the occurrence of side effects of oncological treatment. This is more prominent in upper GI cancer due to the extent of upper GI surgery, with potentially severe complications, as well as the use of multimodality treatment (radiation, chemotherapy), which cannot always spare vital organs. This may severely impact quality of life and functional outcome of these patients.

Unfortunately, the majority of patients have advanced disease at the time of presentation, rendering palliative systemic treatment combined with best supportive care as the only treatment of choice. Median overall survival data for patients with metastatic disease in population-based studies varies from 2 months for pancreatic cancer to less than a year for esophagogastric cancer.

Trends over time show a rising incidence of both esophageal cancer and pancreatic cancer. Esophageal cancer has two histological subtypes: adenocarcinoma and squamous cell carcinoma. The European standardized rate (ESR) increased for esophageal cancer from 5/100,000 in 1990 to 10/100,000 in 2015. Over the past three decades, in the Western world the rates of esophageal squamous-cell carcinoma have declined, while those of esophageal adenocarcinoma have been progressively increasing. Gastric cancer markedly decreased in the Netherlands with an ESR in 1998 of 25/100,000 compared to an ESR in 2008 of 14/100,000. Despite these increasing trends for esophageal adenocarcinoma and pancreatic cancer, it should be noted that upper GI cancers are relatively uncommon in the Western World. For example, in the Netherlands in 2015 2369 new patients were diagnosed with esophageal cancer - this is six times lower than the incidence of breast cancer in 2015. Likewise, in 2015 2284 patients were diagnosed with pancreatic cancer and 1556 patients with gastric cancer. This implies that individual caregivers may have limited experience with the treatment of this disease, unless care is centralized. In the Netherlands, high complex, low volume surgery is centralized because outcome of patients treated in a high-volume specialized center is usually better compared to outcome of patients treated in low volume hospitals. However, for palliative treatment
with systemic therapy this association has not been investigated in upper gastro intestinal cancer. The poor prognosis, the potentially severe toxicity of treatment and late presentation of the disease together with the relatively low incidence pose a great challenge to the optimization of outcomes of patients with upper GI cancer. The main aim of this thesis is to investigate toxicity and functional outcome of treatment of locally advanced esophageal cancer and to investigate treatment strategies for metastatic esophagogastric and pancreatic cancer, with a special focus on differences in management and survival between Dutch hospitals in daily practice.

Part 1: Treatment of locally advanced esophageal cancer
Nowadays the treatment of choice for locally advanced resectable (clinical tumor stage T1-3, any N (with the exception of T1N0) esophageal cancer in the Netherlands is multimodality treatment consisting of neoadjuvant chemoradiation followed by resection, based on the results of the Dutch CROSS trial. This treatment consists of five times weekly intravenous chemotherapy (carboplatin area under the curve of 2 mg per milliliter per minute and paclitaxel 50 mg per square meter of body surface area). A radiation dose of 41.4 Gray (Gy) is given (23 x 1.8 Gy), with 5 fractions administered per week, starting on the first day of the first chemotherapy cycle. Resection is planned six to ten weeks after the end of neoadjuvant treatment.

The updated results of the CROSS trial show a median survival of 49 months. Although survival benefit was found for both histological subtypes, in the subgroup of patients with squamous cell carcinomas the median survival was even 82 months.

In the light of the gradual but continuing improvement of survival of resectable esophageal cancer, long-term side effects of chemoradiotherapy may become increasingly relevant. During the radiation treatment, margins around the target volume are needed to compensate for daily setup variations and daily mobility of the esophagus, leading inevitably to dose delivery to normal organs such as the heart. In cancers with a high proportion of cancer survivors long-term effects of radiation-induced cardiotoxicity have been investigated. For example, in breast cancer an increased rate of mortality from heart disease in the group of long-term surviving women treated with radiation therapy was reported. Cardiac toxicity was confirmed in population-based data showing that exposure of the heart to ionizing radiation during radiotherapy for breast cancer increased the subsequent rate of ischemic heart disease. Subsequently, modern tangential techniques and inspiration breath-hold techniques have been introduced to reduce the irradiated heart volume and thus late cardiac toxicity. In contrast to late cardiac toxicity, limited data are
available on acute cardiac toxicity of chemoradiotherapy. Acute cardiac toxicity may have impact on treatment tolerance but may also be a predictor of late chronic cardiac toxicity. Therefore, in Chapter 2 we describe the hemodynamic aspects of changes in heart volume during neoadjuvant chemoradiation. Furthermore, we explore whether changes in heart volume during chemoradiation have impact on the dose distribution of the target volume. If during neoadjuvant chemoradiation of esophageal cancer there are signs of subclinical cardiac toxicity, measures will need to be taken to further minimize cardiac toxicity and delivery of radiation dose to other organs at risk.

A clinician-reported outcome such as toxicity is a very important outcome measure used in clinical trials and in daily practice. However, grading adverse events is not necessarily identical to functional outcome and quality of life (QOL). First, some treatment side effects as pain and emotional effects are preferably defined by the patient. Second, only patients can determine how relevant toxic effects are to their functional outcome. Functional outcome can be assessed with QOL questionnaires and measurement of functional status. Functional status refers to routine activities of daily living such as self-care, housekeeping and outdoors activities. They might truly reflect a patient's day-to-day functioning. Multimodality treatment showed a temporary negative effect on most aspects of quality of life, but normalized or even improved one to two years after surgery. These combined findings might provide patients and health workers with essential information; for patients to guide expectations on functional status during treatment, for health workers to provide extra support. To date, these data are lacking and, therefore, in chapter 3 we evaluate activities of daily living and quality of life of the patient during neoadjuvant chemoradiation and after surgery.

Besides physical and practical consequences, patients undergoing neoadjuvant chemoradiation followed by surgery must cope with numerous social and emotional challenges due to treatment-related toxicity and risk of recurrence. This not only poses a burden on the patient, but also on their caregiver. Moreover, with the shift of delivery of care from the hospital to the home as a result of increased use of outpatient services for cancer treatment and shortened hospital visits, especially family caregivers are taking more responsibility for patient care. In general, caregivers are responsible for organizing the appropriate food supply, for example ground food, have to manage medical emergencies when they arise, are expected to understand medical information, and need to make the time to escort the patient to the hospital. Next to these responsibilities, they are expected to provide psychological, spiritual and emotional support. The broad array of support tasks may be accompanied by high levels of distress and unmet supportive
In the period after treatment, persistent psychological distress and role adjustment problems experienced by caregivers of non-upper GI cancer survivors have been reported to be higher than healthy controls. In case of esophageal cancer, the burden of caregivers - defined as the extent to which caregivers feel that their emotional or physical health, social life, and financial status have suffered as a result of caring - can be associated with practical matters, such as adjusting the frequency of meals. Furthermore, also the particularly poor prognosis may have a large impact on caregiver burden. To possibly assist health care providers to provide resources to the spousal caregivers most in need, we describe the spousal caregivers’ burden of esophageal cancer survivors after treatment with curative intent. Furthermore, we explore associations for spousal caregiver burden after neoadjuvant chemoradiation and surgery in chapter 4.

Although surgery is considered the mainstay of curative treatment for esophageal cancer, in the period 2005-2013 in the Netherlands less than 30% of all cases with esophageal cancer underwent surgery with curative intent. This is related to various patient- and tumor characteristics. First, most patients present with advanced disease and are therefore treated with palliative intent without surgery. Second, patients can have an irresectable tumor because of disease extent or a proximal localization. And third, patients may be medically inoperable because they are considered unfit for esophagectomy because of comorbidity. In case of irresectability or inoperability definitive chemoradiotherapy (dCRT) is an alternative to surgery that can achieve long-term disease control and even cure. Definitive chemotherapy, as generally applied in the Netherlands, consists of six times weekly chemotherapy. A total radiation dose of 50.4 Gy is given (28 x 1.8 Gy), in 5 fractions per week, starting on the day of the first chemotherapy cycle. Although irresectable and inoperable patients may both be treated with dCRT, both groups are quite distinct with inoperable patients potentially being disposed to more toxicity because of underlying disease. In a single center retrospective series of 291 patients undergoing definitive chemoradiation 5-year overall survival rate was 20%, grade 3 and/or 4 toxicity was 48%. Other studies report grade 3 toxicity ranging from 29-56%. In these studies, no reporting of toxicity was made on the basis of the reason of non-surgical treatment, i.e. having an irresectable tumor or being inoperable because of comorbidity. Next to information on survival (the benefit of treatment) information on the extent of toxicity (the harm of treatment) is essential for a patient when deciding to opt for a specific treatment. To fill the knowledge gap on the toxicity of dCRT for inoperable patients, we describe the tolerability of this treatment regimen for this patient group in chapter 5.
Part 2: Treatment for metastatic disease of esophagogastric and pancreatic cancer

In terms of efficacy, palliative chemotherapy has been shown to be superior compared to best supportive care for esophagogastric cancer.\[33\] A standard first-line treatment, however, has not been established. It is a matter of debate whether a three-drug of two-drug regimen should be used. Landmark studies from the American and Asian continent generally use two drug regimens consisting of a fluoropyrimidine analogue and a platinum compound.\[34, 35\] In Europe conducted randomized phase 3 trials often use three drug regimens.\[36-39\] To put this in a historical context: Cullinan et al. reported in 1985 on monotherapy 5-fluorouracil (5-FU), the doublet 5-FU and doxorubicine and the triplet 5-FU, doxorubicine and mitomycine C (FAM).\[40\] None of the regimens showed an improvement in overall survival. In 1991, a randomized controlled trial, conducted by the EORTC compared the triplet FAM vs the triplet 5-FU, doxorubicine, methotrexate (FAMTX), which showed an advantage in median survival for FAMTX (44 weeks versus 29 weeks).\[41\] Until the turn of the century FAMTX was widely used in European trials.\[39, 42, 43\] However, since the publication of a phase 3 randomized trial with 274 patients in which FAMTX showed a median survival of 5.7 months compared to epirubicine, cisplatin and 5-FU (ECF) 8.7 months, ECF became the common comparator in Europe.\[39\] (figure 1)

![Diagram](image_url)

**FIGURE 1** Development of palliative systemic chemotherapy for metastatic esophagogastric cancer

**Abbreviations:**
- 5-FU=5-fluorouracil
- doxo = doxorubicine
- FAM=5-fluorouracil, doxorubicine, mitomycine C
- FAMTX=5-fluorouracil, doxorubicine, methotrexate
- ECF=epirubicine, cisplatin, 5-fluorouracil
In 2008 Wagner et al.\cite{33} published a Cochrane review investigating the optimal chemo-therapeutical treatment consisting of a fluoropyrimidine analogue and a platinum compound. Since 2008 new results from randomized trials have been published, including two-drug combinations. Although treatments may be effective in terms of survival, the level of side effects should also be taken into account. In order to select the optimal treatment balancing survival gain and toxicity, in chapter 6 we investigate the efficacy and safety of triplet versus doublet chemotherapy in patients with advanced and metastatic gastro-esophageal disease in a systematic review and meta-analysis.

In metastatic pancreatic cancer, progress in identifying effective novel treatments has been limited. Until recently, gemcitabine was the standard of care, based on findings of a study conducted more than fifteen years ago. In the pivotal trial by Burris et al in 1997\cite{44} gemcitabine vs. 5-FU monotherapy was shown to have a small significant benefit in overall survival from 4.4 months to 5.7 months. The clinical benefit was a composite measure of pain (analgesic consumption and pain intensity), performance status, and weight. Clinical benefit required a sustained (≥4 weeks) improvement in at least one parameter without worsening in any of the others and occurred in almost one quarter of the patients treated with gemcitabine compared to a scarce five percent in the 5-FU arm. Since the introduction of gemcitabine as first line therapy, numerous phase III studies have evaluated different gemcitabine-based regimens as first-line therapy, but in all cases, observed benefits, if any, have been small.\cite{45-49}

However, in 2011 Conroy et al.\cite{50} published the results of FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, 5-fluorouracil) compared to gemcitabine that resulted in longer survival (11.1 vs. 6.8 months, respectively) as well as a delay in deterioration of quality of life. Also, nab-paclitaxel added to gemcitabine was shown to improve survival from 6.7 to 8.5 months.\cite{51} The two trials included somewhat different patient groups: the FOLFIRINOX regimen was administered to patients with WHO performance score 0 and 1, while the gemcitabine and nab-paclitaxel regimen was administered to patients with WHO performance score of 0 to 2. The two regimens have not been compared head to head; both are considered standard of care in the first-line setting for patients with metastatic disease.\cite{52} (figure 2)
Because survival is poor and treatment is complex with a wide range of local and systemic treatment options, variation in treatment modalities for esophageal and pancreatic cancer may exist. Moreover, survival from randomized studies usually does not reflect daily practice, because patients with comorbidities and elderly patients are often underrepresented in clinical trials.[53] To assess whether patterns of care and the effectiveness of treatment confers to a real benefit in the general population, population-based observational research can provide insight. Therefore, in chapter 7 and chapter 8 we use population-based data to describe treatment and outcome in patients with metastatic esophageal and pancreatic cancer, respectively.

The cancer care task force of the Dutch Cancer Society concluded that quality of cancer care in the Netherlands is high. However, they posed that improvements of outcomes are possible by reducing variation between hospitals.[16] For pancreatic and esophageal cancer, since 2006 it has been recommended to concentrate the surgical treatment for upper gastro intestinal cancer to improve quality of care. For gastric cancer in 2011 a minimum volume of ten annual gastrectomies was implemented. Esophagectomies, gastrec-
tomies and pancreatectomies have been referred to as highly complex, low volume surgery. Surgical outcomes appear to be better in high-volume centers, related to the lower incidence and the better management of postoperative complications.\textsuperscript{14, 15, 54, 55} For the association between volume and outcome, the overall hospital volume has been shown to be even more relevant than the volume of patients treated per individual surgeon \textsuperscript{56}, indicating the importance of experienced nonsurgical support for this specific group of patients. Currently, it is unknown whether outcomes for palliative chemotherapy show an identical volume association. It may be hypothesized that for treatment of patients with metastatic cancer, the experience of medical oncologists, as defined by the number of annually treated patients, as well as the combined experience of the whole multidisciplinary team providing upper gastrointestinal cancer care may be a relevant factor determining patient outcome. Chapters 9 and 10 describe volume outcome relations for treatment with palliative chemotherapy in gastro-esophageal cancer and pancreatic cancer, respectively, on the basis of population-based data.

Finally, chapter 11 contains a general discussion and future perspectives on treatment in patients with upper gastrointestinal cancer in daily practice.
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