Treatment and survival
of patients with metastatic
upper gastrointestinal cancer

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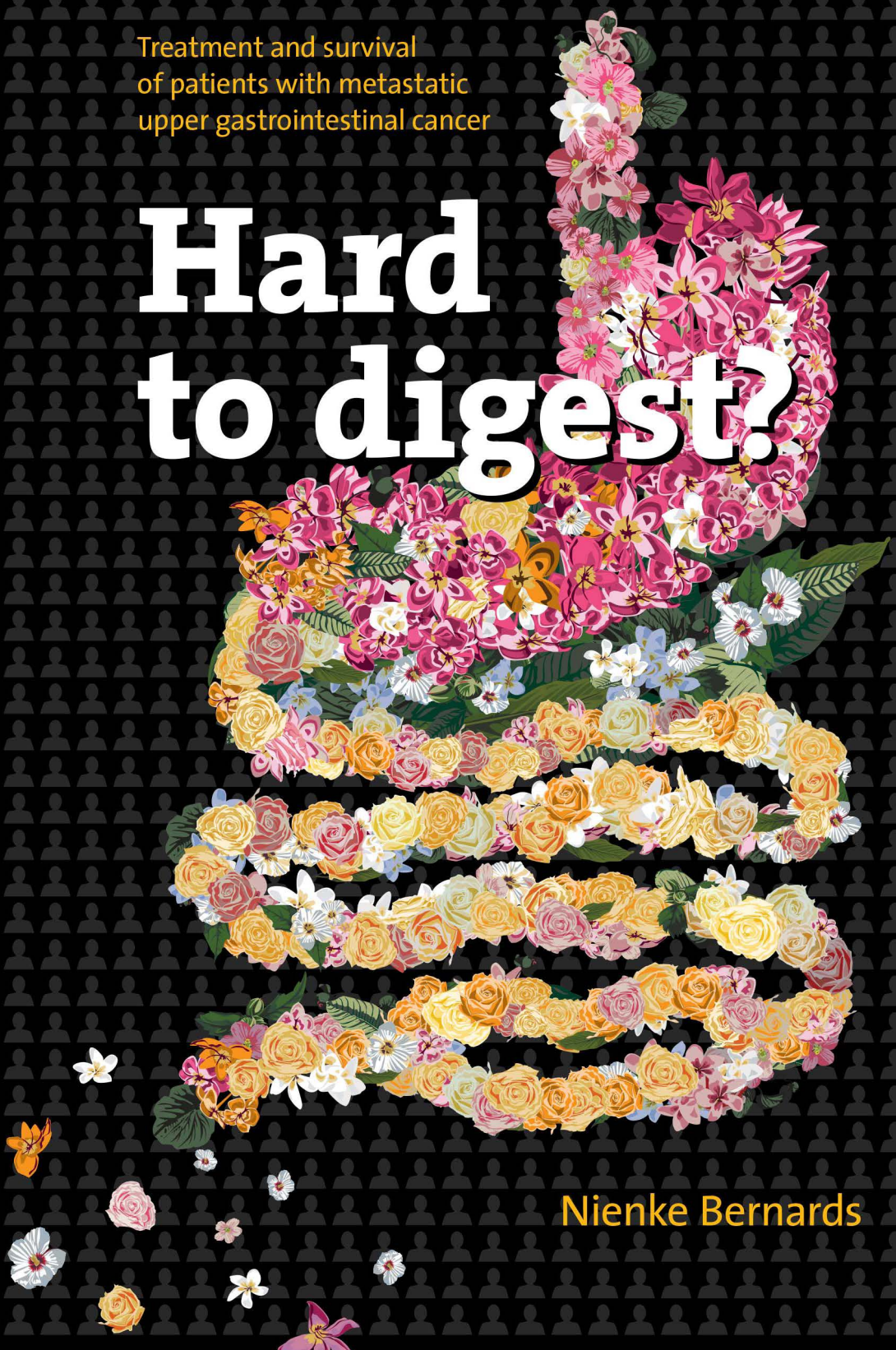

Nienke Bernards

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Colophon

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Moeilijk te verteren?

Treatment and Survival of Patients with Metastatic Upper Gastrointestinal Cancer

Hard to digest?

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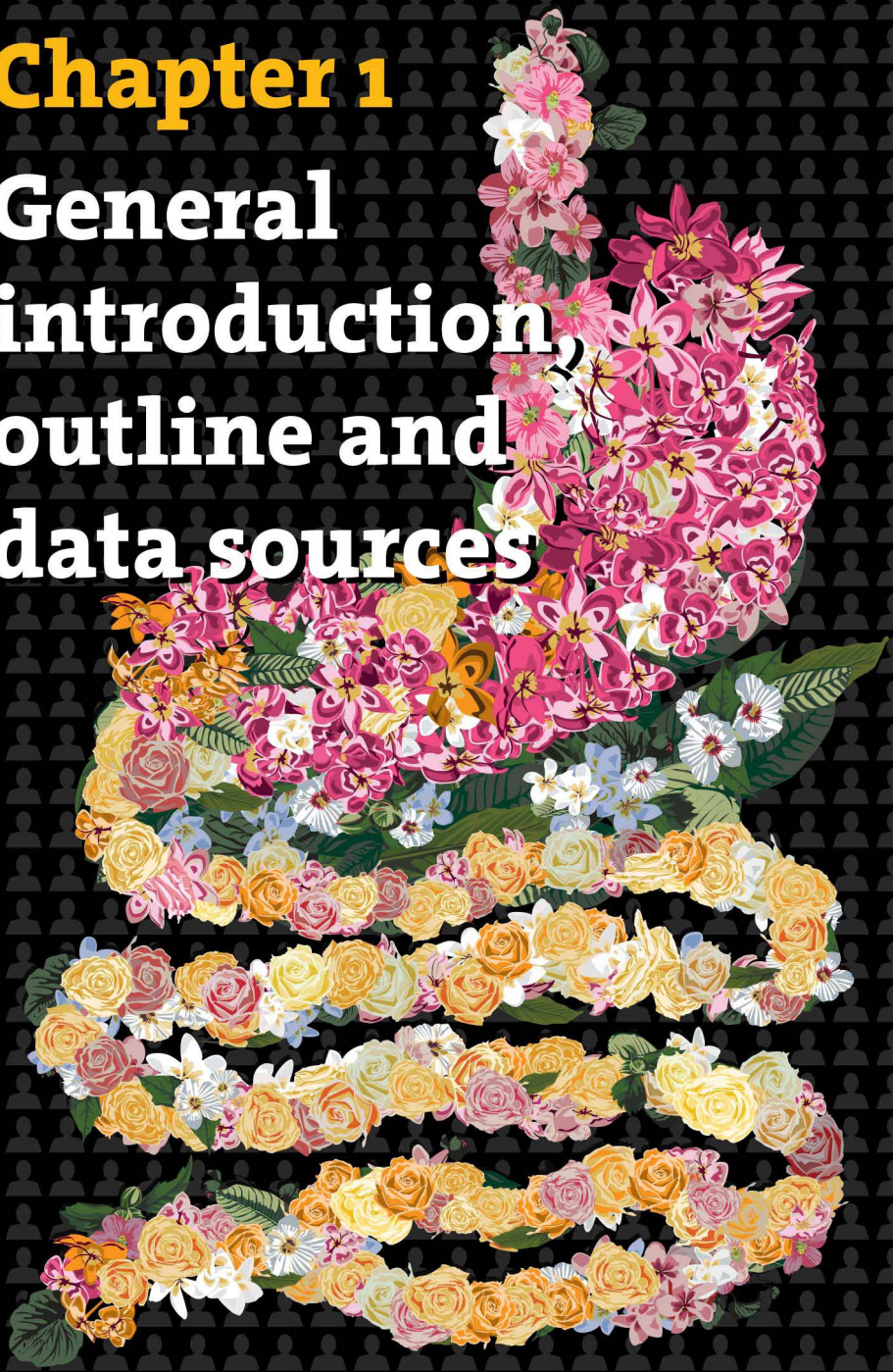
Chapter 1
General introduction, outline and data sources



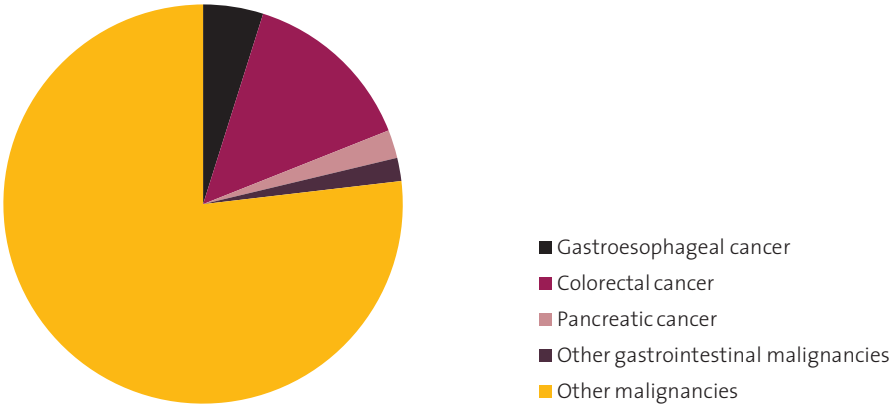
General introduction

Cancer is a major threat to public health. Last decades the global burden of cancer increased, due to a growing and ageing population. Currently, most developed countries face a phenomenon called double-ageing, elderly people are not only increasing in number but their life expectancy increased too.[1] As cancer is primarily a disease of older age this phenomenon will result in a further increase of absolute incidence rates. In the Netherlands, the most frequently diagnosed cancers are prostate cancer and breast cancer in men and women respectively.[2]

Incidence of gastrointestinal cancer

Gastrointestinal malignancies represent a substantial proportion of the newly diagnosed cancers as well (figure 1). Colorectal cancer for instance, is the second most common cancer in both men and women. The high incidence rates of colorectal cancer have been attributed to the western lifestyle, including physical inactivity, smoking, alcohol consumption and a high consumption of red and processed meat.[3] Even so, gastric cancer is an important health problem, being the fourth most common cancer and the second leading cause of cancer death worldwide. Fortunately, in western European countries the burden of gastric cancer decreased, most likely as a result of the eradication of *Helicobacter Pylori*. *Helicobacter Pylori* is the most common chronic bacterial infection in humans, affecting approximately 50% of the global population.[4] A large prospective Japanese study investigating the association between *Helicobacter Pylori* infection and the development of gastric cancer, found that 2.9% of the infected patients developed gastric cancer. Patients with severe atrophy and intestinal metaplasia had an even higher risk.[5] Esophageal cancer is the eight most common cancer worldwide and the sixth leading cause of cancer-related mortality. Globally, squamous cell carcinoma is the predominant histologic subtype, however in the Netherlands the incidence of adenocarcinomas significantly increased and now exceeds the incidence of squamous cell cancers. The most important risk factors for the development of esophageal adenocarcinomas include gastro-esophageal reflux disease and obesity. In contrast to gastric cancer, an inverse relationship was found between *Helicobacter Pylori*

Figure 1 Proportion of newly diagnosed cancer patients presenting with gastrointestinal malignancies in the Netherlands



infection and esophageal adenocarcinomas. The risk of developing esophageal cancer seems to be reduced in patients with a *Helicobacter pylori* infection.[6]

In the Netherlands, pancreatic cancer is the tenth most common cancer and in developed countries it ranks the fourth leading cause of cancer related deaths.[7] Most patients present with advanced disease. In our dataset 55% of the patients presenting with pancreatic cancer between 2009 and 2013 had metastases at time of diagnosis. In general, 27% percent of the patients diagnosed with gastrointestinal malignancies had metastases at time of diagnosis. This percentage increased from 23% in 1989 to 30% in 2013. The lowest percentage of metastatic disease was found in patients with colorectal cancer, 23% of these patients had metastases at time of diagnosis, compared to 37% in patients with gastroesophageal cancer and 55% in patients diagnosed with pancreatic cancer.

Advances in systemic treatment

Last decades, major changes have been made in the systemic treatment of advanced cancers. The first cytotoxic agent, nitrogen mustard, an alkylating agent was introduced shortly after World War II. However, for a long time researchers were very sceptic about the usefulness of chemotherapeutic agents. The turning point came when Li et al. demonstrated in 1958 that methotrexate, an antimetabolite, could cure women suffering from choriocarcinomas

or related trophoblastic disease.[8] The evolution of chemotherapy in gastrointestinal cancers started in that period with the discovery of the antimetabolite fluorouracil, nowadays still the cornerstone in the treatment of many gastrointestinal malignancies.[9] After the antimetabolites, antitumor antibiotics were introduced. These agents, derived from micro-organisms, were initially introduced to treat infections.[10] Subsequently, they appeared to have an antitumor effect.[11]

The antimitotic agents, including taxanes and vinca alkaloids, were discovered in the 1960s as well. The taxanes had a difficult start.[8] Paclitaxel, the first taxane reached it's approval in 1992, almost three decades after its initial discovery.[10] Another subgroup of chemotherapeutic agents with a difficult start were the camptothecins. The first derivative of camptothecin, a topoisomerase I inhibitor, that achieved approval was irinotecan for the treatment of metastatic colorectal cancer in 1996.[8] Shortly after the introduction of irinotecan the cytotoxic agent oxaliplatin, a platin derivative showed to have efficacy in colorectal cancer.[12]

Besides the increasing number of chemotherapeutic agents over time, new indications and drug combinations arose. In the 1960s, it was shown that administering multiple drugs simultaneously resulted in better outcomes. Nowadays drug combinations, dosing and scheduling have been carefully refined to maximize effectiveness and minimize side effects.[13]

Initially, chemotherapy was solely prescribed in patients with metastatic disease. Around 1970, the first studies were initiated to investigate the role of chemotherapy after complete surgical resection in an attempt to reduce recurrence rates. The first large study investigating the effect of adjuvant chemotherapy in patients with resected colon cancer was published in 1990.[14] The study concluded that levamisole combined with 5-fluorouracil reduced the recurrence rate and improved overall survival of patients with Dukes C colon cancer. Anno 2016, adjuvant chemotherapy and neoadjuvant strategies are standard for the treatment of breast cancer, colorectal cancer, gastroesophageal cancer and pancreatic cancer.

In the 21th century, a stagnation occurred in the discovery of new clinically relevant cytotoxic agents. However, new insights in the development of tumors led to the development of an entire new class of drugs, known as 'targeted-agents'.[8,15] These agents inhibit specific targets such as growth factors, signaling molecules and molecules that promote angiogenesis.[8]

Targeted agents can be subdivided in monoclonal antibodies and small molecules. Monoclonal antibodies target specific antigens on the cell surface such as transmembrane receptors or extracellular growth factors. Small molecules do not act on the surface of the cell but can penetrate through the cell membrane to interact with target proteins or enzymes.

One of the landmark events in the 'targeted therapy' revolution was the introduction of bevacizumab, an angiogenesis inhibitor, approved in 2004 for the treatment of metastatic colorectal cancer. Bevacizumab is a monoclonal antibody directed against the vascular endothelial growth factor and is designed to slow down the growth of new blood vessels to the tumor.[16] Nowadays, bevacizumab is used in the systemic treatment of metastatic colorectal cancer, cervical cancer, ovarian cancer, non small cell lung cancer and breast cancer. A second class of monoclonal antibodies shown to be effective in metastatic colorectal cancer, are antibodies directed against the epidermal growth factor receptor (EGFR). The EGFR inhibitors (cetuximab, panitumumab) disrupt the key signaling pathway that is controlled by EGFR.[15]

Trends in the prescription of systemic treatments

The advances in cancer treatment had an enormous impact on clinical practice. In 1989 only 9% of all patients with solid malignancies in the Netherlands received chemotherapy, this percentage more than doubled to 22% in 2013. Together with the growing burden of cancer, the increased prescription rates resulted in a more than four-fold increase in absolute patient number, from 4,800 patients in 1989 to 21,000 patients in 2013.

Trends in prescription of systemic treatments in patients with non-metastatic malignancies

In patients with non-metastatic malignancies, the prescription rate of (neo) adjuvant chemotherapy increased from 8% in 1989 to 18% in 2013. Significant increases were observed in patients with gastrointestinal malignancies, lung cancer and breast cancer. The prescription rate of adjuvant chemotherapy increased from 1% in 1989 to 60% in 2013 in patients with stage III colon cancer. In 1996, the Dutch national guidelines recommended 5-fluorouracil based chemotherapy in patients with stage III colon cancer resulting in a sharp increase in the prescription of adjuvant chemotherapy (figure 2).[17] Prescription rates increased after the publication of two important trials. In 2004, the published MOSAIC trial

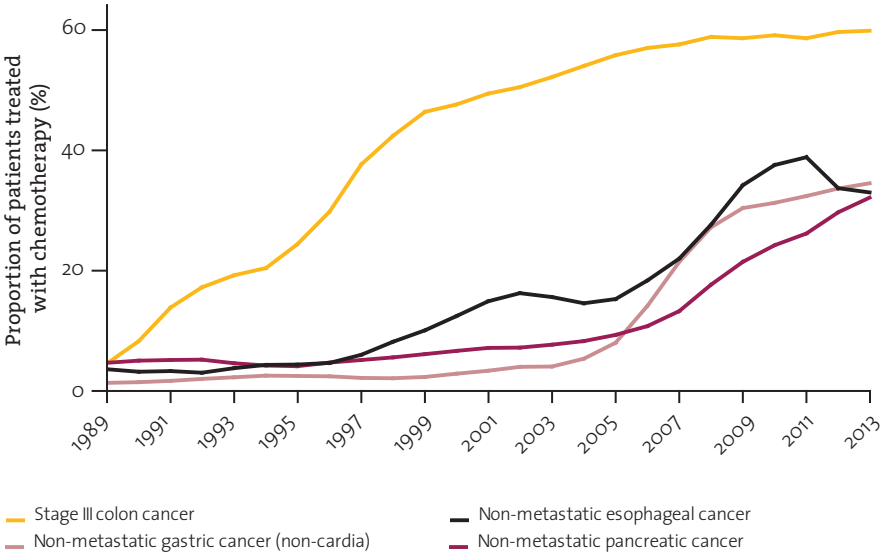
demonstrated that adding oxaliplatin to 5-fluorouracil further reduced recurrence rates in patients with stage III colon cancer after surgical resection.[18] One year later in 2005, the published X-ACT trial showed that oral capecitabine was at least as effective as intravenous fluorouracil. Furthermore, capecitabine was more patient convenient and associated with significantly fewer adverse events.[19]

The management of locoregional esophageal cancer had undergone a major evolution over the past 15 years. For a long time, survival was poor after surgical resection due to locoregional or metastatic recurrence. Several studies have been conducted to improve outcome, investigating the effectiveness of perioperative chemotherapy and chemoradiotherapy. An important study in esophageal cancer was the Dutch CROSS study, which compared chemoradiotherapy followed by surgery with surgery alone in patients with esophageal or esophagogastric junction cancer. From March 2004 through December 2008, 368 patients were randomly assigned to chemoradiotherapy, with weekly administration of carboplatin and paclitaxel for 5 weeks with concurrent radiotherapy 41.4 Gy in 23 fractions, followed by surgery or to surgery alone. The study found that preoperative chemoradiotherapy significantly improved the median overall survival from 24 months to 49 months. Furthermore, the regimen was associated with acceptable adverse-event rates.[20]

One of the landmark trials in resectable gastric cancer was the British MAGIC trial, published in 2006. This trial evaluated the efficacy of perioperative chemotherapy in patients with resectable adenocarcinomas of the stomach. Five hundred and three patients were randomly assigned to perioperative chemotherapy and surgery or surgery alone. Chemotherapy consisted of three preoperative and three postoperative cycles, including epirubicin, cisplatin and fluorouracil. Patients treated with perioperative chemotherapy had a significantly higher likelihood of progression-free survival and overall survival, with five-year survival rates of 36% compared to 23% in patients who underwent surgical resection alone.[21] Significant increased prescription rates were observed after the publication of this trial.

For the treatment of resectable pancreatic cancer some progress has been made with the introduction of adjuvant chemotherapy. In 2004 the results of the ESPAC-1 study were published, which found that adjuvant chemotherapy with 5-fluorouracil resulted in an improvement of median overall survival from 15.5 months (5-year survival rate 8%) to 20.4 months (5-year survival rate 8%).[22]

Figure 2 Proportion of newly diagnosed patients with non-metastatic gastrointestinal cancers, treated with chemotherapy in the Netherlands from 1989-2013



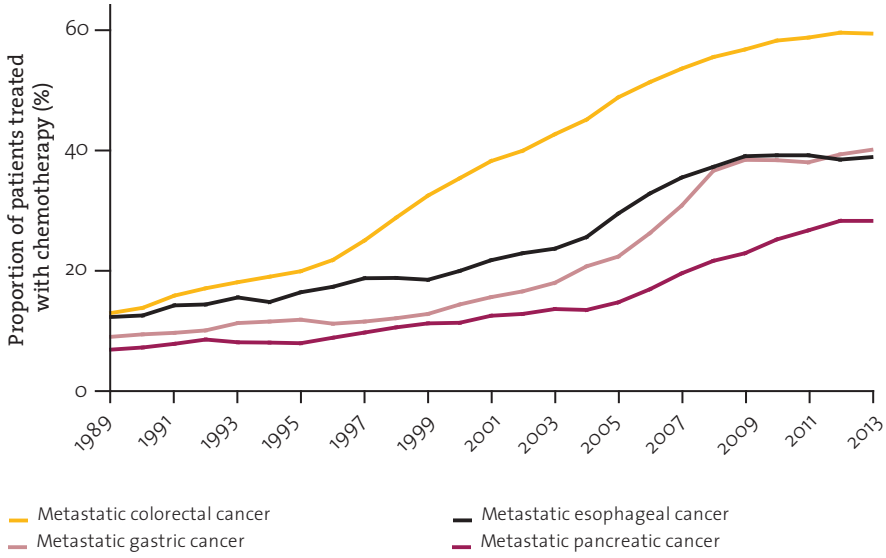
In 2007, Oettle et al. found an improvement of disease free survival in patients treated with adjuvant gemcitabine. In 2008 the final result of this study showed a significant improvement of overall survival.[23] Gemcitabine became the reference adjuvant regimen in resectable pancreatic cancer.

Trends in prescription of systemic treatments in patients with metastatic malignancies

In the period 1989-2013 a more than twofold increase in prescription rate was seen in patients with metastatic solid tumors, rates increased from 16% in 1989 to 39% 2013.

A sixfold increase was seen in the prescription of palliative chemotherapy in patients diagnosed with metastatic colorectal cancer (figure 3). Major advances have been achieved in the systemic treatment of colorectal cancer. Currently, there are several active drugs for patients with metastatic disease: fluorouracil, oxaliplatin, irinotecan, bevacizumab, cetuximab, panitumumab, aflibercept and regorafenib. The choice of the systemic regimen, single agent or combination

Figure 3 Proportion of newly diagnosed patients with metastatic gastrointestinal cancers, treated with chemotherapy in the Netherlands from 1989-2013



therapy with or without targeted therapy, depends on the goals of the treatment, the type and timing of prior treatment, the mutational profile of the tumor, the toxicity profiles of the drugs and patient related factors (e.g. comorbidity, age). [24] Guidelines recommend a combination of a fluorpyrimidine, oxaliplatin and/or irinotecan, with or without targeted agents in first line. The ongoing introduction of successful agents resulted in an impressive increase in prescription rates.

Although for other metastatic gastrointestinal malignancies, such as metastatic esophageal cancer, gastric cancer and pancreatic cancer, advances in the systemic treatment were limited, a significant increase in prescription rates was observed. Trends in treatment of patients with metastatic upper gastrointestinal malignancies will be discussed more detailed in this thesis.

Trends in survival of patients diagnosed with gastrointestinal malignancies

The 5-year relative survival rate after diagnosis of cancer in the Netherlands improved. Among men, the relative 5-year survival rate increased from 41% in 1989-1993 to 54% in 2003-2007. Among women, the rate increased from 57% to 63% in the respective periods.[1] The increased survival rate in men is mainly attributable to an increase in the incidence of prostate cancer and a decreased incidence of highly fatal cancers such as lung and gastric cancer. In women the increased survival is the result of the increased incidence of breast cancer with a relatively favorable survival.

The overall survival in patients diagnosed with colon and rectal cancer improved, from respectively 54% in 1999-2001 to 58% in 2005-2007 for colon cancer and from 52.1% in 1999-2001 to 57.6% in 2005-2007 for rectal cancer.[2] The advances in the systemic treatment of metastatic colorectal cancer are likely to attribute to the improved survival in these subgroups of patients. In the era of single agent fluorouracil overall survival was approximately 12 months in patients with metastatic colorectal cancer. Nowadays, the median overall survival is more than two years.[25]

Only modest improvement of the very poor overall survival was achieved in gastroesophageal cancer. In Europe, the five year relative overall survival for patients diagnosed with esophageal cancer increased from 9.8% in 1999-2001 to 12.6% in 2005-2007. The relative five year overall survival in gastric cancer increased from 23.3% in 1999-2001 to 25.1% in 2005-2007. In Europe, the survival of these subgroup of patients remained dismal, especially when compared to the survival of patients diagnosed with gastric cancer in Asia.[26]

Five-year relative survival in patients diagnosed with small bowel cancer increased from 41% in 1999-2001 to 49% in 2005-2007.[26] Presumably, the improvement in survival is partially explained by centralization of the surgery. Although this centralization occurred for pancreatic cancer as well, the 5-year relative overall survival of patients diagnosed with pancreatic cancer in Europe increased with only 1%, from 5% in 1997-2001 to 6% in 2005-2007.

The improvements in survival of patients diagnosed with tumors of the upper gastrointestinal tract are mainly the result of advancements in the treatment of non-metastatic disease, such as centralization of surgery, neoadjuvant chemoradiotherapy in resectable esophageal cancer, perioperative chemotherapy in resectable gastric cancer and adjuvant chemotherapy in resectable

pancreatic cancer.

However, a significant proportion of the patients presents with metastatic upper gastrointestinal cancer varying from 32% esophageal cancer to 59% in pancreatic cancer. In this thesis, we will focus on these subgroups of patients. We will investigate the impact of treatment advances on overall survival in patients with metastatic upper gastrointestinal malignancies.

Hospital variation & volume-outcome relationship

Previous research showed that the care for cancer patients varied between hospitals. Guidelines recommend adjuvant chemotherapy including oxaliplatin combined with fluorouracil plus leucovorin or capecitabine. Steenbergen et al. showed that the initiation of adjuvant chemotherapy varied widely between ten community hospitals in the southern Netherlands. In patients < 65 years the prescription rate of adjuvant chemotherapy varied from 82% to 96%, in patients aged between 65-74 years the rate varied from 59% to 78% and in patients older then 75 years the rate varied between 9% and 25%.[27]

In patients with metastatic upper gastrointestinal cancers, guidelines state that palliative chemotherapy can be considered. We want to investigate if this consideration also leads to variation in the prescription of palliative chemotherapy between ten community hospitals.

During the past decade, centralization of high complex upper gastrointestinal surgery has been discussed extensively. Multiple publications showed that centralization positively impacts the overall survival of patients diagnosed with resectable gastroesophageal and pancreatic cancer. It has been hypothesized that this improvement is not explained solely by the experience of the surgeon. Different aspects of the hospital structure such as the presence of an intensive care unit, interventional radiology, experienced gastroenterologists and medical oncologists are hypothesized to influence the outcome as well.[28] In this thesis ,we investigate if being diagnosed or being treated in a high-volume center improves the survival of patients with metastatic pancreatic cancer.

Outline of this thesis

This thesis presents an analysis of trends in incidence, treatment and overall survival in patients diagnosed with tumors along the upper gastrointestinal tract, with a focus on metastasized disease. The four anatomical subsites discussed in detail are the esophagus, stomach, pancreas and small intestine.

The main objectives of the studies described in this thesis were:

- To investigate trends in treatment and overall survival of patients diagnosed with metastatic upper gastrointestinal cancers, including esophageal cancer, gastric cancer, small bowel cancer and pancreatic cancer.
- To investigate hospital variation in the prescription of palliative chemotherapy in patients with metastatic gastric and pancreatic cancer.
- To investigate the influence of incidence volume and treatment volume on median overall survival of patients diagnosed with metastatic pancreatic cancer.

In **chapter 2,** the trends in treatment and overall survival of patients with synchronous metastatic esophageal cancer have been studied. Factors influencing the likeliness of receiving external beam radiotherapy, brachytherapy, chemoradiotherapy or chemotherapy were analyzed and the impact of these treatment modalities on overall survival was studied.

In chapter 3.1 an overview of the descriptive epidemiology of metastatic gastric cancer in the south of the Netherlands is given. Besides the influence of different patient and tumor characteristics on the prescription of palliative chemotherapy, this chapter investigates if there is an inter-hospital variation in the prescription of palliative chemotherapy. **Chapter 3.2** reports on the subgroup of patients with peritoneal carcinomatosis of gastric origin.

Chapter 4 provides an overview of the incidence, treatment and overall survival of patients diagnosed with an adenocarcinoma of the small bowel in the Netherlands.

Trends in chemotherapeutic treatment in patients with metastatic pancreatic cancer and the effect of treatment on population-based survival are evaluated and reported in **chapter 5.1.** Studying pancreatic cancer we observed that a large proportion of the pancreatic cancer patients did not have pathological verification of their tumor. Currently the guidelines in pancreatic cancer recommend pathological verification for patients with suspected pancreatic cancer,

except for those with resectable disease where a biopsy prior to surgery is not always necessary. However, obtaining tissue for verification can be very difficult, therefore we conducted a population-based study to assess the relevance of pathological verification in **chapter 5.2.** Data of the studies represented in chapter 5.1 and 5.2 showed that only a small proportion of the patients had an overall survival exceeding two years. In **chapter 5.3,** we questioned whether long-term survival actually exists in pancreatic cancer.

In an attempt to improve survival of patients diagnosed with resectable pancreatic cancer the surgical care for these patients is centralized in high volume centers. Different studies showed that centralization of pancreatic surgery positively impacted overall survival. In **chapter 5.4** we hypothesize that being diagnosed or being treated in a high-volume incidence and/or high-volume treatment center might influence the prognosis of patients with metastatic pancreatic cancer.

Data sources

Eindhoven cancer registry

The Eindhoven Cancer Registry (ECR) started in 1955 as part of a program for nationwide cancer registration. In the beginning, the registry comprised of data from three hospitals located in Eindhoven, which covered an area with almost 1 million inhabitants. The area gradually expanded, since 1986 it covers almost the entire province Noord-Brabant and the northern part of Limburg. This area now hosts 2.4 million inhabitants and is served by 10 community hospitals, two radiotherapy institutions and six pathology laboratories. The pathology laboratories participate in the nationwide automated pathological archive (PALGA) which notifies the cancer registry on all newly diagnosed malignancies. Within 6-18 months after notification, information on patient characteristics, tumor characteristics and treatment is routinely extracted from medical records by trained registrars working on behalf of the cancer registry.

Netherlands Cancer Registry

With the exception of the Eindhoven cancer registry, the other regional registries discontinued their activities, until a new nationwide program was established in 1984. Since 1989 the entire Dutch population is covered by nine regional cancer registries, together establishing the Netherlands Cancer Registry, governed by

the Association of Comprehensive Cancer Centers. The Netherlands Cancer Registry is also notified by the national automated pathological archive, PALGA. The trained registrars collect information on the patients' past and current health status. Information on the vital status of patients was obtained from civil municipal registries and the central bureau for genealogy, which collect data on all deceased Dutch inhabitants.

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Chapter 2

Epidemiology of esophageal cancer

Chapter 2.1

Improvement in survival for patients diagnosed with synchronous metastatic esophageal cancer in the south of the Netherlands from 1994 to 2013

N. Bernards, N. Haj Mohammad, G.J.M. Creemers, T. Rozema, J.A. Roukema, G.A.P. Nieuwenhuijzen, H.W.M. van Laarhoven, M. van der Sangen, V.E.P.P. Lemmens Acta Oncologica 2016 May13;1-7 2016. Sep-Oct;55(9-10):1161-1167

Abstract

Background: We assessed the use of external beam radiotherapy, brachytherapy, chemoradiotherapy and chemotherapy in patients with metastatic esophageal cancer and evaluated the effect on overall survival.

Methods: We included all patients diagnosed with synchronous metastatic esophageal cancer in the south of the Netherlands between January 1, 1994 and December 31, 2013. Proportions of patients treated with external beam radiotherapy, brachytherapy, chemoradiotherapy and chemotherapy were described with respect to the period of diagnosis, patient and tumor characteristics. Independent risk factors for death were discriminated.

Results: A total of 1,020 patients were included, 61.5% of these patients received palliative treatment with external beam radiotherapy, chemoradiotherapy, brachytherapy and/or chemotherapy. The use of external beam radiotherapy decreased from 44.5% in 1994 to 22.2% in 2013 ($p=0.0001$), whereas the use of chemoradiotherapy increased from 2.9% in 1994 to 19.1% in 2013 ($p<0.0001$). The prescription of systemic chemotherapy as a single modality increased from 13.9% to 30.5% ($p<0.0001$). The use of brachytherapy decreased from 20.9% in 1994 to 7.4% in 2013 ($p=0.0013$). The odds of receiving external beam radiotherapy, brachytherapy, chemoradiotherapy and chemotherapy, were influenced by different tumor and patient characteristics such as age, gender, histologic subtype and number of metastatic sites. The median overall survival in patients with metastatic esophageal cancer significantly improved over time from 18 weeks (one-year survival rate 14.4%) in 1994–1998 to 25 weeks (one-year survival rate 22.4%) in 2009–2013.

Patients treated with chemoradiotherapy had the most favorable prognosis, followed by patients treated with chemotherapy as a single modality.

Conclusion: The median overall survival of patients diagnosed with metastatic esophageal cancer improved from 18 weeks in 1994–1998 to 25 weeks in 2009–2013. Although this increase could be attributed to stage migration, our population-based study suggests that major changes in treatment strategies and appropriate patient selection might play a role as well.

Introduction

About 35% of the patients with esophageal cancer present with metastatic disease.[1] These patients have an extremely poor prognosis, with a 1-year survival rate of 18%.[2] Treatment of patients with metastatic esophageal cancer is complex, due to a wide range of local and systemic treatment options. In order to achieve adequate locoregional palliation, different modalities can be used, such as external beam radiotherapy, brachytherapy, chemoradiotherapy or endoscopic stent placement. Historically, external beam radiotherapy has played an important role in the management of locoregional disease. However, in 1992 the radiation therapy oncology group (RTOG) published a landmark trial (RTOG-85-01), which showed that chemoradiotherapy was superior to external beam radiotherapy in terms of survival and locoregional control in patients with locally advanced esophageal cancer.[3,4] The benefit of both treatments is often slow in onset, whereas a more rapid relief of dysphagia can be achieved with brachytherapy or endoscopic stent placement. Brachytherapy is recommended for patients with a life expectancy between 3 and 6 months. In patients with a shorter life expectancy or those with a firm stenosing tumor, endoscopic stent placement is preferred, which offers instant relief of symptoms.[5-7]

Systemic chemotherapy can provide palliation, improve quality of life, and prolong survival in patients with metastatic gastroesophageal cancers.[8,9] There is no consensus regarding which regimen should be used in first line. Most guidelines advise that patients with a good performance status should be offered combination chemotherapy, including a platinum and fluoropyrimidine derivative.[5,10] Population-based data on the use of the above mentioned

modalities in patients with metastatic esophageal cancer are sparse. In 2007, Cronin-Fenton et al. assessed trends over time for treatment of esophageal and gastric cancer. They observed an increased use of chemotherapy and radiotherapy in surgically and non-surgically treated patients. However, they were unable to distinguish between curative and palliative treatments.[11]

In the present population-based study we aimed to assess the use of external beam radiotherapy, brachytherapy, chemoradiotherapy and chemotherapy in patients with metastatic esophageal cancer. We evaluated which factors were associated with the use of the different modalities and assessed the effect on overall survival.

Methods

Data collection

We obtained data from the Eindhoven Cancer Registry (ECR), which is maintained by the Comprehensive Cancer Centre Netherlands. The ECR is a population-based registry that collects data on all patients with newly diagnosed cancer in the southern part of the Netherlands. The registry area comprises about 2,4 million inhabitants and encompasses 10 general hospitals, 2 large radiotherapy institutions and 6 pathology laboratories. These pathology laboratories participate in the nationwide automated pathological archive (PALGA), which notifies the cancer registry on all newly diagnosed malignancies. Within 6 to 18 months after notification, information on patient and tumor characteristics are extracted from medical records, including age, gender, comorbidity (modified version of the Charlson comorbidity index), socioeconomic status (defined at neighborhood level, combining mean household income and mean value of the house/apartment), date of diagnosis, hospital of diagnosis, subside of primary tumor (International Classification of Diseases for Oncology (ICD-O) topotopography codes), morphology (ICD-O morphology codes), tumor stage (TNM classification staged following recommendations of the International Union Against Cancer in the respective period (4^{th}-7^{th} edition)), tumor grade and subsite of metastasis (ICD-O topography codes).

We included all patients diagnosed with esophageal cancer (ICD-O topography codes C15.0-C15.9) in the south of the Netherlands between January 1, 1994 and December 31, 2013. Our inclusion was limited to adenocarcinomas (ICD-O morphology codes 8140, 8142, 8144, 8145, 8210, 8211, 8255, 8260-8263,

8480, 8481, 8490, 8560, 8570, 8574) and squamous cell carcinomas (ICD-O morphology codes 8070-8076, 8078) of the esophagus. Other morphology codes were excluded or did not occur during the study period.

In this study, we focused on the treatment and survival of patients with metastatic adenocarcinomas or squamous cell carcinomas of the esophagus. We did not classify cervical and celiac lymph node involvement (M1a in the 5th and 6th TNM edition) as metastatic disease, since after the introduction of the 7th TNM edition in 2010 these nodal metastases, regardless of the primary tumor location, are no longer regarded as distant metastatic disease.

The Eindhoven Cancer Registry contains information on primary therapies defined as therapies administered or planned within 6 months after the initial diagnosis. Trends in treatment with external beam radiotherapy, brachytherapy, chemoradiotherapy and chemotherapy over time are shown using three-year moving averages. Unfortunately, no information is available on endoscopic stent placement.

To establish survival, patients' vital status at January 1, 2015 was assessed through linkage with civil municipal registries and the central Bureau for Genealogy, which collects data on all deceased Dutch Citizens.

Statistical analyses

We described proportions of patients treated with external beam radiotherapy, brachytherapy, chemoradiotherapy and chemotherapy according to different patient and tumor characteristics. Trends in time were analyzed by means of a Cochran-Armitage trend test. Multivariable logistic regression analysis was used to identify predictive factors. Variables included in the analysis were sex, age, comorbidity, socioeconomic status, histologic subtype, number of metastatic sites and period of diagnosis.

Survival time was defined as the time from diagnosis till death or till January 1, 2015 for patients still alive. Survival was calculated based on all-cause mortality. Differences between survival curves were evaluated by means of a log-rank test. Independent risk factors for death were discriminated by means of multivariable proportional hazard regression modeling. To investigate the effect of different treatment modalities on the hazard ratios (HRs) of death, we built the model with and without treatment variables.

Statistical analyses were carried out using SAS statistical software. (Version 9.4, SAS institute, Cary, NC, U.S.A.). For all analyses, a two sided *p*-value $p<0.05$ was considered statistically significant.

Table 1 Characteristics of patients with metastatic esophageal cancer, diagnosed between 1994 and 2013 in the southern Netherlands (N = 1,020)

	Number	Percentage
Sex		
Male	810	79.4
Female	210	20.6
Age (yrs.)		
<50	72	7.0
50–59	237	23.2
60–69	341	33.4
70–79	270	26.5
≥80	100	9.8
No. of comorbid conditions		
0	463	45.4
1	343	33.6
2 or more	159	15.6
Unknown	55	5.4
Social economic status (SES)		
Low	245	24.0
Intermediate	415	40.7
High	281	27.6
Institutions	46	4.5
Unknown	33	3.2
Histologic subtype		
Adenocarcinoma	718	70.4
Squamous cell carcinoma	302	29.6
No. of metastatic sites		
1	704	69.0
2	227	22.3
3 or more	89	8.7
Period of diagnosis		
1994-1998	111	10.9
1999–2003	214	21.0
2004-2008	307	30.1
2009-2013	388	38.0
Treatment		
No treatment	393	38.5
External beam radiotherapy (EBRT)	247	24.2
Brachytherapy (BRT)	178	17.5
Chemoradiotherapy (CRT)	99	9.7
Chemotherapy (CT)	218	21.4

Figure 1 Percentage of patients presenting with metastases and number of affected organs, in patients with esophageal cancer diagnosed between 1994 and 2013 in the southern Netherlands (N=1,020)

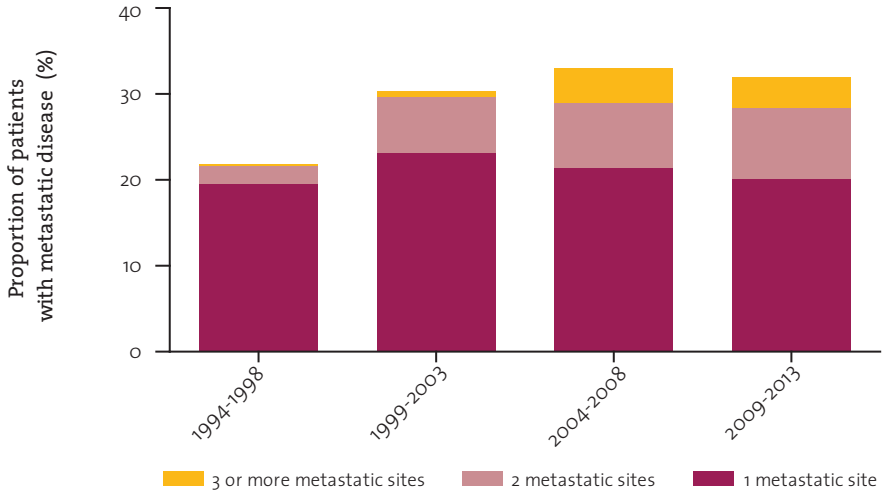
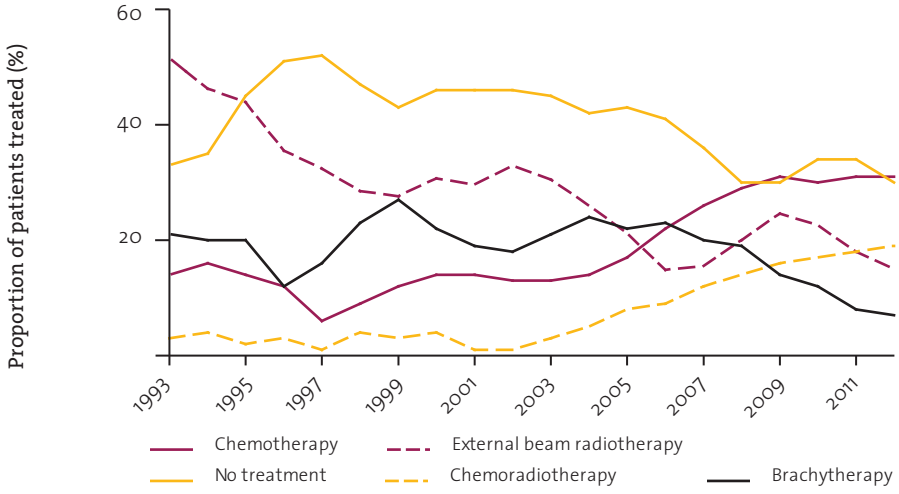


Figure 2 Percentage of patients treated with external beam radiotherapy, brachytherapy, chemoradiotherapy and chemotherapy over time in patients with metastatic esophageal cancer, diagnosed between 1994 and 2013 in the southern Netherlands (N=1,020)



Results

Between 1994 and 2013, 3,349 patients were diagnosed with esophageal cancer in the south of the Netherlands, of whom 1,020 (30,5%) were diagnosed with synchronous metastases. The characteristics of patients presenting with metastatic disease are depicted in table 1. Overall, 79,4% of these patients were male and the median age at time of diagnosis was 66 years (range 31-93). Adenocarcinoma was the predominant subtype of esophageal cancer in our study (70,4%). In the course of time the proportion of adenocarcinomas increased from 48,7% in 1994-1998 to 75,8% in 2009-2013.

The proportion of patients presenting with metastatic disease also increased over time from 21,9% in the period 1994-1998 to 32,1% in 2009-2013 (figure 1). Of the patients with metastatic disease, 69,0% had single site metastases, in 22,3% 2 organs were affected and in the remaining 8,7% 3 or more organs were affected. The proportion of patients presenting with metastases in multiple organs increased significantly over time, from 10,8% in 1994-1998 to 37,4% in 2009-2013 ($p<0.0001$). The most often affected sites were the liver (42,6%), the extra regional lymph nodes (44,5%) and the lungs (22,7%).

Of the patients with metastatic esophageal cancer, 61,5% received external beam radiotherapy, chemoradiotherapy, brachytherapy and/or chemotherapy. The proportion of patients receiving treatment increased from 55,9% in 1994-1998 to 69,9% in 2009-2013 ($p=0.0001$). Trends over time are depicted in figure 2. The use of external beam radiotherapy decreased during the study period from 44,5% in 1994 to 22,2% in 2013 ($p=0.0001$). Similarly, the use of brachytherapy decreased from 20,9% in 1994 to 7,4% in 2013 ($p=0.0013$). The use of chemoradiotherapy increased from 2,9% in 1994 to 19,1% in 2013 ($p<0.0001$). Chemotherapy as a single treatment modality increased from 13,9% to 30,5% ($p<0.0001$). Within the first 6 months after diagnosis, 82,6% of the treated patients (N=518) received treatment with one modality. Multiple modalities were used in 17,4% of the treated patients (N=109); 42 patients (6,7%) received external beam radiotherapy and brachytherapy, 22 patients (3,5%) received brachytherapy and chemotherapy and 38 patients (6,1%) received chemoradiotherapy and chemotherapy. The majority of patients treated with chemoradiotherapy and chemotherapy was treated between 2009 and 2013.

Table 2a and 2b present the crude percentages and adjusted odds ratios for the use of external beam radiotherapy, brachytherapy, chemoradiotherapy and chemotherapy. Young patients (<50 yrs.) were more often treated

Table 2a Crude percentages and odds of receiving external beam radiotherapy, brachytherapy and chemoradiotherapy in patients with metastatic esophageal cancer, diagnosed between 1994 and 2013 in the southern Netherlands (N=1,020)

	Crude % EBRT	Odds ratio (95% CI)	Crude % BRT	Odds ratio (95% CI)	Crude % CRT	Odds ratio (95% CI)
Sex						
Male	22.7	1.00 (reference)	18.9	1.00 (reference)	9.6	1.00 (reference)
Female	30.0	1.33 (0.93-1.90)	11.9	0.58 (0.37–0.93)	10.0	1.05 (0.59–1.87)
Age (yrs.)						
<50	8.3	0.25 (0.10–0.62)	18.1	1.41 (0.70–2.87)	13.9	1.55 (0.68–3.53)
50–59	23.2	0.89 (0.59–1.33)	22.8	1.80 (1.15–2.80)	12.7	1.13 (0.66–1.94)
60–69	23.8	1.00 (reference)	13.8	1.00 (reference)	12.9	1.00 (reference)
70–79	30.7	1.52 (1.04–2.21)	17.0	1.30 (0.82–2.06)	5.6	0.33 (0.17–0.53)
≥80	22.0	1.03 (0.58–1.81)	18.0	1.55 (0.83–2.89)	0.0	Not applicable
No. of comorbid conditions						
0	24.0	1.00 (reference)	18.6	1.00 (reference)	19.2	1.00 (reference)
1	27.4	1.07 (0.77–1.51)	17.2	1.04 (0.71–1.53)	17.6	1.19 (0.71–1.97)
2 or more	20.8	0.68 (0.43–1.09)	17.0	1.07 (0.64–1.78)	14.9	1.07 (0.53–2.16)
Unknown	16.4	0.54 (0.25–1.17)	10.9	0.48 (0.20–1.18)	10.0	0.53 (0.12–2.39)
Social economic status (SES)						
Low	26.1	0.98 (0.67–1.43)	17.1	0.98 (0.63–1.50)	8.6	0.97 (0.54–1.74)
Intermediate	24.8	1.00 (reference)	18.1	1.00 (reference)	10.4	1.00 (reference)
High	23.8	1.02 (0.70–1.47)	16.7	0.94 (0.62–1.43)	11.7	1.10 (0.66–1.85)
Institutions	10.9	0.34 (0.13–0.90)	13.0	0.68 (0.27–1.70)	2.2	0.31 (0.04–2.44)
Unknown	24.2	1.13 (0.48–2.67)	24.2	1.72 (0.72–4.12)	3.0	0.23 (0.03–1.81)
Histology						
Adenocarcinoma	21.2	1.00 (reference)	18.0	1.00 (reference)	9.3	1.00 (reference)
Squamous-cell carcinoma	31.5	1.52 (1.10–2.11)	16.2	0.92 (0.63–1.35)	10.6	1.12 (0.67–1.86)
No. of metastatic sites						
1	26.4	1.00 (reference)	18.2	1.00 (reference)	11.2	1.00 (reference)
2	21.6	0.82 (0.56–1.18)	17.6	1.01 (0.67–1.51)	7.5	0.49 (0.28–0.88)
3 or more	13.5	0.58 (0.30–1.11)	11.2	0.58 (0.29–1.18)	3.4	0.15 (0.05–0.52)
Period						
1994–1998	36.0	1.00 (reference)	16.2	1.00 (reference)	2.7	1.00 (reference)
1999–2003	30.8	0.69 (0.41–1.15)	22.0	1.40 (0.75–2.58)	2.3	0.91 (0.21–3.94)
2004–2008	17.3	0.41 (0.24–0.70)	23.1	1.55 (0.86–2.81)	7.5	3.91 (1.13–13.54)
2009–2013	22.7	0.40 (0.24–0.66)	10.8	0.60 (0.32–1.12)	17.5	11.82 (3.55–39.36)

** EBRT: External Beam Radiotherapy, BRT: Brachytherapy, CRT: chemoradiotherapy*

Table 2b Crude percentages and odds of receiving chemotherapy in patients with metastatic esophageal cancer, diagnosed between 1994 and 2013 in the southern Netherlands (N =1,020)

	Crude % CT	Odds ratio(95% CI)
Sex		
Male	23.2	1.00 (reference)
Female	14.3	0.75 (0.47–1.19)
Age (yrs.)		
<50	43.1	2.37 (1.31–4.31)
50–59	29.5	1.37 (0.92–2.04)
60–69	26.1	1.00 (reference)
70–79	9.3	0.24 (0.15–0.40)
≥80	3.0	0.07 (0.02–0.22)
No. of comorbid conditions		
0	26.6	1.00 (reference)
1	19.5	0.92 (0.63–1.35)
2 or more	13.2	0.78 (0.44–1.37)
Unknown	12.7	0.59 (0.25–1.43)
Social economic status (SES)		
Low	18.0	1.04 (0.66–1.62)
Intermediate	20.7	1.00 (reference)
High	25.6	1.15 (0.77–1.72)
Institutions	10.9	0.76 (0.27–2.16)
Unknown	33.3	1.73 (0.71–4.22)
Histology		
Adenocarcinoma	26.2	1.00 (reference)
Squamous cell carcinoma	9.9	0.30 (0.19–0.48)
No. of metastatic sites		
1	20.5	1.00 (reference)
2	23.8	0.96 (0.64–1.44)
3 or more	22.5	0.62 (0.34–1.13)
Period of diagnosis		
1994–1998	12.6	1.00 (reference)
1999–2003	12.6	0.83 (0.40–1.73)
2004–2008	18.9	1.57 (0.80–3.10)
2009–2013	30.7	3.56 (1.84–6.89)

** CT: chemotherapy*

with chemotherapy, whereas external beam radiotherapy was prescribed less frequently to young patients. Patients aged 70 or older had lower odds of receiving chemotherapy and chemoradiotherapy. Histologic subtype was associated with the receipt of chemotherapy and external beam radiotherapy, patients with squamous cell cancers were more often treated with external beam radiotherapy and less often with chemotherapy compared to patients with adenocarcinomas. In patients with metastases in multiple organs, the odds of receiving chemoradiotherapy were lower.

The median overall survival in patients with metastatic esophageal cancer improved from 18 weeks (1-year survival rate 14,4%) in 1994-1998 to 25 weeks (1-year survival rate 22,4%) in 2009-2013. Table 3 shows the results of a proportional hazard regression analysis. This improvement in survival was no longer observed after adjusting for treatment. Also, we found that the different therapeutic approaches had different survival outcomes. The worst survival was found in 'untreated' patients, who had a median overall survival of 9 weeks (1-year survival rate 4,6%). Patients treated with external beam radiotherapy and brachytherapy had a comparable prognosis of approximately 21-23 weeks (1-year survival rate 9,4%-15,0%). Superior survival was seen in patients treated with chemotherapy, with a median survival of 42 weeks (1-year survival rate 36,0%). Patients treated with chemoradiotherapy had the most favorable prognosis, with a median survival of 51 weeks (1-year survival rate 50,0%). A separate multivariable analysis demonstrated a survival benefit of chemoradiotherapy over systemic chemotherapy (HR 0.63, 95% CI 0.45-0.89, p=0.0086).

Table 3 Crude median overall survival, crude 1-year survival and risk of dying (hazard ratios) of patients with metastatic esophageal cancer, diagnosed between 1994 and 2013 in the southern Netherlands (N = 1,020) »

	Crude median survival (weeks)	Crude 1-year survival (%)	HR (95% CI) without treatment	HR (95% CI) with treatment
Sex				
Male	21.0	16.8	1.00 (reference)	1.00 (reference)
Female	20.1	19.5	0.94 (0.80–1.11)	0.92 (0.78–1.08)
Age6 (yrs.)				
<50	30.6	36.1	0.72 (0.55–0.95)	0.65 (0.49–0.85)
50–59	25.6	21.5	0.86 (0.73–1.02)	0.84 (0.70–0.99)
60–69	22.6	17.0	1.00 (reference)	1.00 (reference)
70–79	19.5	13.7	1.26 (1.07–1.49)	0.97 (0.82–1.15)
≥80	11.0	5.0	2.38 (1.88–3.02)	1.64 (1.29–2.09)
No. of comorbid conditions				
0	24.1	20.3	1.00 (reference)	1.00 (reference)
1	18.7	16.6	1.02 (0.88–1.18)	0.98 (0.85–1.14)
2 or more	17.4	12.0	1.20 (0.99–1.45)	1.08 (0.89–1.31)
Unknown	17.4	12.7	1.24 (0.93–1.65)	0.97 (0.73–1.29)
Social economic status (SES)				
Low	21.1	16.3	0.94 (0.80–1.11)	0.97 (0.82–1.14)
Intermediate	20.7	17.1	1.00 (reference)	1.00 (reference)
High	21.3	19.2	1.03 (0.88–1.20)	1.07 (0.91–1.25)
Institutions	16.1	8.7	1.17 (0.86–1.61)	0.79 (0.57–1.09)
Unknown	26.0	24.2	0.74 (0.50–1.08)	0.83 (0.57–1.23)
Histology				
Adenocarcinoma	21.0	17.6	1.00 (reference)	1.00 (reference)
Squamous cell carcinoma	20.6	16.9	1.03 (0.89–1.19)	1.05 (0.90–1.21)
No. of metastatic sites				
1	24.3	19.7	1.00 (reference)	1.00 (reference)
2	17.4	12.8	1.46 (1.25–1.71)	1.52 (1.30–1.78)
3 or more	10.3	10.1	2.00 (1.58–2.52)	1.87 (1.48–2.37)
Period of diagnosis				
1994–1998	18.3	14.4	1.00 (reference)	1.00 (reference)
1999–2003	19.2	13.1	0.96 (0.75–1.21)	0.99 (0.78–1.25)
2004–2008	19.3	15.0	0.85 (0.68–1.06)	0.93 (0.74–1.17)
2009–2013	25.1	22.4	0.63 (0.50–0.79)	0.87 (0.68–1.10)
Treatment				
No treatment	9.4	4.6	not applicable	2.46 (2.05–2.96)
External beam Radiotherapy	23.3	15.0	not applicable	1.00 (reference)
Brachytherapy	20.7	9.4	not applicable	1.23 (0.97–1.57)
Chemoradiotherapy	50.6	50.0	not applicable	0.40 (0.29–0.56)
Chemotherapy	41.9	36.0	not applicable	0.63 (0.50–0.80)
BRT and EBRT	29.6	26.2	not applicable	0.87 (0.62–1.23)
BRT and CT	32.4	27.3	not applicable	0.75 (0.47–1.20)
CRT and CT	40.4	34.2	not applicable	0.49 (0.23–1.05)

** EBRT: External Beam Radiotherapy, BRT: Brachytherapy, CRT: chemoradiotherapy, CT: chemotherapy*

proportional

Discussion

We assessed the use of external beam radiotherapy, brachytherapy, chemoradiotherapy and chemotherapy in 1,020 patients diagnosed with synchronous metastatic esophageal cancer. Over time, the prescription rate of chemotherapy and chemoradiotherapy increased drastically. Together with appropriate patient selection and stage migration these increases resulted in an improved median overall survival for patients with metastatic esophageal cancer, from 18 weeks in the period 1994-1998 to 25 weeks in 2009-2013.
During the study period, the proportional incidence of synchronous metastases in esophageal cancer increased from 21,9% to 32,1%. The most likely explanation for this phenomenon is stage migration.[12] Earlier and increased detection of metastases was facilitated by the evolution of diagnostic techniques, for instance the improvement of the computed tomography scan (CT) and the introduction of ^{18}F-fluorodeoxyglucose PET.[5] This explanation is supported by the observation that in our study the number of metastatic sites increased in the course of time.

For patients with metastatic esophageal cancer there are several therapeutic options aiming to improve the quality of life and/or prolong survival. The use of the various treatment modalities changed drastically. Since 2004 the use of chemoradiotherapy has increased.[2] In the past decade, several studies demonstrated that chemoradiotherapy in non-metastatic disease resulted in a survival benefit and an impressive downsizing of the primary tumor.[11,13,14] In 2004 the Dutch CROSS trial started investigating the role of preoperative chemoradiotherapy with weekly administration of carboplatin (AUC 2) and paclitaxel (50 mg/m2) during 5 weeks with concurrent radiotherapy (41.4 Gy, in 23 fractions, 5 days per week).[15] This preoperative chemoradiation scheme improved overall survival and was very well-tolerated. We hypothesize that this well-tolerated scheme has been administered increasingly to patients with limited metastatic esophageal cancer as well. However, no additional information on the scheme or dosage of radiotherapy was available in our population-based study.

The use of systemic chemotherapy as a single modality also increased during the study period.[2,11] This increase, especially seen after 2006, parallels the increased use of palliative chemotherapy in metastatic gastric cancer.[16] The palliative chemotherapy schedules of esophageal, esophagogastric junctional and gastric cancer are identical and are often discussed in the same guidelines.

These guidelines state that patients with advanced esophageal cancer derive the same benefits from systemic chemotherapy as patients with gastric cancer.[5] Unfortunately, our dataset contained no additional information on the prescribed agents or combinations.

Our logistic regression analysis showed that treatment choice was not only influenced by the period of diagnosis, but also by patient characteristics. We found that younger patients had lower odds of receiving external beam radiotherapy and higher odds of receiving chemotherapy. Physicians seem reluctant to use chemotherapy in the elderly, either as a single modality or in combination with radiotherapy. This treatment selection according to age has been described previously. Cronin-Fenton et al. stated that the effect of age was explained by the existence of comorbidities.[11] However, after adjustment for comorbidity in our logistic regression analysis, age-related differences persisted. Treatment choice was also influenced by tumor characteristics such as histological subtype and extent of disease. We observed that fewer patients with metastasized squamous cell cancers received chemotherapy. It has been reported that the results achieved with palliative chemotherapy in patients with squamous cell esophageal cancer are inferior to the results achieved in esophageal adenocarcinomas.[10] Another explanation could be the worse physical condition of patients with metastatic squamous cell cancer compared to patients with metastatic adenocarcinomas of the esophagus. Ninety percent of all squamous cell cancers in the developed world are caused by substantial alcohol intake and smoking.[17] Both are well known risk factors for a variety of comorbidities, in particular cardiovascular and pulmonary comorbidities, which might have negatively influenced the prescription of chemotherapy. Consistent with findings of previous studies, we found that external beam radiotherapy was offered less frequently to patients with adenocarcinomas, possibly because less effect is expected from radiation of adenocarcinomas compared to squamous cell tumors.[11,18] Furthermore, patients with metastases in multiple organs had lower odds of receiving chemoradiotherapy. It seems that this modality was preserved for patients with limited metastatic disease.[19] Chemoradiotherapy requires treatment during several weeks and has substantial side effects which, for patients with more advanced disease and a limited lifespan, may not outweigh the potential benefits. We found that the choice of brachytherapy was not influenced by extent of disease, nor by any other patient or tumor characteristic. Single-dose brachytherapy is a safe

modality, with an acceptable toxicity profile and a rapid relief of dysphagia. Therefore it can be widely used in patients with metastatic esophageal cancer with symptomatic stenosis.[20-22]

The survival of patients with synchronous metastatic esophageal cancer increased from 18 weeks in 1994-1998 to 25 weeks in 2009-2013. This finding has been reported before in another Dutch population-based study.[12] The authors suggested that the increase in survival can be attributed to stage migration. It is indeed likely that improved diagnostic accuracy leads to earlier detection of metastases, resulting in a smaller tumor load at time of diagnosis and an improvement of overall survival. Still, the prolonged survival may also have been due to the major changes in treatment strategies, as the beneficial influence of time was not observed anymore after adjusting for treatment in our multivariable hazard regression analysis. In our study, the median overall survival of patients treated with chemoradiotherapy was 51 weeks (1-year survival rate of 50,0%), versus 23 weeks in patients treated with external beam radiotherapy (1-year survival rate of 15,0%). Furthermore, we found a survival benefit of chemoradiotherapy over chemotherapy (median survival 42 weeks, 1-year survival rate of 36,0%). However, no survival benefit of palliative chemoradiotherapy, even over radiotherapy, was found in the TROG 03.01-NCIC CTG ES2 multinational phase III study, which compared palliation of dysphagia and survival in patients treated with radiotherapy or chemoradiotherapy.[23] Our results seem to reflect appropriate patient selection rather than a true effect of treatment. Patients with advanced metastatic disease (metastases in two or more organs) were less likely to be treated with chemoradiotherapy, whereas the extent of disease did not influence the prescription of external beam radiotherapy or chemotherapy. In our study, it was impossible to correctly adjust for extent of disease due to the lack of important variables, such as number of metastases, size of metastases, disease related symptoms and performance status. We hypothesize that chemoradiotherapy was more likely to be prescribed in the fitter patients with a limited number and size of metastases and thus a predetermined improved survival.

The evolving therapeutic options for the treatment of patients with metastatic esophageal cancer, together with appropriate patient selection and stage migration resulted in a prolonged overall survival. Therefore, optimal treatment for patients with metastatic esophageal cancer requires intensive cooperation between different specialists and it is of utmost importance that all patients are discussed in dedicated multidisciplinary teams.

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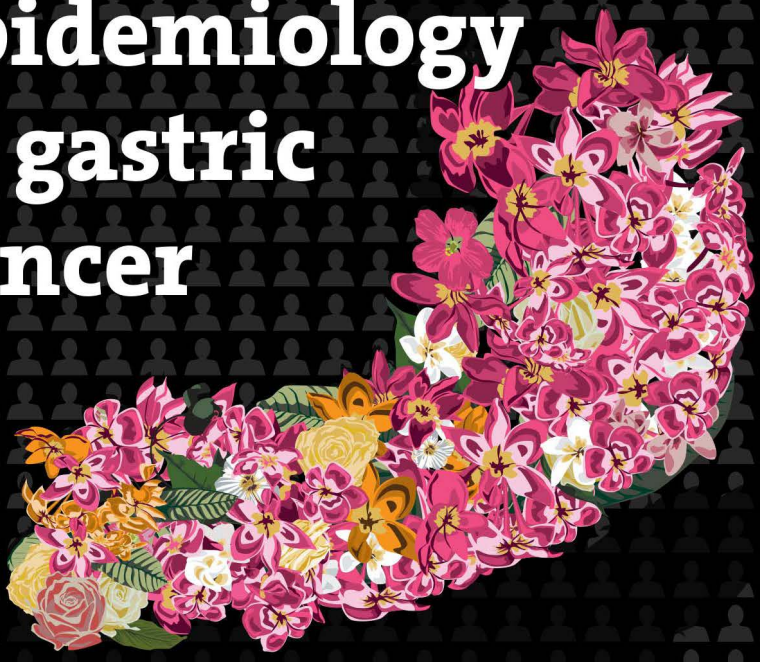
Chapter 3

Epidemiology of gastric cancer



Chapter 3.1
No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy

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Abstract

Background: Gastric cancer often presents in a metastasized stage. We conducted a population-based study to evaluate trends in systemic treatment and survival of metastatic non-cardia gastric cancer.

Methods: All patients with a non-cardia adenocarcinoma of the stomach, diagnosed between 1990 and 2011 in the southern Netherlands were included (N=4,797). We conducted a multivariable logistic regression analysis to evaluate trends in administration of palliative chemotherapy and a multivariable proportional hazards regression analysis to evaluate trends in crude overall survival.

Results: The proportion of patients presenting with metastatic gastric cancer increased from 24% in 1990 to 44% in 2011 (p<0.0001). The use of palliative chemotherapy increased, from 5% in 1990 to 36% in 2011, with a strong increase in particular after 2006 (p<0.0001). Younger patients (<50 yrs: (adjusted odds ratio (OR_{adj}) 3.9, (p<0.001; 50-59 yrs, OR_{adj} 1.7, p=0.01) and patients with a high socioeconomic status (OR_{adj} 1.7, p=0.01) received chemotherapy more often. In contrast, older patients (70-79 yrs OR_{adj} 0.3, p<0.001; 80+ yrs OR_{adj} 0.02, p<0.001), patients with comorbidity (OR_{adj} 0.6, p=0.03), linitis plastica (OR_{adj} 0.5, p=0.03) and multiple distant metastases (OR_{adj} 0.5, p=0.01) were treated with chemotherapy less often. A large inter-hospital variation was observed in the administration of palliative chemotherapy (9-27%). Median overall survival remained constant between 15 (95% CI 11.9-17.7) and 17 (95% CI 15.0-20.0) weeks (p=0.10).

Conclusion: The increased administration of chemotherapy in patients with metastatic gastric cancer did not lead to an increase in population-based overall survival. Identification of the subgroup of patients which benefits from palliative chemotherapy is of utmost importance to avoid unnecessary treatment.

Introduction

Due to lack of early symptoms, gastric cancer often presents in an metastasized stage, characterized by poor survival.[1,2] Several studies have shown that palliative chemotherapy is superior to 'best supportive care' for selected patients, in terms of prolonged survival, reduction of disease-related symptoms and improved quality of life.[3] Although most studies were small and of moderate methodological quality, this evidence has led to the implementation of palliative chemotherapy into national guidelines on the treatment of gastric cancer.[4-6] The NCCN guideline Gastric Cancer for instance, recommends chemotherapy with a two or three drug regimen for patients with metastatic gastric cancer.[5] The Dutch guideline corresponds to the NCCN guideline and recommends a combination including epirubicine, a platinum derivative, and a fluoropyrimidine as first-line palliative treatment.[4]

A recent population-based Dutch study showed that adherence to national guidelines for resectable gastric cancer was suboptimal, only 47% and 56% of the patients received recommended preoperative and postoperative chemotherapy.[7] Data on the prescription of palliative chemotherapy for patients diagnosed with metastatic gastric cancer on daily practice are scarce. In this study we examined trends in the use of chemotherapy for patients metastatic (non-cardia) gastric cancer, diagnosed between 1990 and 2011 in the southern part of the Netherlands. In addition, we assessed to which extent patient and tumor related factors influenced the administration of chemotherapy and if there was any variation in prescription between ten community hospitals. Finally, we evaluated trends in overall survival for patients with metastatic gastric cancer.

Methods

Data collection

Data were obtained from the Eindhoven Cancer Registry in the Netherlands which collects data on diagnosis, staging and treatment of all patients with newly diagnosed cancer. Registration takes place within 6-9 months after diagnosis by specially trained administrators. The Eindhoven Cancer Registry serves approximately 2,4 million inhabitants, about 15% of the Dutch population. It contains data of six pathology departments, the medical records of ten community hospitals and two radiation therapy institutes.

Patients diagnosed with non-cardia adenocarcinoma of the stomach between January 1st 1990 and December 31st 2011 were included. Topography and morphology were coded according to the International Classification of Disease. The following morphology codes were used to classify tumors as adenocarcinoma: 8140-8145, 8210, 8211, 8255, 8260-8263, 8480-8481, 8490, 8560, 8570. Other morphologies were excluded or did not occur during the study period. Tumors were classified according to the TNM classification and staged following the recommendations of the International Union Against Cancer in the respective period (4th-7th edition). Clinical stage was used in case of missing pathological stage. If tumor stage was unknown, it was classified as X.

Since 1993, clinically relevant comorbidities were registered according to a slightly modified version of the Charlson comorbidity index. The social economic status (SES) of individual patients was defined at neighbourhood level using postal codes (17 households on average), combining mean household income and mean value of the house/apartment. Postal codes were assigned to three SES categories: low (1st-3rd deciles), intermediate (4th-7th) and high (8th-10th).[8]

Vital status of patients at January 1st 2012 was assessed through linkage with civil municipal registries and the central Bureau for Genealogy, which collects data on all deceased Dutch Citizens. Survival was calculated based on all-cause mortality.

Statistical analyses

Differences in the prescription of systemic chemotherapy between periods of diagnosis, hospitals of diagnosis and other subgroups were tested by means of a χ^2 test. The independent influence of hospital, patient and tumor characteristics on the administration of palliative chemotherapy was evaluated by means of a logistic regression analysis.

Survival time was defined as the time from diagnosis to death, patients still alive at January 1, 2012 were censored. A log rank test was carried out to evaluate significant differences between survival curves. To discriminate independent risk factors for death a multivariable proportional hazard regression analysis was used.
All tests were two-sided and considered statistically significant if p-values < 0.05. SAS Statistical software (version 9.3) was used to perform all analyses.

Results

Patients with non-cardia gastric cancer diagnosed between January 1st 1990 and December 31st 2011 in the southern part of the Netherlands were included. The final cohort consisted of 4,797 patients, 2,865 men (60%) and 1,932 women (40%) with a median age of 72 years (range 13-100) at the time of diagnosis. The incidence rate of non-cardia gastric cancer in the above mentioned region decreased in the last two decades, from 27 per 100,000 in 1990 to 13 per 100,000 in 2010. A significant proportion of patients with non-cardia gastric cancer presented with metastatic disease at the time of diagnosis (N=1,618). In total, 40% of the patients with metastatic gastric cancer presented with liver metastases with or without concomitant metastases elsewhere, and 44% with peritoneal dissemination. The proportion of patients presenting with metastatic disease at time of diagnosis increased from 24% in 1990 to 44% in 2011 (p<0.0001).

Overall, the proportion of patients with metastatic gastric cancer receiving palliative chemotherapy increased from 5% in 1990 to 36% in 2011 (figure 1). A remarkable increase was seen after 2006. Table 1 shows the odds of receiving chemotherapy for patients with metastatic gastric cancer adjusted for age, gender, SES, comorbidity, histologic subtype, tumor grade, presence and location of distant metastasis, period and hospital of diagnosis. After adjustment, elderly patients (70-79 yrs, ≥80 yrs), patients with concomitant comorbidity and those with multiple distant metastases or linitis plastica received chemotherapy less often. In contrast, chemotherapy was administered more frequently to young patients (< 60 yrs) and patients with a higher SES. Furthermore a large inter-hospital variation was seen in the proportion of patients receiving chemotherapy, varying from 9% to 27%. No improvement in overall survival was observed in the last two decades (figure 2).

The median survival for patients with metastatic gastric cancer remained 15-17 weeks (p=0.10). The overall survival for patients not treated with chemotherapy worsened. Initially, the median survival for untreated patients with metastatic gastric cancer was 16 weeks, whereas in 2008-2011 the median overall survival was only 9 weeks (p<0.001). For patients treated with chemotherapy, the overall survival remained stable between the 32-37 weeks (p=0.39). In a multivariate model chemotherapy was positively associated with survival. After adjustment, male gender, a poor or undifferentiated tumor, the presence of liver or multiple metastases were negative prognostic factors (table 2).

Table 1 Crude percentages and adjusted odds for receiving chemotherapy among patients diagnosed with metastatic gastric cancer, in the southern Netherlands between 1990 and 2011 (N=1,618)

	Crude % treated with chemo	Odds ratio (95% CI)
Sex		
Male	18.2	1.00 (reference)
Female	16.0	0.89 (0.64-1.23)
Age		
<50	44.9	3.90 (2.31-6.59)
50-59	28.7	1.71 (1.11-2.64)
60-69	22.4	1.00 (reference)
70-79	10.6	0.30 (0.20-0.45)
≥80	1.2	0.02 (0.01-0.08)
Social economic status (SES)		
Low	12.3	1.00 (reference)
Intermediate	17.8	1.30 (0.86-1.95)
High	24.4	1.75 (1.16-2.64)
Comorbidity [b]		
0	27.0	1.00 (reference)
1	17.0	0.65 (0.44-0.96)
≥2	16.3	0.82 (0.54-1.25)
Histologic subtype		
Adenocarcinoma	16.3	1.00 (reference)
Signetcell carcinoma	22.8	0.84 (0.54-1.31)
Linitis plastica	18.1	0.52 (0.29-0.93)

Table 1 Continued

	Crude % treated with chemo	Odds ratio (95% CI)
Tumour grade		
Well/moderate	16.4	1.00 (reference)
Poor/undifferentiated	50.7	0.93 (0.60-1.44)
Unknown	32.9	1.03 (0.63-1.69)
Metastasis		
Lung	30.8	2.69 (0.60-12.09)
Liver	15.8	1.00 (reference)
Peritoneum	16.8	0.66 (0.42-1.02)
Extra regional nodes	19.0	0.94 (0.54-1.63)
Other	14.7	0.51 (0.27-0.97)
2 organs	18.3	0.54 (0.33-0.86)
3+ organs	28.9	0.83 (0.35-1.99)
Period of diagnosis		
1990-1995	7.4	1.00 (reference)
1996-2001	12.6	1.10 (0.64-1.87)
2002-2007	20.8	2.72 (1.64-4.54)
2008-2011	33.9	7.89 (4.58-13.59)
Hospital of diagnosis		
Hospital A	8.9	1.00 (reference)
Hospital B	16.5	2.84 (1.28-6.31)
Hospital C	17.4	2.58 (1.27-5.22)
Hospital D	9.1	0.92 (0.36-2.33)
Hospital E	20.5	3.68 (1.82-7.46)
Hospital F	16.0	2.69 (1.48-4.88)
Hospital G	27.2	5.18 (2.92-9.19)
Hospital H	17.3	3.37 (1.71-6.65)
Hospital I	25.2	5.52 (2.88-10.59)
Hospital J	15.7	1.98 (0.96-4.08)

[a] *Adjusted for all variables listed. Included in the analysis but results not shown for SES institutions, SES unknown, comorbidity unknown and tumor grade unknown.*

[b] *Comorbidity is registered since 1993*

Figure 1 Prescription of chemotherapy in patients diagnosed with metastatic non-cardia gastric cancer over time 1990-2011 (N=1,618)

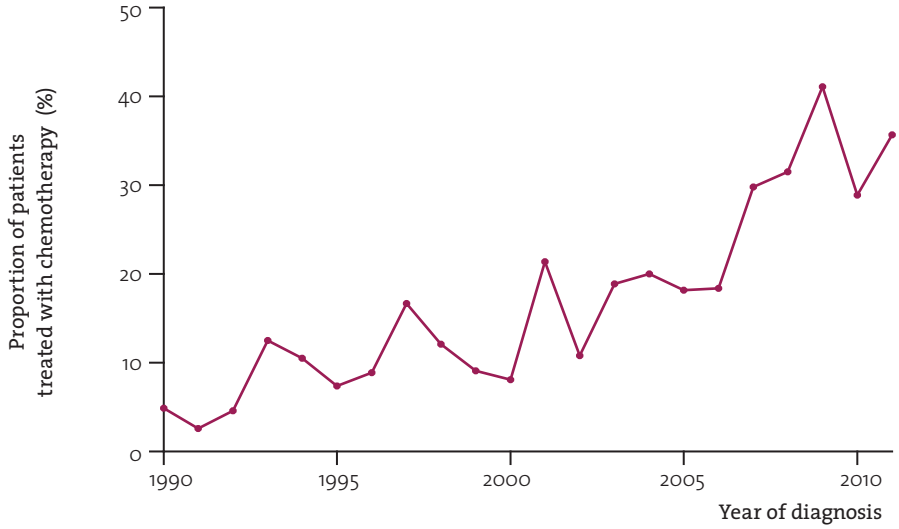

Figure 2 The overall survival in weeks of patients diagnosed with metastatic non-cardia gastric cancer between 1990 and 2011 in the southern Netherlands according to the period of diagnosis (N=1,618)

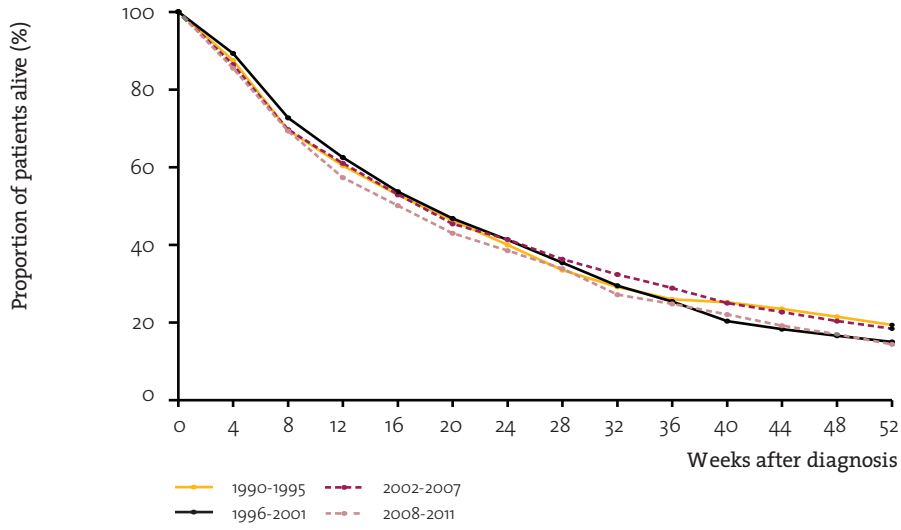

Table 2 Risk of dying (Hazard ratios)[a] for patients with metastatic non-cardia gastric cancer, diagnosed between 1990 and 2011 in the South of the Netherlands (N=1,618)

	HR	(95% CI)
Sex		
Male	1.00	(Reference)
Female	0.83	(0.74-0.92)
Age		
<50	0.98	(0.79-1.22)
50-59	0.86	(0.73-1.02)
60-69	1.00	(Reference)
70-79	1.06	(0.93-1.20)
≥80	1.12	(0.94-1.33)
SES		
Low	1.00	(Reference)
Intermediate	0.94	(0.83-1.07)
High	0.95	(0.83-1.09)
Comorbidity		
0	1.00	(Reference)
1	0.96	(0.84-1.11)
≥2	0.99	(0.85-1.15)
Histologic subtype		
Adenocarcinoma	1.00	(Reference)
Signetcell carcinoma	1.00	(0.86-1.16)
Linitis plastica	1.21	(0.99-1.47)
Tumour grade		
Well/moderate	1.00	(Reference)
Poor/undifferentiated	1.33	(1.15-1.53)
Unknown	1.28	(1.09-1.50)
Location metastasis		
Lung	0.40	(0.22-0.71)
Liver	1.00	(Reference)
Peritoneum	0.63	(0.54-0.72)
Extra regional nodes	0.45	(0.37-0.54)
Other locations	0.70	(0.57-0.87)
2 > locations	0.96	(0.82-1.13)
3 > locations	0.83	(0.60-1.15)

Table 2 Continued

	HR	(95% CI)
Period of diagnosis		
1990-1995	1.00	(Reference)
1996-2001	1.08	(0.92-1.27)
2002-2007	1.09	(0.93-1.27)
2008-2011	1.38	(1.14-1.67)
Hospital of diagnosis		
Hospital A	1.00	(Reference)
Hospital B	1.27	(0.99-1.63)
Hospital C	1.24	(0.99-1.54)
Hospital D	1.08	(0.84-1.38)
Hospital E	1.26	(1.00-1.57)
Hospital F	1.17	(0.98-1.40)
Hospital G	1.01	(0.84-1.21)
Hospital H	1.18	(0.95-1.45)
Hospital I	1.13	(0.92-1.39)
Hospital J	1.29	(1.04-1.61)
Chemotherapy		
No	1.00	(Reference)
Yes	0.50	(0.43-0.59)

[a] *Adjusted for all variables listed. Included in the analysis but results not shown for SES institutions, SES unknown, comorbidity unknown, and tumor grade unknown.*

[b] *Comorbidity is registered since 1993*

Discussion

An increasing percentage of patients with gastric cancer is diagnosed with metastatic disease. Although the proportion of patients treated with palliative chemotherapy increased drastically, it did not lead to an increase in the population-based overall survival in patients with metastatic gastric cancer.

The proportion of patients presenting with metastatic disease at time of diagnosis increased from 25% in 1990 to 44% in 2011. Improved staging procedures have played an important role. The modern improved computed tomography

scan (CT) sometimes in combination with positron emission tomography (PET scan) further enhanced the diagnostic process.[9,10] These evolving technologies presumably led to stage migration by earlier and increased detection of distant metastases, mostly occurring in liver and peritoneum.[10] In addition, altered and more aggressive biological behavior of gastric cancer, could also be related to the rising proportion of patients presenting with metastatic disease. Nevertheless, to our knowledge no data are available on this subject and further investigation is needed.

Several randomized trials have shown that systemic chemotherapy can reduce disease related symptoms and improve median survival, from approximately 4 months to 11 months in selected patients with metastatic gastric cancer.[3] This benefit of palliative chemotherapy over best supportive care alone was already reported in several studies in the early nineties.[3] The last Cochrane review on chemotherapy for advanced and metastatic gastric cancer concluded that combination regimens including 5-FU or capecitabine and oxaliplatin or cisplatin, with or without an anthracycline, or docetaxel and irinotecan-based regimens can be considered as reasonable treatment options.[3]

The newly introduced agents, oxaliplatin, docetaxel and irinotecan have an altered and often a more favorable toxicity profile, but provide similar overall survival as previous studied agents. Despite modest changes for the treatment of metastatic gastric cancer, the administration of palliative chemotherapy increased drastically, in particular after 2006. In 1990, 5% of patients with metastatic gastric cancer was treated with palliative chemotherapy. Gradually, the percentage increased to 20% in 2006, and even 36% in 2011. In 2005, Cunningham published the results of the REAL-2 trial in which capecitabine and oxaliplatin were established as equal substitutes of fluorouracil and cisplatin in triplet regimens for the treatment of metastatic gastric cancer.[11] Furthermore, in 2006 Cunningham et al published the MAGIC trial in which they demonstrated that perioperative chemotherapy with a regimen of epirubicin, cisplatin and infused fluorouracil (ECF) significantly improved progression-free and overall survival for patients with resectable gastric cancer.[12] Presumably, the growing experience with combination chemotherapy for the treatment of gastric cancer has led to a stronger increase in the administration of palliative chemotherapy in the past years..

The current study demonstrates that patients with a lower socio-economic status (SES), advanced age and comorbidity were less likely to be treated

with chemotherapy. In addition, tumor-related factors such as metastases in multiple organs and linitis plastica were adversely related to the prescription of chemotherapy as well. The increased hazard of death for patients with linitis plastica, although of borderline significance, suggests that this is a negative prognostic factor. The presence of metastases in multiple organs was not associated with an increased risk of dying compared to patients with liver metastases only. However, due to the population-based nature of our data we do not know to which extent above mentioned conditions had impact on performance status, nutritional status etc and in this manner influenced the prescription of chemotherapy. The reluctance to prescribe chemotherapy for elderly patients has already been described in previous studies.[13,14] Also, treatment selection according to SES has frequently been reported for curative cancer treatments.[15-17] However, only a few studies have reported the effect of SES on treatment decisions in the palliative setting. Recently, Swedish investigators established high education level as an important socioeconomic variable, associated with more intensive treatments.[18] In a multivariate model adjusting for case-mix, a marked hospital variation was found in the prescription of palliative chemotherapy, varying between 9-27%. Decisions concerning the use of chemotherapy in patients with metastatic cancer are complex.[19,20] A recent study found that the physicians' individual treatment recommendations were strongly influenced by the amount of experience and their judgment about the benefit of the treatment and biological age of the patient.[20]

Despite the increased prescription of palliative chemotherapy and the presumed stage migration, the overall survival of all patients with metastatic gastric cancer did not change over time. Median survival of patients with metastatic disease remained poor, between 15 and 17 weeks. As expected, poor/undifferentiated tumors and the presence of multiple metastases were associated with poor survival.[21] Consistent with previous reports, in case of single site metastases, dissemination to the liver was identified as an independent adverse prognostic factor as well.[22] In addition to tumor related prognostic factors, there was a significant effect of gender on overall survival. We found that women with metastatic gastric cancer had a better survival compared to their male counterparts. According to the study of Yang et al, using the data of the SEER registry, this difference was associated to race and limited to African Americans and White patients. This race specific gender difference in survival is possibly related to sex hormones, their receptor expression and possible

interaction with her2neu receptor pathways.[23] Our data do not confirm the finding from Yang et al that younger patients with metastatic gastric cancer have an improved overall survival. However, the SEER registry lacks information on systemic chemotherapy.[24]

Survival of patients treated with systemic chemotherapy in the last two decades remained stable between 32 and 37 weeks. This may reflect the lack of a major breakthrough in the efficacy of the cytotoxic drugs used for the treatment of gastric cancer. The survival of patients not treated with palliative chemotherapy worsened in the last two decades, from an initial survival of 16 weeks to a survival of only 9 weeks in the most recent period. This is probably due to selection bias, patients who are medically fit are more likely to be treated with palliative chemotherapy. The oldest and/or most frail patients remain untreated. Due to the population-based nature of our data, detailed information on the patients health and nutritional status were not available. Even so, information concerning established prognostic factors such as body mass index, ECOG performance status of the patient and symptoms like ascites are lacking in our database.[25,26] These factors influence prognosis and presumably the administration of chemotherapy in daily practice.

Conclusion

In conclusion, the increased administration of chemotherapy for patients with metastatic gastric cancer did not lead to an increased population-based overall survival. A subgroup of patients might benefit from palliative chemotherapy, but more research is necessary to establish prognostic and in particular predictive factors for patients with metastatic gastric cancer.

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Chapter 3.2
Chemotherapy as palliative treatment for peritoneal carcinomatosis of gastric cancer

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Introduction

Gastric cancer is known for its aggressive behavior. Most patients present with advanced, inoperable or metastatic disease. In the absence of curative treatment modalities, systemic chemotherapy can be considered as a reasonable treatment option for these patients. Previous studies showed that, in selected patients, chemotherapy is superior to ' best supportive care ' in terms of prolonged survival, reduction of disease-related symptoms and improved quality of life.[1] Therefore, international guidelines recommend palliative chemotherapy with a two or three drug regimen for patients with metastatic gastric cancer.[2,3]

In patients with gastric cancer, dissemination to the peritoneum is common. Up to 14% of all newly diagnosed patients presents with peritoneal carcinomatosis (PC).[4] The efficacy of palliative chemotherapy in patients with PC from gastric origin has not been well studied. It is hypothesized that the effect of intravenous chemotherapy on peritoneal metastases is limited due to the peritoneal blood barrier. Peritoneal dissemination is therefore thought to be an adverse prognostic factor.[5] Comprehensive data regarding the use and effectiveness of systemic chemotherapy for this subset of patients is virtually absent. The aim of this population-based study was to evaluate trends in systemic treatment and survival of patients with PC of gastric origin.

Methods

Data collection

The Eindhoven Cancer Registry registers all newly diagnosed cancer patients in the southern part of the Netherlands, including ten community hospitals, six pathology departments and two radiotherapy institutions, comprising 2.4 million inhabitants. All patients diagnosed between 1995 and 2011 with an

adenocarcinoma of gastric origin were included. Information on patient and tumor characteristics was extracted from the medical records by specially trained administrators of the cancer registry. Anatomical sites of distant metastases are registered according to the International Classification of Disease-Oncology (ICD-O). Chemotherapy (yes vs. no) was defined as receiving cytostatic drugs of any kind. By means of an independent case ascertainment method, the completeness of the registration is estimated to exceed 95%.[6] The vital status of all patients was assessed on January 1, 2012 through merging with the Municipal Administrative Databases in which all deceased and emigrated persons in the Netherlands are registered.

Statistical analyses

Statistical analysis differences between patients who were treated with palliative chemotherapy and patients who were not, were tested by means of a χ^2 -test. To investigate trends in treatment and survival, patients were categorized into four groups by period of diagnosis: 1995 – 1998, 1999 – 2002, 2003 – 2006 and 2007 – 2011. Survival time was defined as the time from cancer diagnosis until death; patients still alive at January 1, 2012 were censored. Crude survival was determined by the Kaplan-Meier method and compared using a log-rank test. Cox regression analysis, adjusting for age, gender, period of diagnosis, co-morbidity, tumor differentiation grade, tumor stage, lymph node stage, and surgery, was used to determine the relationship between chemotherapy and two-year mortality among patients with PC. A hazard ratio (HR) was provided with the 95% confidence interval (CI). All tests of statistical significance were two sided. SAS/STAT statistical software (SAS system 9.3, SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Between 1995 and 2011, 5,220 patients were diagnosed with gastric cancer, of whom 2,029 patients (39%) had metastatic disease at presentation[4]. Of these patients, 706 patients (34%) were diagnosed with PC, of whom 491 patients had PC as the only metastatic site and 215 patients had PC combined with other metastases. In total, 168 patients (24%) were treated with palliative chemotherapy. Younger patients, patients with less co-morbidities and patients with lower N-stage were significantly more likely to be treated with chemotherapy (table 1).

Table 1 General characteristics of patients diagnosed between 1995 and 2011 in the south of the Netherlands with peritoneal carcinomatosis of gastric origin (N=706)

	Chemotherapy		No chemotherapy		P-value
	N = 168	%	N = 538	%	
Age (years)					<.0001
<60	82	40	121	60	
60-69	51	25	150	75	
70-79	34	16	182	84	
>80	1	1	85	99	
Gender					0.743
Male	102	24	319	76	
Female	66	23	219	77	
Peritoneal carcinomatosis					0.586
without other metastases	114	23	377	77	
with other metastases	54	25	161	75	
Period of diagnosis					<.0001
1995-1998	20	11	155	89	
1999-2002	24	16	130	84	
2003-2006	28	19	123	81	
2007-2011	96	42	130	58	
Number of comorbid conditions					0.006
0	71	32	153	68	
1	77	20	308	80	
≥2	12	18	56	82	
Unknown	8	28	21	72	
Localization of the primary tumor					0.002
Cardia	29	32	63	68	
Fundus of stomach	2	20	8	80	
Body of stomach	24	30	55	70	
Gastric antrum	19	15	112	85	
Pylorus	3	9	31	91	
Lesser curvature	4	13	28	87	
Greater curvature	9	43	12	57	
Overlapping lesions/ NOS	78	25	229	75	

Table 1 Continued

	Chemotherapy		No chemotherapy		P-value
	N = 168	%	N = 538	%	
T stage of the primary tumor					0.086
T0	0	0	1	100	
T1	1	20	4	80	
T2	17	22	59	78	
T3	27	27	73	73	
T4	30	21	115	79	
Tx	93	25	286	75	
N stage of the primary tumor					0.012
N0	33	35	62	65	
N1	9	14	57	86	
N2	11	18	50	82	
Nx	115	31	260	69	
Differentiation grade of the primary tumor					0.061
Well/moderately	21	18	97	82	
Poorly/ undifferentiated	87	23	294	77	
Unknown	60	29	147	71	
Tumor histology					0.483
Adenocarcinoma	97	22	341	78	
Signet ring cell	45	28	116	72	
Linitis plastica	22	25	65	75	
Other	4	20	16	80	
Resection					0.081
Yes	25	18	113	82	
No	143	75	425	25	

PC: peritoneal carcinomatosis; NOS: not otherwise specified

Figure 1 Percentage of patients treated with chemotherapy in patients diagnosed with peritoneal carcinomatosis of gastric cancer origin only, peritoneal carcinomatosis combined with other metastases and non-metastatic gastric cancer according to period of diagnosis

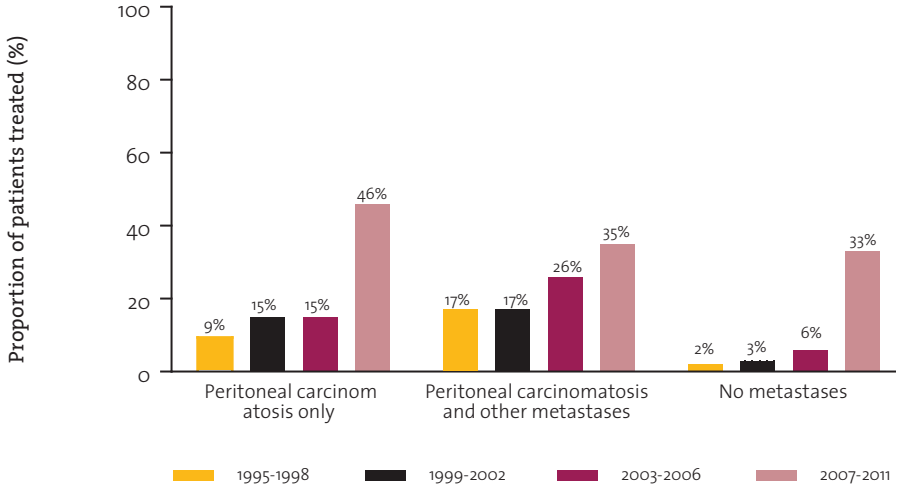

Table 2 Median overall survival for patients with peritoneal carcinomatosis from gastric origin, diagnosed between 1995-2011 in the South of the Netherlands, according to treatment (N=706)

	Chemotherapy		No chemotherapy		Total	
	N	MS(95%CI)	N	MS(95%CI)	N	MS(95%CI)
1995-2011	168	7.7 (6.8-8.6)	538	3.4 (3.0-3.7)	706	4.1 (3.7-4.6)
1995-1998	20	5.7 (4.1-9.7)	155	4.3 (3.6-5.8)	175	5.1 (3.8-5.8)
1999-2002	24	7.5 (4.4-8.9)	130	3.8 (3.0-5.2)	154	4.5 (3.4-5.3)
2003-2006	28	7.7 (5.8-11.0)	123	3.2 (2.3-3.7)	151	3.7 (2.8-4.5)
2007-2011	96	7.9 (6.8-10.5)	130	2.2 (1.7-2.7)	226	4.0 (3.1-4.8)
P log-rank	0.310		<.0001		0.740	

MS: median survival in months, CI: confidence interval

Table 3 Risk of dying (hazard ratios) for patients with peritoneal carcinomatosis from gastric origin, diagnosed between 1995-2012 in the South of the Netherlands (N=706)

	HR (95%CI)
Age	
<60	1.0 (reference)
60-69	1.0 (0.8-1.2)
70-79	1.2 (1.0-1.5)
≥80	1.4 (1.1-1.9)
Gender	
Male	1.0 (reference)
Female	0,9 (0.7-1.0)
Period of diagnosis	
1995-1998	1.0 (reference)
1999-2002	1.0 (0.8-1.3)
2003-2006	1.1 (0.9-1.4)
2007-2011	1.3 (1.0-1.7)
T stage of primary tumour	
T1,2	1.0 (reference)
T3	0,8 (0.6-1.1)
T4	0,9 (0.7-1.2)
TX	1.5 (1.1-2.0)
N stage of primary tumour	
N0	1.0 (reference)
N+	1.4 (0.7-2.8)
Nx	1.8 (0.7-4.3)
Differentiation grade of primary tumour	
Well/moderately	1.0 (reference)
Poorly/undifferentiated	1.4 (1.1-1.8)
Unknown	1.4 (1.1-1.8)
Surgery	
Yes	0.6 (0.3-1.2)
No	1.0 (reference)
Chemotherapy	
Yes	0.5 (0.4-0.6)
No	1.0 (reference)

HR: hazard ratio; CI: confidence interval

Furthermore, the percentage of patients treated with chemotherapy increased over time (p<0.001, figure 1). In the period 1995 – 1998, 11% of the patients with PC were treated with chemotherapy as compared with 42% in the most recent period.

Median survival of patients with PC was 4 months. For those receiving chemotherapy, this was 7.7 months compared to 3.4 months in patients receiving best supportive care (p<0.001, table 2). Crude median survival did not significantly increase over time among all PC patients and among patients treated with chemotherapy (p=0.740 and p=0.310, respectively). Crude survival of patients who did not receive chemotherapy decreased over time (p<0.0001). After adjusting for age, gender, period of diagnosis, co-morbidity, tumor differentiation grade, tumor stage, lymph node stage, and surgery, patients with PC who were treated with palliative chemotherapy had a reduced risk to die within two years after gastric cancer diagnosis (HR=0.48, 95% CI 0.38 – 0.60, table 3).

Discussion

Gastric cancer is the second most common cause of cancer-related death in the world.[7] Although the age-standardized incidence rates have decreased in the Netherlands, a growing proportion of patients presents in a more advanced or metastatic disease stage.[8] Peritoneal dissemination is the most common metastatic site.

There has been a strong increase in the prescription of combination chemotherapy in patients with advanced gastric cancer, especially after publication of the REAL-2 trial in 2005 and MAGIC trial in 2006.[9,10] Despite the increased prescription rates of palliative chemotherapy in patients with peritoneal carcinomatosis, crude median overall survival did not improve over time. This might suggest that palliative chemotherapy is of limited value for gastric cancer patients suffering from PC. As mentioned previously, the effect of intravenous chemotherapy in this subgroup of patients might be limited due to the peritoneal blood barrier. Ross et al. revealed that systemically treated patients with PC had a response rate of 15% compared to 43% in patients with metastases of other origin.[11] The theory of Ross seems to be in conflict with our multivariable logistic regression analysis showing a reduced risk of dying for PC patients treated with palliative chemotherapy compared to non-treated PC patients. However, this study also showed that younger patients, patients with less

co-morbidities and patients with a lower N-stage were more likely to be treated with chemotherapy, which is in line with previous studies, as is the reluctance to prescribe chemotherapy to old and frail patients.[12] Therefore, the reduced risk of dying might also be attributed in part by a selection bias. Younger and fitter patients, those with a better overall survival beforehand, are more likely to be treated with chemotherapy. We hypothesize that other patient characteristics such as performance status, nutritional status and disease related symptoms played a role as well. Unfortunately, due to the population-based character of our study we were unable to adjust for these possible confounders.

Few clinical studies have reported on the effect of chemotherapy in patients with peritoneal carcinomatosis from gastric cancer. One study, including 172 PC patients, found that treatment with chemotherapy improved the one-year survival rate from 4.6% to 23.9%. However, after correction for tumor and patient characteristics this survival benefit was not reproduced in a multivariate analysis ($p<0.082$).[13] A promising agent for the treatment of advanced gastric cancer might be S-1. Shigeyasu et al. found a median overall survival of 15.3 months in a small phase II study, including 19 patients with PC of gastric origin. In this study S-1 was combined with docetaxel.[14] Izuishi et al. reported a survival benefit of S-1 over 5-FU in patients with peritoneal carcinomatosis of gastric origin.[15] Although S-1 has proven to be a useful alternative to 5-FU for patients with advanced gastric cancer, it is mainly prescribed in Asian countries.[16]

Furthermore, it might be effective to combine cytoreductive surgery with intra-peritoneal chemotherapy. A systemic review by Gill et al. showed an improvement of median overall survival from 7.9 months to 15 months in patients with PC from gastric origin.[17]

Conclusion

In conclusion, the use of chemotherapy increased in patients with PC of gastric origin. However, this did not result in prolongation of median overall survival on a population-based level. The beneficial effect of current chemotherapy regimens remains questionable in this subgroup of patients. Given the poor prognosis of these patients if left untreated, further research should be performed to optimize therapy, which may include multi-modality treatment with intra-peritoneal chemotherapy.

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Chapter 4
Epidemiology of adenocarcinomas of the small bowel

Chapter 4.1
Trends in incidence, treatment and survival of small bowel adenocarcinomas between 1999-2013: A population-based study in the Netherlands

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Abstract

Background: We conducted a population-based study to establish the incidence, treatment and overall survival over time of patients with small bowel adenocarcinoma.

Methods: All patients diagnosed with small bowel adenocarcinoma in the Netherlands between 1999 and 2013 were included (N=1,775). Age-standardized incidence rates were calculated per 100.000 person-years using the European standardized population rate. The influence of patient and tumor characteristics on the administration of chemotherapy was analyzed by means of a multivariable logistic regression analysis. The Cochran-Armitage trend test was conducted to evaluate trends in treatment and survival and the cox proportional hazards model was used to identify prognostic factors of overall survival.

Results: The incidence of small bowel adenocarcinomas increased, mainly due to an almost twofold increase of duodenal adenocarcinomas. Patients with locoregional duodenal tumors were less likely to undergo surgery (58%), compared to 95% of the locoregional jejunal and ileal tumors (p<0.0001). The use of chemotherapy doubled for adjuvant (7 to 15%) and palliative chemotherapy (19 to 37%). Median overall survival of patients with locoregional disease increased from 19 to 34 months (p=0.0006), whereas median overall survival of patients with metastatic disease remained 4-5 months. Favorable prognostic factors in locoregional disease, identified by multivariable survival analysis, included age < 60 years, tumor stage I or II, diagnosis in 2009-2013, surgical treatment and

treatment with chemotherapy. Favorable prognostic factors in metastatic disease were age < 50 years, jejunal tumors, surgical treatment and treatment with chemotherapy.

Conclusion: Small bowel adenocarcinomas are rare tumors with an increasing incidence. The administration of adjuvant and palliative chemotherapy doubled, but median overall survival only increased for patients with locoregional disease. Given the rarity and dismal prognosis, it is important to develop international studies to determine the optimal treatment for these patients.

Introduction

Small bowel tumors are rare malignant tumors, accounting for less than 5% of all gastrointestinal tumors, but the incidence is rising.[1] Small bowel tumors have an unequal distribution in the small intestine. The preferred location depends on the histological subtype. The four major subtypes of small bowel tumors are adenocarcinomas, neuroendocrine tumors (including carcinoids), gastro-intestinal stromal tumors (GIST) and lymphomas.[2] Adenocarcinomas and neuroendocrine tumors are the most common subtypes in the small intestine, both accounting for approximately 40% of small bowel tumors.[3-5]

Patients with small bowel adenocarcinomas merely present with non-specific symptoms, such as vague abdominal pain, weight loss, nausea and vomiting, bowel obstruction, gastrointestinal bleeding or anemia, which challenges the diagnosis. Known predisposing risk factors for these tumors are autoimmune disorders including celiac disease, Crohn's disease and several hereditary cancer syndromes, including familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC) and the Peutz-Jeghers syndrome. These predisposing genetic disorders also play a role in the pathogenesis of colon cancer. Although the precise pathogenesis of small bowel adenocarcinomas is unknown, most available data suggest a carcinoma sequence driven multistep process of specific genetic changes similar to colorectal cancers.[5-9]

Due to the rarity of the disease, data about small bowel adenocarcinomas are scarce, diverse and contradictory. Therefore we conducted a population-based

study to establish the incidence, treatment and overall survival over time of patients with a small bowel adenocarcinoma in the Netherlands between 1999 and 2013.

Methods

Data collection

For this study, data were retrieved from the Netherlands Cancer Registry (NCR), which is managed by the Comprehensive Cancer Organization the Netherlands. The nationwide NCR covers nearly 17 million inhabitants and comprises population-based data on all newly diagnosed malignancies. Primary source of notification of the NCR is the automated nationwide pathological archive (PALGA), supplemented with data from the National Registry of Hospital Discharge Diagnoses. Required information on diagnosis, treatment, patient- and tumor characteristics are routinely extracted from hospital medical records by specially trained registrars operating on behalf of the NCR.

Patients were included if they were diagnosed between 1999 and 2013 with an adenocarcinoma of the small intestine, according to the third version of the International Classification of Disease for Oncology (ICD-O) (topography code C17). Tumors with the following morphology codes were classified as adenocarcinomas: 8140, 8144, 8145, 8210, 8255, 8260, 8261, 8263, 8480, 8481, 8490, 8560, 8570, 8574. Patients with adenocarcinomas arising from a Meckel's diverticulum, as well as patients with neuroendocrine tumors, gastrointestinal stromal tumors, lymphomas or undifferentiated tumors in the small intestine were excluded from analysis.

All adenocarcinomas were classified according to the Tumor Lymph Node Metastasis (TNM) classification and were staged following the recommendations of the International Union Against Cancer in the respective period. The tumors were categorized in two groups, either as locoregional ($T_{1-4}N_{0-2}M_0$) or metastatic cancer ($T_{1-4}N_{0-2}M_1$).

Vital status of patients was assessed at January 1, 2014 through linkage with civil municipal registries and the central bureau for genealogy, which collects data on all deceased Dutch inhabitants. Survival was computed based on all-cause mortality.

Statistical analyses

Descriptive statistics were used to describe the patient and tumor characteristics. Differences in certain tumor characteristics and treatment between the locoregional and metastatic group were compared and analyzed using a two-sided χ^2-test. To evaluate trends in treatment and survival, patients were categorized by period of diagnosis (1999-2003, 2004-2008 and 2009-2013), and subsequently, trends between the subgroups were analyzed by means of a Cochran-Armitage trend test.

Age-standardized incidence rates were calculated per 100,000 person-years using the European standardized population rate (ESR) for the respective study period. Estimated annual percentage changes (EAPCs) in incidence were estimated by Poisson regression models. The independent influence of relevant patient and tumor characteristics on the administration of chemotherapy for patients with locoregional and metastatic disease was analyzed by means of a multivariable logistic regression analysis, including the 95% confidence interval (CI).

Survival time was defined as the time from date of diagnosis to death. Patients who were lost to follow-up or still alive at 1 January 2014 were censored. Evaluation of significant differences of survival between the subgroups occurred by means of a log-rank test. Multivariable survival analyses, using the cox proportional hazards model, were carried out to identify independent prognostic factors of overall survival. In order to investigate the effect of therapy on the hazard ratios (HR) of dying, two separate multivariable models were run with and without treatment variables (surgery yes vs. no and chemotherapy yes vs. no). Hazard ratios were presented with 95% confidence intervals.
The statistical package SAS Statistical software (version 9.4, SAS institute, Cary, NC, USA) was used to analyze the data. For all statistical tests, a two-sided p-value $p < 0.05$ was considered as statistically significant.

Results

A total of 3,930 patients were diagnosed with a small bowel tumor between January 1, 1999 and December 31, 2013 in the Netherlands. The most common histological subtype was adenocarcinoma, accounting for 1,775 cases (45%), followed by neuroendocrine tumors (1,429 patients, 36%) and gastro-intestinal stromal tumors (529 patients, 13%). The 1,775 patients diagnosed with an adenocarcinoma were enrolled in this study.

The patients' characteristics are summarized in table 1. We found an equal gender distribution, the median age at time of diagnosis was 69 (range 17-97). The tumors were mainly located in the duodenum (58%), and respectively 19% and 14% in the jejunum and the ileum. A comparison between patients diagnosed with tumors located in the duodenum versus patients with tumors located elsewhere in the small intestine showed that patients with tumors in the duodenum were often slightly older and more frequently had a tumor with a higher or unknown tumor stage.

The age-standardized incidence of small bowel adenocarcinomas increased from 0.5 per 100,000 inhabitants in 1999 to 0.7 per 100,000 inhabitants in 2013 with an estimated annual percentage change (EAPC) of 3.7% ($p<0.001$). The increased incidence of small bowel adenocarcinomas was mainly caused by a twofold increase of duodenal adenocarcinomas from 233 in 1999-2003 to 478 cases in 2009-2013 ($p= 0.013$) (figure 1).

Thirty-three percent of the patients had metastatic disease. Over time the proportion of patients presenting with metastases increased from 27% in 1999-2003 to 38% in 2009-2013 ($p<0.0001$). Moreover, the percentage of patients presenting with metastases in multiple organs increased as well from 8% in 1999-2003 to 28% in 2009-2013 ($p=0.0003$). The most common metastatic site was the liver (46%), followed by the peritoneal cavity (29%) and extra regional lymph nodes (12%). Patients with metastatic disease arising from duodenal origin showed a different metastatic pattern compared to patients with primary tumors located elsewhere in the small intestine. The majority of patients with metastatic duodenal adenocarcinomas had metastases located in the liver (54%), whereas in patients with metastases from non-duodenal adenocarcinomas the peritoneal cavity was the most frequently affected site (44%).

In the group of patients with locoregional disease, 73% underwent a surgical resection of the primary tumor in contrast to 30% of the patients with metastatic disease ($p<0.0001$). The percentage of patients with locoregional disease undergoing a resection slightly increased from 71% in 1999-2003 to 77% in 2009-2013, while the percentage of patients with metastatic disease undergoing a surgical resection of the primary tumor decreased from 38% to 25% ($p=0.0031$).

Tumor location was an important predictive factor for surgery. In locoregional disease, 58% of the patients with duodenal carcinomas underwent a surgical intervention with curative intent compared to 95% of the patients with jejunal and ileal carcinomas ($p<0.0001$). The percentage of patients with

Table 1 Characteristics of patients diagnosed with a small bowel adenocarcinoma, in the Netherlands between 1999 and 2013 according to primary tumor localization (N=1,775)

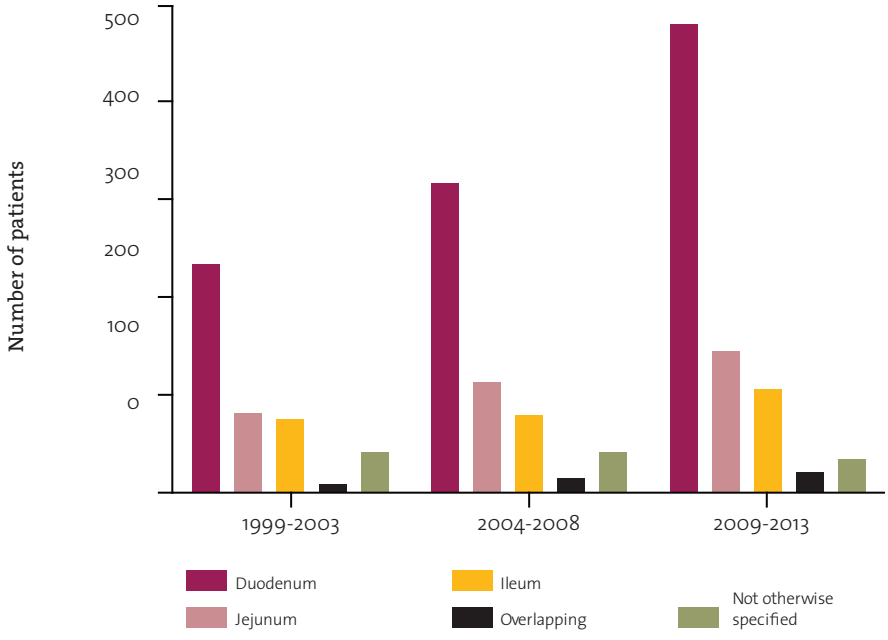
	Total		Duodenum		Non-Duodenum		p-value
	N	(%)	N	(%)	N	(%)	
Sex							
Male	909	(51.2)	541	(52.7)	368	(49.1)	0.1343
Female	866	(48.8)	485	(47.3)	381	(50.9)	
Age (years)							
< 50	178	(10.0)	84	(8.2)	94	(12.6)	0.0028
50-59	281	(15.8)	155	(15.1)	126	(16.8)	
60-69	458	(25.8)	257	(25.1)	201	(26.8)	
70-79	509	(28.7)	307	(29.9)	202	(27.0)	
≥ 80	349	(19.7)	223	(21.7)	126	(16.8)	
Location primary tumor							
Duodenum	1026	(57.8)	1026	(100.0)	Not applicable		n.a.
Jejunum	336	(18.9)	Not applicable		336	(44.9)	
Ileum	257	(14.5)	Not applicable		257	(34.3)	
Overlapping	42	(2.4)	Not applicable		42	(5.6)	
Unknown/NOS	114	(6.4)	Not applicable		114	(15.2)	
TNM stage group							
I	115	(6.5)	66	(6.4)	49	(6.5)	< 0.0001
II	501	(28.2)	219	(21.4)	282	(37.7)	
III	419	(23.6)	257	(25.1)	162	(21.6)	
IV	581	(32.7)	352	(34.3)	229	(30.6)	
X	159	(9.0)	132	(12.9)	27	(3.6)	
Number of metastatic sites							
1	447	(76.9)	286	(81.3)	161	(70.3)	0.0092
2	97	(16.7)	48	(13.6)	49	(21.4)	
≥ 3	37	(6.4)	18	(5.1)	19	(8.3)	
Period of diagnosis							
1999-2003	436	(24.6)	233	(22.7)	203	(27.1)	0.0207
2004-2008	559	(31.5)	315	(30.7)	244	(32.6)	
2009-2013	780	(43.9)	478	(46.6)	302	(40.3)	

Table 1 Continued

	Total N (%)	Duodenum N (%)	Non-Duodenum N (%)	p-value
Surgery				
Yes	1045 (58.9)	418 (40.7)	627 (83.7)	< 0.0001
No	730 (41.1)	608 (59.3)	122 (16.3)	
Chemotherapy				
Yes	321 (18.1)	165 (16.1)	156 (20.8)	0.0103
No	1454 (81.9)	861 (83.9)	593 (79.2)	
Total	1775	1026	749	

NOS = not otherwise specified

Figure 1 Primary tumor location within the small bowel for patients diagnosed with a small bowel adenocarcinoma between 1999 and 2013 in the Netherlands according to period of diagnosis (N=1,775).



duodenal adenocarcinomas undergoing surgery increased from 54% to 64% throughout the study period (p=0.0179). In metastatic disease, only 7% of the patients with duodenal adenocarcinomas underwent surgical resection of the primary tumor, in contrast to respectively 63% and 81% of the patients with jejunal and ileal tumors (p<0.0001). Other palliative interventions, such as a bilio-digestive or intestinal bypass, endoscopic stent placement or celiac plexus block, were performed in 24% of the patients with metastatic duodenal adenocarcinomas, and respectively in 5% and 6% of the patients with metastatic jejunal and ileal tumors. In addition, 14% of the patients with locoregional duodenal adenocarcinomas received a palliative intervention.

Eleven percent of the patients with locoregional disease received chemotherapy, while 33% of the patients with metastatic disease did. The use of chemotherapy increased over time for patients with locoregional disease from 7% in 1999-2003 to 15% in 2009-2013 (p=0.0001). Of the 91 patients with locoregional disease, undergoing both surgical resection and chemotherapy, the majority received chemotherapy in the adjuvant setting. Multivariable logistic regression analyses showed that chemotherapy in patients with locoregional disease was more often offered to younger patients, patients with ileal tumors, stage III tumors and patients who were diagnosed in the period 2009-2013 (table 2). In patients with metastatic disease the prescription of palliative chemotherapy significantly increased from 19% in 1999-2003 to 37% in 2009-2013 (p=0.001). In metastatic disease, younger patients and patients who were diagnosed after 2003 received chemotherapy more frequently.

The median overall survival of patients diagnosed with a small bowel adenocarcinoma remained stable around 13-14 months, with one and five year survival rates of 53% and 25% respectively. Patients with locoregional disease had a median overall survival of 25 months (one and five year survival rates 65% and 36% respectively). The median overall survival of patients with locoregional disease increased from 19 months in the first period to 34 months in the last period (p=0.0006). Patients with locoregional disease who underwent a surgical resection with a curative intent, had a median overall survival of 48 months. Patients receiving (neo-)adjuvant chemotherapy in combination with surgery exhibited a significantly better median overall survival of 66 months (p=0.0338).

The median overall survival of patients with metastatic disease remained stable around 4-5 months (one and five year survival rates 26% and 3% respectively). A median overall survival of 10 months was found in patients with

Table 2 Crude percentages and adjusted odds for receiving chemotherapy among patients diagnosed with small bowel adenocarcinomas, in the Netherlands between 1999 and 2013 by extent of disease (N=1,775)

	Locoregional disease (n = 1194)		Metastatic disease (n = 581)	
	Crude percentage (%)	Odds ratios (95% CI)	Crude percentage (%)	Odds ratios (95% CI)
Sex				
Male	12.1	1.00 (reference)	31.0	1.00 (reference)
Female	9.9	0.85 (0.57–1.27)	34.0	1.18 (0.80–1.73)
Age (years)				
< 50	25.9	2.16 (1.22–3.81)	56.5	1.99 (1.08–3.67)
50-59	18.9	1.54 (0.92–2.59)	51.1	1.63 (0.95–2.78)
60-69	16.0	1.00 (reference)	39.4	1.00 (reference)
70-79	5.6	0.34 (0.19–0.61)	23.7	0.48 (0.29–0.78)
≥ 80	0.0	Not applicable	3.2	0.05 (0.02–0.16)
Location primary tumor				
Duodenum	9.5	1.00 (reference)	28.7	1.00 (reference)
Jejunum	13.0	1.61 (0.97–2.68)	43.3	1.49 (0.90–2.48)
Ileum	15.1	2.00 (1.16–3.47)	34.7	1.16 (0.64–2.12)
Overlapping	8.3	1.03 (0.21–5.02)	38.9	1.11 (0.40–3.06)
Unknown/NOS	9.7	1.28 (0.52–3.16	33.3	1.33 (0.61–2.86)
TNM stage group				
I	0.0	Not applicable		
II	7.6	1.00 (reference)	Not	
III	20.8	3.45 (2.22–5.35)	included in	
X	4.4	1.89 (0.77–4.66)	the analysis	
Period of diagnosis				
1999-2003	6.6	1.00 (reference)	18.6	1.00 (reference)
2004-2008	9.8	1.74 (0.96–3.16)	34.7	2.31 (1.27–4.19)
2009-2013	15.0	3.10 (1.79–5.38)	36.9	3.00 (1.72–5.26)

NOS = not otherwise specified

metastatic disease who were treated with palliative chemotherapy, compared to a median overall survival of only 3 months in patients who did not receive palliative chemotherapy.

Favorable prognostic factors in patients with locoregional disease, identified by a separate multivariable survival analysis, were age < 60 years, low tumor stage (stage I, II) and diagnosis in the period 2009-2013 (table 3). Factors that were associated with poor survival included age ≥ 70 years, tumor localization in the duodenum and an unknown tumor stage (stage X). Surgical treatment and chemotherapy were added separately to the model to investigate its effect on the hazard ratio of death according to period of diagnosis and different patient and tumor characteristics. Surgical treatment and chemotherapy were both favorable prognostic factors. Remarkably, after adjustment for surgery only, having a tumor located in the duodenum was no longer a negative prognostic factor and being diagnosed in the period 2004-2008 became a positive prognostic factor. Chemotherapy did not influence the effect of any characteristic on the hazard ratio of death.

In a multivariable survival analysis without adjustment for treatment including patients with metastatic disease, age < 50 years and a primary tumor located in the jejunum or ileum were positive prognostic factors (table 4). Age > 80 years was the only negative prognostic factor. No beneficial influence of time was seen. After adjustment for chemotherapy and surgery, both positive prognostic factors, a primary tumor located in the ileum became a negative prognostic factor.

Table 3 Crude median overall survival, crude 1-year survival rate, crude 5-year survival rate, adjusted hazard ratios with and without adjustment for treatment in patients diagnosed with a locoregional small bowel adenocarcinoma in the Netherlands between 1999 and 2013 (N=1,194)

	Crude median overall survival (months)	Crude 1-year survival (%)	Crude 5-year survival (%)	Multivariate HR (95% CI)	Multivariate HR (95% CI) adjusted for treatment
Sex					
Male	26.1	65.8	35.6	1.00 (reference)	1.00 (reference)
Female	24.5	64.7	35.5	0.87 (0.75-1.00)	0.82 (0.71-0.95)
Age (years)					
< 50	73.0	84.9	52.3	0.61 (0.44–0.83)	0.66 (0.48-0.91)
50-59	66.4	79.8	53.6	0.66 (0.51–0.86)	0.68 (0.53-0.89)
60-69	32.4	72.1	40.0	1.00 (reference)	1.00 (reference)
70-79	21.9	62.8	32.1	1.34 (1.09–1.64)	1.21 (0.98-1.48)
≥ 80	7.9	40.9	13.7	2.18 (1.76–2.71)	1.52 (1.21-1.90)
Location primary tumor					
Duodenum	16.3	57.8	28.1	1.00 (reference)	1.00 (reference)
Jejunum	62.6	81.9	50.9	0.62 (0.51–0.77)	0.93 (0.74–1.16)
Ileum	40.2	73.3	42.8	0.79 (0.63–0.98)	1.22 (0.97–1.54)
Overlapping	41.3	79.1	33.4	0.76 (0.45–1.29)	0.97 (0.58–1.65)
Unknown/NOS	22.6	55.5	37.1	0.75 (0.55–1.02)	1.12 (0.82–1.54)
TNM stage group					
I	77.2	84.8	60.3	0.39 (0.29–0.53)	0.42 (0.31–0.56)
II	42.7	73.4	44.7	0.65 (0.55–0.77)	0.63 (0.53–0.75)
III	20.5	65.0	29.3	1.00 (reference)	1.00 (reference)
X	4.7	26.4	5.7	1.73 (1.39–2.17)	0.85 (0.67-1.07)
Period of diagnosis					
1999-2003	18.5	61.3	27.7	1.00 (reference)	1.00 (reference)
2004-2008	23.1	63.7	37.3	0.87 (0.73–1.03)	0.84 (0.70–0.99)
2009-2013	34.1	69.4	40.8	0.68 (0.56–0.81)	0.74 (0.61–0.89)
Surgery					
Yes	50.3	79.8	47.9	Not included in	0.23 (0.18–0.28)
No	5.6	73.6	3.2	the analysis	1.00 (reference)
Chemotherapy					
Yes	35.5	84.3	41.1	Not included in	0.55 (0.41–0.73)
No	23.5	63.0	34.9	the analysis	1.00 (reference)

NOS = not otherwise specified

Table 4 Crude median overall survival, crude 1-year survival rate, crude 5-year survival rate, adjusted hazard ratios with and without adjustment for treatment in patients diagnosed with a metastatic small bowel adenocarcinoma in the Netherlands between 1999 and 2013 (N=581)

	Crude median overall survival (months)	Crude 1-year survival (%)	Crude 5-year survival (%)	Multivariate HR (95% CI)	Multivariate HR (95% CI) adjusted for treatment
Sex					
Male	4.5	21.2	1.4	1.00 (reference)	1.00 (reference)
Female	5.1	30.5	3.9	0.89 (0.75–1.06)	0.90 (0.75–1.07)
Age (years)					
< 50	8.3	38.7	12.8	0.69 (0.50–0.95)	0.79 (0.57–1.08)
50–59	5.7	31.0	1.5	0.97 (0.73–1.27)	1.00 (0.76–1.32)
60–69	5.2	28.9	1.9	1.00 (reference)	1.00 (reference)
70–79	4.7	23.1	1.0	1.16 (0.93–1.46)	1.02 (0.81–1.29)
≥ 80	2.4	12.2	1.9	1.64 (1.26–2.15)	1.21 (0.91–1.60)
Location primary tumor					
Duodenum	4.0	19.2	1.2	1.00 (reference)	1.00 (reference)
Jejunum	9.7	40.5	7.2	0.54 (0.42–0.70)	0.90 (0.68–1.18)
Ileum	5.0	29.9	7.5	0.74 (0.56–0.97)	1.57 (1.13–2.17)
Overlapping	4.9	29.6	0.0	0.83 (0.51–1.36)	1.19 (0.72–1.97)
Unknown/NOS	5.7	39.1	0.0	0.79 (0.56–1.12)	1.48 (1.03–2.15)
Period of diagnosis					
1999–2003	4.5	27.1	3.8	1.00 (reference)	1.00 (reference)
2004–2008	4.8	27.7	2.9	0.92 (0.72–1.17)	1.10 (0.86–1.41)
2009–2013	5.2	23.9	1.7	0.95 (0.76–1.20)	1.12 (0.89–1.42)
Surgery					
Yes	10.6	47.2	8.0	Not included inthe analysis	0.38 (0.30–0.50)
No	3.9	16.6	0.4		1.00 (reference)
Chemotherapy					
Yes	10.5	43.4	4.5	Not included inthe analysis	0.50 (0.40–0.61)
No	3.2	17.5	1.9		1.00 (reference)

NOS = not otherwise specified,

Discussion

This population-based study examined the incidence, treatment and median overall survival over time in patients diagnosed with a small bowel adenocarcinoma in the Netherlands between 1999 and 2013. The study is one of the largest conducted studies in the field of small bowel adenocarcinomas so far. Our study, showed that the incidence of small bowel adenocarcinomas is rising. Furthermore, we found that the resection rates in non-metastatic small bowel cancer increased and the median overall survival in patients with locoregional disease improved over time. The median overall survival of patients with metastatic disease remained stable, despite increased treatment with palliative chemotherapy.

The intestinal distribution pattern of small bowel adenocarcinomas that we found in our study was comparable with the distribution pattern found in previous studies.[3-5,7] It has been hypothesized that the duodenum might be more susceptible for carcinogenesis than the jejunum and ileum due to the metabolism or dilution of ingested carcinogens in transit through the small bowel or interactions of the carcinogens with the pancreaticobiliary secretions. [3,7,10,11]

Based on our comparison between patients diagnosed with tumors located in the duodenum and patients diagnosed with tumors located elsewhere in the small intestine, it could be questioned whether these tumors should be considered as one entity. Patients with tumors located in the duodenum are often slightly older, have more advanced disease stages and have a different metastatic pattern.

A slight increase in the incidence of small bowel adenocarcinomas was seen between 1999 and 2013, which is mainly caused by the twofold increase of duodenal adenocarcinomas. The exact cause for the specific increase in duodenal adenocarcinomas is unknown. Partially it can be explained by improved diagnostics, resulting in a reduction of misclassification of duodenal adenocarcinomas as pancreatic tumors and adenocarcinoma of unknown primary (ACUP).[10,12] The modified food consumption might have attributed to increased incidence rates as well. Previous studies found sugar, refined carbohydrates, red meat and smoked food to be associated with the development of small bowel adenocarcinomas.[2,11]

The percentage of patients diagnosed with metastatic disease increased over time, which can be explained by stage migration caused by new and improved diagnostics, such as multidetector row computed tomography scans and magnetic resonance enteroclysis.[13]

Surgical resection is the only therapy for potential cure in small intestine adenocarcinoma.[2] In line with previous studies, 73% of the patients with locoregional disease underwent an intentionally curative resection.[5,7] Resection rates were higher in jejunal and ileal tumors compared to resection rates in duodenal tumors, since surgical resection of upper duodenal tumors requires a pancreaticoduodenectomy, which is specialized major surgery in comparison to the more simple segmental resections with removal of surrounding tissue for jejunal and ileal tumors.[5,7]

Over time the resection rates increased, especially due to an increased number of resections in patients with duodenal tumors. We hypothesize that may be due to the centralization of pancreaticoduodenectomies in the Netherlands.[14,15] The amount of surgical interventions in patients with metastatic disease decreased drastically, which is probably the result of improved palliative interventions, such as endoscopically placed (bilio-)duodenal endoprotheses, and the increased use of chemotherapy.[16] Palliative interventions in patients with non-metastatic small bowel cancer were mostly performed in patients with duodenal adenocarcinomas, which are more often irresectable compared to jejunal and ileal tumors.[7]

The proportion of patients receiving chemotherapy doubled during the study period, both for patients with locoregional and metastatic disease. Especially in patients with locoregional disease the twofold increase is remarkable, since non-observational studies addressing the beneficial effect of chemotherapy are lacking. Overman et al. found adjuvant chemotherapy to be associated with an improvement of disease free survival, but not with improvement of overall survival.[17] Recently, a population-based study conducted by Ecker et al. showed a survival benefit of 16 months (42 vs 26 months) for patients with stage III tumors treated with adjuvant chemotherapy.[18] We demonstrate that in patients with locoregional disease chemotherapy was more often offered to younger patients, patients with ileal or stage III tumors and patients who were diagnosed in the period 2009-2013. In metastatic disease however, the doubling of palliative chemotherapy is not surprising, since a survival benefit of several months has already been observed in multiple retrospective studies.[5,19-21] In patients with metastatic disease, only a younger age and diagnosis after 2003 were positive predictive factors for receiving palliative chemotherapy.

The median overall survival of patients with an adenocarcinoma of the small intestine did not improve over time and remained 13-14 months. Our results are

inferior to the reported overall survival of approximately 20 months in other population-based studies, but these studies were merely conducted before the millennium and might have included neuroendocrine tumors with a more indolent behavior.[5,7,22,23]

The median overall survival of patients with locoregional disease improved from 19 months in 1999-2003 to 34 months in 2009-2013, which might be explained by stage migration, increased use of chemotherapy and the centralization of surgery. Moreover, we found that patients treated with adjuvant chemotherapy after surgical resection had a significantly better survival, 66 months compared to 48 months for patients not treated with adjuvant chemotherapy. However, it should be noted that the amount of patients receiving both treatments were limited in our study. Furthermore, selection bias might have played a role. Fitter patients, those with a better survival beforehand, might have received chemotherapy more frequently. Other favorable prognostic factors for prolonged survival in patients with locoregional disease, identified by multivariable analysis, were age < 60 years, tumor stage I and II, surgical treatment and chemotherapy. These findings are comparable to previously determined prognostic factors.[3,5,7,20,22,24] In addition, in patients with locoregional disease, duodenal tumors appeared to be an adverse prognostic factor in multivariable analysis without adjustment for treatment. However, after adjustment for surgery only, a duodenal tumor was not a negative prognostic factor anymore, which implies that the poor prognosis of these tumors is the result of the relative lack of possibilities for surgical intervention.

In metastatic disease the median overall survival remained stable around 4-5 months despite doubling of the prescription of palliative chemotherapy from 19% to 37% in the recent years. In patients with metastatic disease, favorable prognostic factors identified by multivariable analysis included age < 50 years, primary tumor located in the jejunum, surgical treatment and chemotherapy. These prognostic factors are consistent with previously published data.[3,7,22]

Limitations

A limitation of our study is that detailed information on performance status, nutritional status, disease related symptoms, the specific tumor localization within the duodenum, type of chemotherapy and type of surgical and palliative interventions are lacking due to the population-based nature of our data. However, our results did not differ from the results of other studies.[3-5,7]

Conclusion

In conclusion, small bowel adenocarcinomas are rare tumors with an increasing incidence, mainly caused by the rise of duodenal adenocarcinomas. The median overall survival of patients with locoregional disease improved significantly over time, which might be due to the increasing use of chemotherapy and the implementation of centralizing pancreatic cancer surgery. However, the median overall survival of patients with metastatic disease remained stable, despite doubling the administration of palliative chemotherapy. Due to the rarity and poor prognosis of this disease, it is of importance to develop international studies to determine the optimal treatment for these patients. The differences found in characteristics and median overall survival between patients diagnosed with tumors located in the duodenum and tumors located elsewhere in the small bowel might suggest that in future research both should be considered as different entities.

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Chapter 5
Epidemiology of pancreatic cancer

Chapter 5.1
Ten weeks to live: A population-based study on treatment and survival of patients with metastatic pancreatic cancer in the south of the Netherlands

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Abstract

Background: A large proportion of patients with pancreatic cancer present with metastatic disease. We conducted a population-based study to evaluate trends in treatment and survival of patients with metastatic pancreatic cancer.

Methods: We included all patients diagnosed with pancreatic cancer between 1993 and 2010 in the South of the Netherlands (N=3,099). Multivariable logistic regression analysis was conducted to evaluate trends in treatment with chemotherapy. Crude overall survival according to period of diagnosis was analyzed, and independent risk factors for death were identified.

Results: Forty-eight percent of the patients (N=1,494) were diagnosed with metastatic disease. The percentage of patients being diagnosed with metastatic disease increased during the study period from 35% in 1993-1996 to 59% in 2009-2010 (p<0.0001). Overall, 18% of these patients received chemotherapy. The prescription of palliative chemotherapy almost tripled from 10% to 27% (p<0.0001). Treatment largely depended on age, ranging from 38% among patients aged <50 years (compared to 60-69 yrs.: adjusted odds ratio (OR_{adj}) 2.5, (95%CI=1.4-4.2)) to 1% among patients aged ≥80 years (OR_{adj} 0.04,(95%CI=0.0-0.2)). Patients were more likely to receive chemotherapy if they had a high socioeconomic status (compared to low socioeconomic status OR_{adj} 2.0, (95%CI=1.3-3.1)), and if diagnosis was pathologically verified (no verification vs. verification: OR_{adj} 0.3, (95%CI=0.2-0.5)). The administration of chemotherapy varied widely between ten hospitals (5-34%, p<0.0001). The median overall survival of patients with metastatic pancreatic cancer remained 9-11 weeks.

Conclusion: A growing proportion of pancreatic cancer patients presented with metastatic disease. Usage of palliative chemotherapy increased over time, but median survival remained 9-11 weeks. In the near future, it should be evaluated if the recently introduced regimens have an impact on population-based survival

Introduction

Pancreatic cancer is a devastating disease, with a 1-year survival rate ranging from 12% to 28% in Europe.[1] It is characterized by an aggressive tumor biology with early metastases. As a result, 95% of the pancreatic cancer patients eventually die of the disease within 5 years.

The only curative treatment modality for pancreatic cancer is surgery. In the last decades, the survival for patients with resectable pancreatic cancer increased due to technical advances in surgical treatment as well as advances in other surgery-related factors, such as the establishment of high volume centers and implementation of adjuvant chemotherapy.[2,3]

However, about 80% of the patients with pancreatic cancer is diagnosed with locally advanced or metastatic disease and does not qualify for surgical treatment. Furthermore, the majority of patients treated with pancreatic surgery eventually relapse and develop local recurrence or distant metastases.[2,4]

Population-based data on treatment and outcome of metastatic pancreatic cancer are scarce. Recently, data from the United States Surveillance, Epidemiology and End Result registry (SEER) showed a modest increase in median overall survival of patients with metastatic pancreatic cancer in the years 1988-2008.[5]

We conducted a population based study to evaluate the shift over time in proportion of patients diagnosed with metastatic disease and in treatment patterns. Furthermore, we evaluated the effect of both shifts on median overall survival in the south of the Netherlands.

Methods

Data collection

For the present study we used data from the Eindhoven Cancer Registry (ECR), maintained by the Comprehensive Cancer Centre South. The ECR is a population-based registry in the southern part of the Netherlands. The registry area comprises about 2.4 million inhabitants and encompasses ten community hospitals, two radiotherapy institutions and six pathology departments. The area does not contain university or specialized cancer hospitals. Information on patient, tumor and treatment characteristics was routinely extracted from medical records by trained registrars operating on behalf of the ECR.

Our study included all patients who were diagnosed with a neoplasm of the pancreas *(International classification of Disease for Oncology (ICD-O), second edition, topography code 157 and third edition, code C25)* between 1 January 1993 and 31 December 2010. We decided to restrict the morphology to adenocarcinoma and excluded patients with neuroendocrine tumors, sarcomas or blastomas of the pancreas. Tumors without histological confirmation were included.

The registrars classified all adenocarcinomas according to the Tumor Lymph Node Metastasis (TNM) classification and staged them following the recommendations of the International Union Against Cancer in the respective period. The clinical Extent of Disease (cEOD) was used for staging if the tumor was not histologically confirmed. We categorized tumors as locoregional (confined to the pancreas, with or without extension to surrounding organs or locoregional lymph nodes) or metastatic pancreatic cancer.

Vital status of patients was assessed at 1 January 2012 through linkage with civil municipal registries and the central bureau for genealogy. The latter is an institution that collects data on all deceased Dutch citizens. Survival was calculated based on all-cause mortality.

Statistical analyses

We described proportions of patients who received chemotherapy according to gender, age, socioeconomic status, number of comorbid conditions, histologic subtype, site of metastases, period of diagnosis and hospital of treatment (A to J). Differences in the administration of systemic chemotherapy between subgroups were tested by means of a χ^2 test. Trends in treatment across the five periods (1993-1996, 1997-2000, 2001-2004, 2005-2008 and 2009-2010) were analyzed by means of a Cochran-Armitage trend test. Furthermore, the

independent influence of these variables on the administration of chemotherapy was evaluated by means of a logistic regression analysis. Missing values were included as separate dummies in the analyses in order not to loose statistical power.

Survival time was defined as the time from diagnosis to death or 1 January 2012, for patients who were still alive. The significance of differences between survival curves were evaluated by means of a log rank test. Independent risk factors for death were discriminated by multivariable proportional hazard regression modelling. In order to investigate the effect of chemotherapy on the hazard ratios (HRs) of dying according to period of diagnosis and hospital of diagnosis, the model was run with and without treatment variable (chemotherapy yes versus no).

SAS Statistical software (version 9.3, SAS institute, Cary, NC, U.S.A.) was used to perform the statistical analyses. For all analyses, a two sided p-value <0.05 was considered statistically significant.

Results

A total of 3,099 patients were diagnosed with pancreatic cancer between 1 January 1993 and 31 December 2010. Forty-eight percent of the patients (N=1,494) were diagnosed with metastatic disease. This percentage increased over time, from 35% in 1993-1996 to 59% in 2009-2010 (p<0.01).

General characteristics categorized by period are depicted in table 1. Fifty-five percent of our study population was male and 68% of the patients had a diagnosis confirmed by pathological examination. The median age at time of diagnosis was 68 years (range 32-99). Over time the proportion of elderly patients diagnosed with metastatic pancreatic cancer increased.

The liver (76%) and the peritoneal cavity (18%) were the most common metastatic sites. Twenty-four percent of the patients had metastases in two or more organs and this proportion increased over time. Patients with liver metastases were more likely to have multiple organs affected compared to patients with non-liver metastases (p=0.03).

The use of chemotherapy among patients with metastatic pancreatic cancer increased, from 10% in 1993-1996 to 27% in 2009-2010 (p<0.001) (figure 1). Several factors influenced the probability of receiving chemotherapy. Table 2 shows the crude proportions of patients treated with chemotherapy

according to relevant patient and tumor characteristics, and the adjusted odds of being treated with chemotherapy. Chemotherapy was administered more often to younger patients and patients with a high socioeconomic status (SES). In contrast, older patients and patients without pathological confirmation received chemotherapy less frequently. Furthermore, there was a large inter-hospital variation in the prescription of chemotherapy (5 - 34%) and this variation was not related to the size of the hospital.

The overall survival of patients with metastatic pancreatic cancer did not change in the course of time. The prognosis remained dismal, with 1-year survival rates between 4-7% and a median overall survival between 9-11 weeks (figure 2). Patients treated with palliative chemotherapy exhibited a median overall survival of 25 weeks (1-year survival rate 17%), compared to 8 weeks in those not treated with chemotherapy (1-year survival rate 3%) (table 3). Other beneficial prognostic factors identified by multivariable survival analysis were female sex, single site metastases in extra regional lymph nodes, and dissemination limited to the lungs. Factors associated with poor survival included older age (70-79 yrs or 80+). Patients without microscopically verified pancreatic cancer carried the same dismal prognosis as patients with verified pancreatic cancer.

Without adjustment for chemotherapy in the multivariable survival analysis, the risk of dying remained similar across the different study periods. After adjustment for chemotherapy the risk of dying increased significantly over time. Patients diagnosed in hospital B and G had a better survival, but after adjustment for chemotherapy this difference was not observed anymore.

Table 1 Characteristics of patients with metastatic pancreatic cancer, by period of diagnosis (N=1,494)

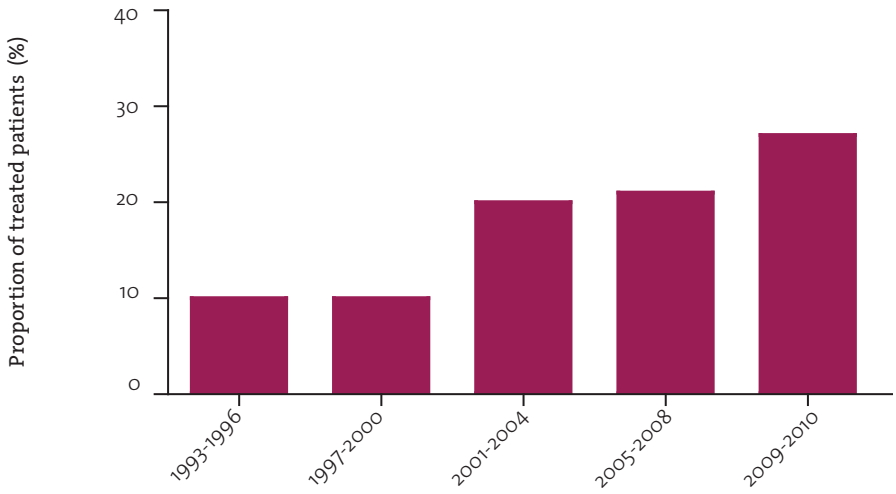
	Total		1993-1996		1997-2000	
	N	(%)	N	(%)	N	(%)
Sex						
Male	829	(55.5)	119	(63.3)	135	(49.6)
Female	665	(44.5)	69	(36.7)	137	(50.4)
Age (yrs)						
<50	93	(6.2)	22	(11.7)	15	(5.5)
50-59	241	(16.1)	36	(19.1)	54	(19.9)
60-69	512	(34.3)	57	(30.3)	92	(33.8)
70-79	469	(31.4)	53	(28.2)	87	(32.0)
≥80	179	(12.0)	20	(10.6)	24	(8.8)
Socioeconomic status (SES)						
Low	372	(24.9)	42	(22.3)	85	(31.3)
Intermediate	584	(39.1)	59	(31.4)	99	(36.4)
High	424	(28.4)	57	(30.3)	70	(25.7)
Institutions	72	(4.8)	14	(7.5)	16	(5.9)
Unknown	42	(2.8)	16	(8.5)	2	(0.7)
No. of comorbid conditions						
0	712	(47.7)	105	(55.9)	151	(55.5)
1	469	(31.4)	34	(18.1)	70	(25.7)
≥2	179	(12.0)	14	(7.4)	22	(8.1)
Unknown	134	(9.0)	35	(18.6)	29	(10.7)
Histologic subtype						
Adenocarcinoma	1023	(68.5)	134	(71.3)	175	(64.3)
No histology	471	(31.5)	54	(28.7)	97	(35.7)
Metastatic site						
Liver	840	(56.2)	114	(60.6)	165	(60.7)
Peritoneal	124	(8.3)	16	(8.5)	31	(11.4)
Lung	47	(3.1)	7	(3.7)	6	(2.2)
Lymphnodes	45	(3.0)	4	(2.1)	12	(4.4)
Other / unknown	78	(5.2)	22	(11.7)	15	(5.5)
2 organs	270	(18.1)	18	(9.6)	40	(14.7)
≥3 organs	90	(6.0)	7	(3.7)	3	(1.1)

	2001-2004		2005-2008		2009-2010		
	N	(%)	N	(%)	N	(%)	*p* value
	171	(55.7)	250	(56.9)	154	(53.5)	0.46
	136	(44.3)	189	(43.1)	134	(46.5)	
	20	(6.5)	26	(5.9)	10	(3.5)	0.03
	50	(16.3)	67	(15.3)	34	(11.8)	
	110	(35.8)	151	(34.4)	102	(35.4)	
	91	(29.6)	140	(31.9)	98	(34.0)	
	36	(11.7)	55	(12.5)	44	(15.3)	
	75	(24.4)	102	(23.2)	68	(23.6)	<0.01
	118	(38.4)	187	(42.6)	121	(42.0)	
	97	(31.6)	127	(28.9)	73	(25.3)	
	13	(4.2)	13	(3.0)	16	(5.6)	
	4	(1.3)	10	(2.2)	10	(3.5)	
	141	(45.9)	198	(45.1)	117	(40.6)	<0.01
	100	(32.6)	155	(35.3)	110	(38.2)	
	30	(9.8)	60	(13.7)	53	(18.4)	
	36	(11.7)	26	(5.9)	8	(2.8)	
	197	(64.2)	303	(69.0)	214	(74.3)	0.12
	110	(35.8)	136	(31.0)	74	(25.7)	
	192	(62.5)	232	(52.8)	137	(47.6)	<0.01
	15	(4.9)	32	(7.3)	30	(10.4)	
	9	(2.9)	10	(2.3)	15	(5.2)	
	9	(2.9)	14	(3.2)	6	(2.1)	
	17	(5.5)	18	(4.1)	6	(2.1)	
	43	(14.0)	108	(24.6)	61	(21.2)	
	22	(7.2)	25	(5.7)	33	(11.5)	

Table 1 Continued

	Total		1993-1996		1997-2000	
	N	(%)	N	(%)	N	(%)
Hospital of diagnosis						
Hospital A	228	(15.3)	21	(11.2)	46	(16.9)
Hospital B	85	(5.7)	16	(8.5)	11	(4.0)
Hospital C	154	(10.3)	13	(6.9)	26	(9.6)
Hospital D	119	(8.0)	14	(7.4)	25	(9.2)
Hospital E	72	(4.8)	11	(5.9)	12	(4.4)
Hospital F	217	(14.5)	23	(12.2)	38	(14.0)
Hospital G	236	(15.8)	33	(17.6)	35	(12.9)
Hospital H	131	(8.8)	17	(9.0)	23	(8.5)
Hospital I	107	(7.2)	21	(11.2)	24	(8.8)
Hospital J	145	(9.7)	19	(10.1)	32	(11.8)
Chemotherapy						
Yes	272	(18.2)	18	(9.6)	26	(9.6)
No	1222	(81.8)	170	(90.4)	246	(90.4)
Total	**1494**		**188**	**(12.6)**	**272**	**(18.2)**

Figure 1 Administration of chemotherapy in patients diagnosed with metastatic pancreatic cancer in the southern Netherlands between 1993 and 2010, according to period of diagnosis (N=1,494)



	2001-2004		2005-2008		2009-2010		
	N	(%)	N	(%)	N	(%)	*p* value
	41	(13.4)	69	(15.7)	51	(17.7)	0.01
	26	(8.5)	13	(3.0)	19	(6.6)	
	29	(9.4)	45	(10.3)	41	(14.2)	
	26	(8.5)	36	(8.2)	18	(6.3)	
	18	(5.9)	19	(4.3)	12	(4.2)	
	38	(12.4)	76	(17.3)	42	(14.6)	
	43	(14.0)	77	(17.5)	48	(16.7)	
	37	(12.1)	32	(7.3)	22	(7.6)	
	17	(5.5)	29	(6.6)	16	(5.6)	
	32	(10.4)	43	(9.8)	19	(6.6)	
	60	(19.5)	90	(20.5)	78	(27.1)	<0.01
	247	(80.5)	349	(79.5)	210	(72.9)	
	307	**(20.6)**	**439**	**(29.4)**	**288**	**(19.3)**	

Figure 2 Overall survival of patients diagnosed with metastatic pancreatic cancer in the southern Netherlands between 1993 and 2010, according to period of diagnosis (N=1,494)

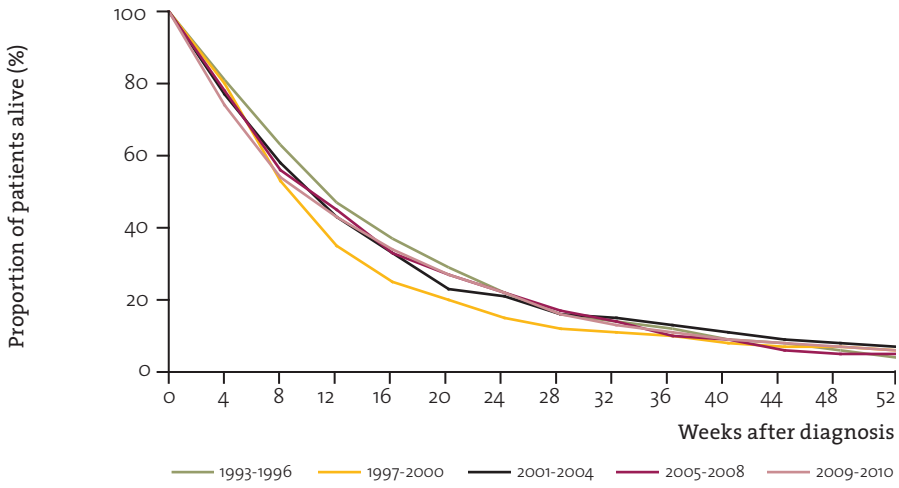


Table 2 Crude percentages, unadjusted and adjusted odds[a] for receiving chemotherapy among patients diagnosed with metastatic pancreatic cancer in the southern Netherlands between 1993 and 2010 (N=1,494)

	Crude percentage %	Univariate Odds ratio (95% CI)	Multivariate Odds ratio (95% CI)
Sex			
Male	19.7	1.00 (reference)	1.00 (reference)
Female	16.4	0.80 (0.61-1.05)	0.91 (0.67-1.24)
Age (yrs)			
<50	37.6	2.21 (1.38-3.53)	2.43 (1.41-4.18)
50-59	29.0	1.50 (1.06-2.12)	1.68 (1.13-2.49)
60-69	21.5	1.00 (reference)	1.00 (reference)
70-79	11.7	0.49 (0.34-0.69)	0.49 (0.33-0.73)
≥80	1.1	0.04 (0.01-0.17)	0.04 (0.01-0.18)
Socioeconomic status (SES)			
Low	13.4	1.00 (reference)	1.00 (reference)
Intermediate	17.8	1.40 (0.97-2.01)	1.18 (0.78-1.79)
High	25.9	2.26 (1.56-3.26)	2.05 (1.34-3.13)
Number of comorbid conditions			
0	21.5	1.00 (reference)	1.00 (reference)
1	17.3	0.76 (0.57-1.03)	0.77 (0.54-1.09)
≥2	14.0	0.59 (0.38-0.94)	0.69 (0.41-1.16)
Histologic subtype			
Adenocarcinoma	23.7	1.00 (reference)	1.00 (reference)
No histology	6.4	0.22 (0.15-0.33)	0.33 (0.21-0.51)
Site of metastases			
Liver	18.6	1.00 (reference)	1.00 (reference)
Peritoneal	17.7	0.95 (0.58-1.55)	0.78 (0.45-1.37)
Lung	12.8	0.64 (0.27-1.54)	1.01 (0.38-2.68)
Extraregional nodes	15.6	0.81 (0.35-1.84)	0.81 (0.32-2.03)
Other	12.8	0.65 (0.33-1.28)	0.76 (0.35-1.63)
2 organs	18.9	1.02 (0.72-1.45)	0.81 (0.54-1.22)
3+ organs	22.2	1.25 (0.74-2.12)	0.80 (0.44-1.48)

Table 2 Continued

	Crude percentage %	Univariate Odds ratio (95% CI)	Multivariate Odds ratio (95% CI)
Period of diagnosis			
1993-1996	9.6	1.00 (reference)	1.00 (reference)
1997-2000	9.6	1.00 (0.53-1.88)	1.71 (0.85-3.46)
2001-2004	19.5	2.29 (1.31-4.02)	4.08 (2.15-7.73)
2005-2008	20.5	2.44 (1.42-4.17)	4.61 (2.48-8.58)
2009-2010	27.1	3.51 (2.02-6.09)	7.40 (3.87-14.15)
Hospital of diagnosis			
Hospital A	14.9	1.00 (reference)	1.00 (reference)
Hospital B	29.4	2.38 (1.32-4.30)	4.08 (2.05-8.14)
Hospital C	18.2	1.27 (0.73-2.19)	1.36 (0.74-2.50)
Hospital D	5.0	0.30 (0.12-0.74)	0.39 (0.15-1.02)
Hospital E	13.9	0.92 (0.43-1.97)	1.07 (0.47-2.44)
Hospital F	11.1	0.71 (0.41-1.24)	0.87 (0.48-1.58)
Hospital G	34.3	2.98 (1.90-4.69)	5.27 (3.15-8.82)
Hospital H	15.3	1.03 (0.56-1.87)	1.22 (0.63-2.35)
Hospital I	22.4	1.65 (0.92-2.95)	1.86 (0.98-3.55)
Hospital J	13.8	0.91 (0.50-1.66)	1.04 (0.55-1.98)

[a] *Adjusted for all variables listed. Included in the analysis but results not shown, SES institutionalised, SES unknown and comorbidity unknown*

Table 3 Crude median overall survival, crude 1-year survival, unadjusted and adjusted hazard ratios[a] for patients diagnosed with metastatic pancreatic cancer in the southern Netherlands between 1993 and 2010 (N=1,494)

	Crude median survival (weeks)	Crude 1-year survival (%)	Univariate HR (95%)	Multivariable HR (95% CI)
Sex				
Male	9.4	6.0	1.00 (reference)	1.00 (reference)
Female	9.9	5.4	0.97 (0.88-1.07)	0.89 (0.80-0.99)
Age (yrs)				
<50	14.3	8.6	0.85 (0.68-1.06)	1.02 (0.81-1.28)
50-59	12.0	7.1	0.92 (0.79-1.07)	1.00 (0.86-1.18)
60-69	11.1	7.6	1.00 (reference)	1.00 (reference)
70-79	7.9	3.2	1.36 (1.20-1.54)	1.20 (1.05-1.37)
≥80	5.1	3.4	1.75 (1.48-2.08)	1.38 (1.14-1.67)
Socioeconomic status (SES)				
Low	8.7	3.8	1.00 (reference)	1.00 (reference)
Intermediate	9.4	4.8	0.93 (0.82-1.06)	0.97 (0.85-1.11)
High	10.9	8.7	0.79 (0.68-0.91)	0.87 (0.75-1.00)
Number of comorbid conditions				
0	10.0	6.6	1.00 (reference)	1.00 (reference)
1	9.0	4.7	1.15 (1.02-1.29)	1.03 (0.91-1.17)
≥2	9.0	2.8	1.27 (1.07-1.49)	1.05 (0.88-1.24)
Histologic subtype				
Adenocarcinoma	10.4	6.5	1.00 (reference)	1.00 (reference)
No histology	7.6	4.0	1.26 (1.13-1.40)	1.02 (0.90-1.16)
Site of metastases				
Liver	9.7	5.6	1.00 (reference)	1.00 (reference)
Peritoneal	8.2	5.7	1.06 (0.88-1.28)	1.05 (0.86-1.27)
Lung	17.9	6.4	0.69 (0.52-0.93)	0.56 (0.41-0.75)
Extra regional nodes	21.6	20.0	0.60 (0.44-0.81)	0.50 (0.37-0.69)
Other	10.6	6.4	0.89 (0.71-1.12)	0.84 (0.66-1.06)
2 organs	7.1	4.1	1.17 (1.02-1.35)	1.13 (0.99-1.31)
3 or more organs	5.6	3.3	1.46 (1.17-1.81)	1.65 (1.32-2.07)
Period of diagnosis				
1993-1996	10.9	3.7	1.00 (reference)	1.00 (reference)
1997-2000	8.7	5.9	1.16 (0.96-1.39)	1.25 (1.03-1.52)
2001-2004	9.7	7.2	1.03 (0.86-1.23)	1.19 (0.99-1.44)
2005-2008	9.7	5.0	1.05 (0.89-1.25)	1.21 (1.01-1.45)
2009-2010	9.0	6.3	1.05 (0.87-1.26)	1.32 (1.08-1.61)

Table 3 Continued

	Crude median survival (weeks)	Crude 1-year survival (%)	Univariate HR (95%)	Multivariable HR (95% CI)
Hospital of diagnosis				
Hospital A	10.4	5.3	1.00 (reference)	1.00 (reference)
Hospital B	12.6	7.1	0.84 (0.66–1.08)	0.92 (0.71–1.20)
Hospital C	9.4	7.1	0.92 (0.75–1.12)	0.86 (0.70–1.07)
Hospital D	7.1	4.2	1.12 (0.90–1.40)	1.00 (0.79–1.25)
Hospital E	9.3	6.9	0.96 (0.74–1.26)	0.86 (0.65–1.12)
Hospital F	8.9	3.7	1.09 (0.91–1.32)	0.98 (0.81–1.19)
Hospital G	10.2	5.9	0.91 (0.76–1.10)	1.01 (0.84–1.23)
Hospital H	8.1	3.8	1.20 (0.96–1.48)	1.15 (0.92–1.43)
Hospital I	9.1	9.4	0.94 (0.75–1.19)	1.02 (0.80–1.30)
Hospital J	10.1	6.2	1.04 (0.85–1.28)	0.97 (0.78–1.20)
Chemotherapy				
No	7.6	3.1	1.00 (reference)	1.00 (reference)
Yes	25.3	17.3	0.41 (0.36–0.47)	0.39 (0.34–0.46)

[a] *Adjusted for all variables listed. Included in the analysis but results not shown, SES unknown, comorbidity unknown, and tumor differentiation grade unknown.*

Discussion

This population-based study showed that an increasing proportion of pancreatic cancer patients presented with metastatic disease. The administration of palliative chemotherapy in these patients increased drastically, and large inter-hospital variations in the administration were noted. In the course of time, the population-based median overall survival remained dismal.

The increasing proportion of pancreatic cancer patients who present with metastatic disease is consistent with previous reports.[6,7] The improvements in the accuracy of the current CT scans and the development of new diagnostic tools are major contributing factors. Once (metastatic) pancreatic cancer is suspected on imaging studies, pathologic confirmation is recommended to establish the definitive diagnosis. In 68% of the patients with metastatic pancreatic cancer the definitive diagnosis was verified by pathological examination. Low overall proportions of verification are common in pancreatic cancer. The EUROCARE-4 study, a study that gathered data from 93 European cancer registries between 1995 and 2002, found a verification rate of 63% (range 30-91%) in all patients with pancreatic cancer.[8] Our data suggest that the rate

is especially low in non-metastatic pancreatic cancer. Obtaining tissue in the absence of metastases can be difficult, since the pancreas is situated in the retroperitoneum and the abundant presence of desmoplastic stroma in pancreatic tumors may hamper the identification of malignant tumor cells.[8,9] In case of metastatic disease, health care practitioners often refrain from diagnostic biopsies in patients who are considered unfit for systemic treatment. Although in several population-based studies, pathologically unverified tumors were not taken into account, we included these patients into our study, in order to obtain a true reflection of the outcome of daily clinical practice in pancreatic cancer care.[10,11] Since the overall survival of patients with histologically unverified pancreatic cancer was poor, the likelihood that these patients indeed suffered from pancreatic cancer is high. We believe it is of clinical relevance to report on the outcome of these patients, as they constitute a significant proportion of pancreatic cancer patients.

Although no considerable progress has been made in the chemotherapeutic treatment of metastatic pancreatic cancer during the study period, the prescription of chemotherapy increased from 10% 1993-1996 to 27% 2009-2010. Since 1997, gemcitabine monotherapy has been the reference regimen for patients with metastatic pancreatic cancer. Although initial studies suggested a low response rate (6 to 11%), gemcitabine was approved for first-line treatment on the basis of significant improvement in 'clinical benefit' (pain relief, improved performance status, or both) and prolongation of survival (5.6 months in gemcitabine-treated patients versus 4.4 months in fluorouracil-treated patients).[12] In numerous trials over the past years, many different (drug) regimens have been tested. Until recently, none of these trials demonstrated a statistically significant survival benefit, except for gemcitabine plus erlotinib which was associated with a very modest and clinically irrelevant increase in overall survival of 2 weeks.[13] In the course of time, the prescription of palliative chemotherapy increased drastically, possibly because physicians became more familiar with the use of chemotherapy in pancreatic cancer after the publication by Neoptolemos et al. in 2001 of adjuvant gemcitabine chemotherapy in patients with resected pancreatic cancer.[14,15] A similar phenomenon has been observed in patients with metastasized gastric cancer, after the introduction of perioperative chemotherapy.[16]

In our study, the odds of receiving chemotherapy was influenced by several patient- and tumor-related factors. First, an inverse relationship between the administration of chemotherapy and age was found, which is consistent with

findings from previous reports.[17] Second, patients with a higher socioeconomic status were more likely to receive chemotherapy.[6,7] This treatment selection according to SES has also been described by Krzyzanowska et. al. for elderly patients with advanced pancreatic cancer and by Chueng et al. for a cohort of patients living in the state of Florida. [17,18] Third, patients without microscopically verified pancreatic cancer had lower odds for receiving chemotherapy. This is not surprising, since most guidelines recommend "a positive biopsy" before systemic treatment is started, and a biopsy will only be omitted when patients are not fit for treatment.

We observed a large hospital variation in prescription of palliative chemotherapy after adjusting for casemix. In the Netherlands, the treatment guidelines state that palliative chemotherapy should be considered in case of metastatic pancreatic cancer.[19] However, a recent study found that this consideration is strongly influenced by the physicians' amount of experience and judgment about the benefit of treatment and performance status of the patient.[20] This could explain the large inter-hospital variation observed in our study.

In the present study, the median overall survival for patients who were treated with chemotherapy was 25 weeks compared to 8 weeks for untreated patients. In our multivariable proportional hazard analyses, chemotherapy was found to reduce the risk of death by 61%. This is high in comparison with the results from a meta-analysis of chemotherapy for locally advanced and metastatic pancreatic cancer. In this meta-analysis the risk of death was reduced by 36%.[21]

The difference can be explained by the observational character of our study and underscores the influence of selection: fitter patients or patients with less advanced disease, i.e. those with a better overall survival beforehand, more often received chemotherapy. Unfortunately information on additional confounders such as performance status and disease related symptoms are lacking due to the population-based nature of our data.

Although patients treated with systemic chemotherapy had a better overall survival, increased administration of chemotherapy did not improve population-based overall survival. Perhaps, population-based improvement was not achieved because the proportion of metastatic pancreatic cancer patients treated with chemotherapy was too small, or the impact of the regimen on overall survival was too little to achieve population-based improvement. However, we found that the significantly worsened survival over time was no longer demonstrated after inclusion of chemotherapy in the multivariable survival analysis. This might be

interpreted as a beneficial effect of increased prescription rates of chemotherapy on an otherwise even increasingly detrimental prognosis of this patient group.

Fortunately, treatment options for metastatic pancreatic cancer have increased with the introduction of new drugs and multidrug regimens. For instance FOLFIRINOX, introduced in 2011, was the first regimen to result in a median overall survival of almost 1 year in patients with metastatic pancreatic cancer.[22,23] However, the regimen is more toxic than gemcitabine and may therefore only be considered for young patients with a good performance status.[22] Recently, a new combination of nab-paclitaxel and gemcitabine was introduced by van Hoff et al. this regimen also showed a clinically meaningful improvement in overall survival of patients with metastatic pancreatic cancer and may be less toxic than FOLFIRINOX.[24] As mentioned before, the impact of a regimen on population-based overall survival depends on the proportion of patients eligible to receive the regimen and the efficacy of the regimen. Although FOLFIRINOX is currently the most effective treatment in metastatic pancreatic cancer, its use is restricted to a selected group of patients.[22] Nab-paclitaxel plus gemcitabine can be used more widely, but improved the median overall survival with only 1.8 months compared to gemcitabine alone.[24] It is questionable if these regimens have enough impact to improve population-based overall survival in the near future.

Considering these new treatment modalities the aforementioned large hospital variation in chemotherapy prescription rates might be of concern. The availability of new, more toxic, treatment regimens warrants more appropriate selection of patients, and possibly treatment by a medical oncologist with more experience with these regimens. It may be hypothesized that - similar to the centralization of surgical care for patients with resectable pancreatic cancer - patients eligible for chemotherapeutical treatment might also benefit from centralization. Local tumor boards might offer a solution until centralization is achieved.[2,25]

Conclusion

In conclusion, the median survival of patients with metastatic pancreatic cancer between 1993 and 2010 remained 10 weeks in spite of a significant increase in the proportion of patients being treated with palliative chemotherapy. In the near future, it should be evaluated if the recently introduced regimens have an impact on population-based survival.

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Chapter 5.2
The relevance of pathological verification in suspected pancreatic cancer

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Abstract

Background: This population-based study assessed which factors were associated with pathological verification of pancreatic cancer.

Methods: All patients diagnosed with a malignancy of the pancreas between 1993 and 2010 in the South of the Netherlands (N=3,321) were included.

Results: Pancreatic cancer was pathologically verified in 59% of the patients. The proportion of verification increased over time from 56% in 1993-1996 to 69% in 2009-2010 (p<0.0001). High rates of verification were found among young patients (<50 years vs. 60-69 yrs: adjusted odds ratio (OR_{adj}) 3.2, (95%CI:1.9-5.4)), patients with a high socioeconomic status (high vs. low: OR_{adj} 1.3 (95%CI:1.1-1.7)), patients with metastatic disease (metastatic vs locoregional: OR_{adj} 3.2, (95%CI:2.7-3.8)) and patients treated with chemotherapy (yes vs. no: OR_{adj} 2.4, (95%CI:1.8-3.2)). The most favorable prognosis was found in patients with verified locoregional disease (median overall survival (mOS) 7.6 months, 95%CI:7.1-8.6). Patients with unverified metastatic disease carried the worst prognosis (mOS 1.7 months, 95%CI:1.4-2.0).

Conclusion: Pathological verification remains preferable and desirable whenever possible. However, the median survival rate exhibited by patients without verification suggests that the vast majority of patients suffered from true invasive pancreatic cancer. This may justify treatment decisions even in the absence of pathologic verification in selected patients.

Introduction

According to the current guidelines, suspected malignancies of the pancreas should be pathologically confirmed whenever possible. For patients with a resectable pancreatic tumor a preoperative biopsy is not always necessary as pathological verification will automatically follow after resection. For patients with locally advanced or metastatic pancreatic cancer, the guidelines recommend fine needle aspiration.[1,2]

Obtaining tissue to establish the diagnosis can be notoriously difficult in patients with suspected pancreatic cancer. It often requires invasive investigations, such as ultrasound guided punctures. These procedures are more complicated in patients with a poor performance status. A German survey revealed that not all physicians treated their patients according to the international recommendations. Of the respondents only 61% agreed with the guideline and stated that pathological verification is mandatory. In addition, for 37% of the respondents an elevation of the tumor marker CA19-9 plus a tumor in the pancreas on imaging was sufficient for the diagnosis.[3]

In the EUROCARE-4 study, a study that collected data from 93 European cancer registries between 1995 and 2002 a microscopic verification rate of 63% (range 30-91%) was found for pancreatic cancer.[4]

Although patients without pathological verification constitute a significant proportion of the patients with pancreatic cancer, no previous studies described this group of patients in detail. Therefore we assessed the clinical relevance and associated factors of pathological verification.

Methods

Data collection

For the present study we used data from the Eindhoven Cancer Registry (ECR), maintained by the Comprehensive Cancer Centre Netherlands. The registry collects data on all patients newly diagnosed with cancer in the southern part of the Netherlands. The area comprises about 2.4 million inhabitants (~15% of the Dutch population) and encompasses ten community hospitals, two radiotherapy institutions and six pathology departments.

In case of histological or cytological verification of a tumor the ECR is notified by the national automated pathological archive (PALGA). If this verification is lacking, notification occurs by additional sources as the national registry of

hospital discharge (LMR), multidisciplinary team reports and diagnosis-therapy combinations (specific codes used for reimbursement purposes). Completeness of the data was estimated to be at least 95%.[5]

Our study included all patients who were diagnosed with a neoplasm of the pancreas *(International classification of Disease for Oncology (ICD-O), second edition, topography code 157 and third edition, code C25),* between 1 January 1993 and 31 December 2010. Trained registrars, operating on behalf of the ECR, extracted patient characteristics such as gender, date of birth, comorbidity and socioeconomic status, as well as tumor characteristics, such as date of diagnosis, anatomic location, histology, stage, and primary treatment from the medical records.

Tumors were categorized as verified whenever there was histological or cytological verification from the primary tumor or one of the metastatic sites. There was no additional information on the timing of verification.

Carcinomas were classified according to the Tumor Lymph Node Metastasis (TNM) classification and staged following the recommendations of the International Union against Cancer in the respective period. For staging of other neoplasms especially those without pathological verification the clinical extent of disease (cEOD) was used. From a practical perspective we classified the tumors as locoregional (confined to the pancreas with or without extension to the surrounding organs) or metastatic disease.

Vital status of all patients on January 1, 2014 was assessed through linkage with civil municipal registries and the Central bureau for genealogy, which collects data on all citizens who die.

Statistical analyses

We performed all statistical analyses using SAS statistical software (version 9.3, SAS institute, Cary, NC, U.S.A.). The percentage of cases for which the diagnosis was based upon pathological verification was described for different subgroups. Differences between those groups were tested by means of a χ^2 test and trends across the five periods (1993-1996, 1997-2000, 2001-2004, 2005-2008 and 2009-2010) were analyzed by means of a Cochran-Armitage trend test. Independent influences on the rate of pathological verification were evaluated by means of a logistic regression analysis.

Survival time was defined as the time from diagnosis to death or January 1, 2014, for patients who were still alive. The median follow-up time (from initial

diagnosis to January 1, 2014) of patients alive (N=134) was 64 months (range 37-250 months). The crude survival was calculated with the life test and differences between survival curves were evaluated by means of a log rank test. The independent prognostic effect of pathological verification was estimated using Cox regression analyses, the hazard rates for death were adjusted for gender, age, socioeconomic status, comorbidity, extend of disease and period of diagnosis. Chemotherapy and resection were added separately to the model to investigate the effect of treatment on the hazard ratio of death.

Patients with an overall survival of more than 2 years (24 months) were defined as long-term survivors.

Results

Between January 1, 1993 and December 31, 2010, a total of 3,321 patients were diagnosed with a neoplasm of the pancreas in the southern part of the Netherlands. The median age at diagnosis was 70 years (range 29-100). Fifty-two percent of the patients were male and 49% of the patients presented with metastatic disease. Table 1 displays the general characteristics by the presence of pathological verification and disease extension (locoregional or metastatic disease).

In 1,960 patients (59%) the diagnosis was confirmed by pathological examination. In 83% of the cases pathological verification was achieved by histopathology, in the remaining patients cytological sampling was used. The percentage of verification increased over time from 56% in 1993-1996 to 69% in 2009-2010 ($p<0.0001$). Figure 1 shows that pathological verification was obtained more often in patients with metastatic disease compared to patients with non-metastatic disease. In patients with non-metastatic disease the verification rate increased significantly over time, from 45% in the first period to 57% in the last period ($p<0.0001$) and in patients with metastatic pancreatic cancer the verification rate remained stable between 74% and 77% ($p=0.10$).

The results of the logistic regression analysis are shown in table 2. Younger patients and patients with a higher socioeconomic status were more likely to have their diagnosis confirmed by cytology or histology. After adding the treatment variables surgery and chemotherapy to the model these differences persisted. The differences between periods of diagnosis disappeared entirely after adding the treatment variables. During the study period the resection

rate in patients with non-metastatic pancreatic cancer increased from 11% in 1993-1996 to 24% in 2009-2010 (p<0.0001). The prescription of chemotherapy increased from 6% to 27% (p<0.0001). In patients with non-metastatic disease, tumors located in the tail were more often pathologically verified (tail 71%, head 45%) . In metastatic disease, high verification rates were found, especially if metastases were limited to the peritoneum (90%) or to extra regional lymph nodes (85%). Low rates of verification were found in patients with pulmonary metastases only (50%). In 73% of the patients with histologically verified metastatic disease, tissue was obtained from one of the metastatic sites. In the remaining patients tissue was sampled from the primary tumor.

Adenocarcinoma was the histological subtype found in 90% of the pathologically verified cases, another 3% was represented by large cell carcinomas. Tumors of neuroendocrine origin accounted for 4% of the verified cases.

The median overall survival for all patients was 3.5 months with a 2-year survival rate of 7%. Figure 2 shows the crude survival curves for patients with and without pathologically verified pancreatic cancer, stratified according to disease extension (locoregional or metastatic disease). Patients with pathologically verified locoregional disease had the most favorable prognosis with a median survival of 7.6 months and a 2-year survival rate of 18%. Patients without pathologically verified locoregional disease had a median survival of 4.4 months and a 2-year survival of 5%. In patients with metastatic disease with or without pathological verification the median survival was 2.5 months and 1.7 months respectively and the 2-year survival was 3% and 2%.

Table 3 shows a multivariable proportional hazard regression analysis modeling the risk of death for patients with a neoplasm of the pancreas. Younger patients, patients with a higher socioeconomic status and those diagnosed in more recent periods had a more favorable prognosis. In contrast, survival was worse for older patients and patients with comorbidity. Almost all differences between subgroups and between periods of diagnosis disappeared after adding treatment, chemotherapy and surgery, into the model.
Ten percent of the patients with pathologically verified pancreatic cancer and only 4% of the patients without verification survived for more than 2 years.

Table 1 General characteristics of patients diagnosed with a neoplasm of the pancreas in the South of the Netherlands, between 1993 and 2010, stratified according to pathological verification and disease extension (non-metastatic or metastatic disease) (N=3,321)

	Total		Locoregional Verified		Locoregional Unverified		Metastatic Verified		Metastatic Unverified		*P*-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Sex											
Male	1734	(52.2)	403	(50.1)	421	(47.3)	676	(58.5)	234	(49.7)	< 0.0001
Female	1587	(47.8)	402	(49.9)	469	(52.7)	479	(41.5)	237	(50.3)	
Age (yrs)											
<50	187	(5.6)	61	(7.6)	11	(1.2)	106	(9.2)	9	(1.9)	< 0.0001
50-59	480	(14.5)	151	(18.8)	56	(6.3)	239	(20.7)	34	(7.2)	
60-69	988	(29.8)	260	(32.3)	175	(19.7)	426	(36.9)	127	(27.0)	
70-79	1141	(34.4)	264	(32.8)	378	(42.5)	310	(26.8)	189	(40.1)	
≥80	525	(15.8)	69	(8.6)	270	(30.3)	74	(6.4)	112	(23.8)	
Socioeconomic status											
Low	925	(27.9)	215	(26.7)	304	(34.2)	270	(23.4)	136	(28.9)	<0.0001
Intermediate	1242	(37.4)	294	(36.5)	313	(35.2)	466	(40.3)	169	(35.9)	
High	864	(26.0)	242	(30.1)	161	(18.1)	346	(30.0)	115	(24.4)	
Institutions	191	(5.7)	26	(3.2)	86	(9.7)	36	(3.1)	43	(9.1)	
Missing	99	(3.0)	28	(3.5)	26	(2.9)	37	(3.2)	8	(1.7)	
Number of comorbid conditions											
0	1518	(45.7)	374	(46.5)	362	(40.7)	583	(50.5)	199	(42.3)	0.0002
1	1042	(31.4)	249	(30.9)	284	(31.9)	355	(30.7)	154	(32.7)	
≥2	430	(12.9)	95	(11.8)	141	(15.8)	128	(11.1)	66	(14.0)	
Unknown	331	(10.0)	87	(10.8)	103	(11.6)	89	(7.7)	52	(11.0)	
Histologic subtype*											
Adeno-carcinoma	1755	(89.5)	736	(91.4)	n.a.		1019	(88.2)	n.a.		0.0334
Neuro-endocrine	85	(4.3)	33	(4.1)	n.a.		52	(4.5)	n.a.		
Other	120	(6.1)	36	(4.5)	n.a.		84	(7.3)	n.a.		

Table 1 Continued

	Total		Locoregional Verified		Locoregional Unverified		Metastatic Verified		Metastatic Unverified		*P*-value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Location primary tumor											
Head	2204	(66.4)	605	(75.2)	745	(83.7)	572	(49.5)	282	(59.9)	< 0.0001
Body	275	(8.3)	52	(6.5)	43	(4.8)	133	(11.5)	47	(10.0)	
Tail	392	(11.8)	62	(7.7)	26	(2.9)	234	(20.3)	70	(14.9)	
Overlapping	232	(7.0)	41	(5.1)	30	(3.4)	128	(11.1)	33	(7.0)	
Unknown/ NOS	218	(6.6)	45	(5.6)	46	(5.2)	88	(7.6)	39	(8.3)	
Location of metastases **											
Liver	912	(56.1)	n.a.		n.a.		601	(52.0)	311	(66.0)	< 0.0001
Peritoneum	131	(8.1)	n.a.		n.a.		118	(10.2)	13	(2.8)	
Lung	52	(3.2)	n.a.		n.a.		26	(2.3)	26	(5.5)	
Lymphnodes	53	(3.3)	n.a.		n.a.		45	(3.9)	8	(1.7)	
Other	83	(5.1)	n.a.		n.a.		63	(5.5)	20	(4.3)	
2	292	(18.0)	n.a.		n.a.		214	(18.5)	78	(16.6)	
3 or more	103	(6.3)	n.a.		n.a.		88	(7.6)	15	(3.2)	
Period of diagnosis											
1993-1996	566	(17.0)	162	(20.1)	195	(21.9)	155	(13.4)	54	(11.5)	< 0.0001
1997-2000	697	(21.0)	162	(20.1)	243	(27.3)	195	(16.9)	97	(20.6)	
2001-2004	642	(19.3)	127	(15.8)	192	(21.6)	213	(18.4)	110	(23.4)	
2005-2008	876	(26.4)	228	(28.3)	165	(18.5)	347	(30.0)	136	(28.9)	
2009-2010	540	(16.3)	126	(15.7)	95	(10.7)	245	(21.2)	74	(15.7)	
Surgery											
Yes	296	(8.9)	282	(35.0)	1	(0.1)	13	(1.1)	0	(0.0)	< 0.0001
No	3025	(91.1)	523	(65.0)	889	(99.9)	1142	(98.9)	471	(100.0)	
Chemotherapy											
Yes	485	(14.6)	143	(17.8)	37	(4.2)	275	(23.8)	30	(6.4)	< 0.0001
No	2836	(85.4)	662	(82.2)	853	(95.8)	880	(76.2)	441	(93.6)	
Total	3321		805		890		1155		471		

** Histological subtype available in 1960 patients (59.0%)*

*** Metastatic subsite available in 1626 patients (49.0%)*

Table 2 Crude percentages and odds[a] of pathological verification in patients diagnosed with a neoplasm of the pancreas, in the southern Netherlands between 1993 and 2010 (N=3,321)

	Crude % Verification	Odds ratio (95% CI)
Sex		
Male	62.2	1.00 (reference)
Female	55.5	0.97 (0.82-1.14)
Age (yrs.)		
<50	89.3	3.20 (1.91-5.35)
50-59	81.3	1.70 (1.27-2.27)
60-69	69.4	1.00 (reference)
70-79	50.3	0.55 (0.45-0.67)
≥80	27.2	0.27 (0.21-0.36)
Socioeconomic status		
Low	52.4	1.00 (reference)
Intermediate	61.2	1.10 (0.90-1.35)
High	68.1	1.32 (1.06-1.66)
Institutions	32.4	0.63 (0.43-0.91)
Number of comorbid conditions		
0	63.0	1.00 (reference)
1	58.0	1.05 (0.87-1.27)
≥2	51.9	1.00 (0.77-1.29)
Extent of disease		
Locoregional	47.5	1.00 (reference)
Metastatic	71.0	3.19 (2.70-3.77)
Period of diagnosis		
1993-1996	56.0	1.00 (reference)
1997-2000	51.2	0.71 (0.55-0.93)
2001-2004	53.0	0.68 (0.52-0.89)
2005-2008	65.6	1.13 (0.87-1.47)
2009-2010	68.7	1.26 (0.93-1.70)
Surgery		
No	55.0	1.00 (reference)
Yes	99.7	329.5 (46.0-999.999)
Chemotherapy		
No	54.4	1.00 (reference)
Yes	86.2	2.40 (1.78-3.24)

[a] *Adjusted for all variables listed. Included in the analysis but results not shown for SES unknown, comorbidity unknown.*

Table 3 Crude median overall survival in months, crude 1-year survival and risk of dying (hazard ratios) in patients diagnosed with a neoplasm of the pancreas, in the southern Netherlands between 1993 and 2010 (N=3,321)

	Crude median overall survival (Months)	Crude 2-year survival (%)	Multivariate HR (95%CI) [a]	Multivariate HR (95%CI) adjusted for treatment [a]
Sex				
Male	3.4	7.2	1.00 (reference)	1.00 (reference)
Female	3.7	7.0	0.97 (0.90-1.04)	0.96 (0.89-1.03)
Age (yrs.)				
<50	5.6	12.3	0.84 (0.71-0.98)	0.92 (0.78-1.08)
50-59	5.2	10.8	0.89 (0.79-0.99)	0.93 (0.83-1.04)
60-69	4.1	8.2	1.00 (reference)	1.00 (reference)
70-79	3.3	5.7	1.27 (1.16-1.39)	1.17 (1.07-1.28)
≥80	2.2	2.9	1.68 (1.49-1.89)	1.43 (1.27-1.61)
Socioeconomic status (SES)				
Low	3.3	6.0	1.00 (reference)	1.00 (reference)
Intermediate	3.6	6.7	0.98 (0.90-1.07)	0.96 (0.88-1.05)
High	3.9	8.2	0.89 (0.81-0.98)	0.92 (0.84-1.01)
Institutions	2.7	4.7	1.01 (0.86-1.18)	1.02 (0.87-1.20)
Number of comorbid conditions				
0	3.8	7.3	1.00 (reference)	1.00 (reference)
1	3.3	6.6	1.11 (1.02-1.20)	1.08 (0.99-1.17)
≥2	3.0	4.4	1.17 (1.05-1.31)	1.12 (1.00-1.25)
Extent of disease/ pathological verification				
Locoregional, verified	7.6	18.3	1.00 (reference)	1.00 (reference)
Locoregional, unverified	4.4	4.8	1.34 (1.20-1.48)	0.98 (0.87-1.09)
Metastatic verified	2.5	3.3	2.46 (2.23-2.70)	1.94 (1.75-2.16)
Metastatic unverified	1.7	1.7	2.87 (2.54-3.24)	2.12 (1.87-2.41)
Period of diagnosis				
1993-1996	3.8	5.3	1.00 (reference)	1.00 (reference)
1997-2000	2.9	5.0	1.05 (0.94-1.18)	1.10 (0.98-1.23)
2001-2004	3.5	6.2	0.90 (0.80-1.01)	0.99 (0.89-1.12)
2005-2008	3.6	8.8	0.84 (0.76-0.94)	0.94 (0.84-1.05)
2009-2010	3.9	10.0	0.73 (0.65-0.83)	0.88 (0.77-1.00)
Surgery				
No	3.2	4.1	Not included in	1.00 (reference)
Yes	15.4	38.2	the analysis	0.44 (0.38-0.51)
Chemotherapy				
No	3.0	6.1	Not included in	1.00 (reference)
Yes	8.3	12.8	the analysis	0.54 (0.48-0.60)

[a] *Adjusted for all variables listed. Included in the analysis but results not shown for SES unknown, comorbidity unknown*

Figure 1 Crude percentage of verification according to disease extension and period of diagnosis, in patients diagnosed with a neoplasm of the pancreas, in the southern Netherlands, between 1993 and 2010 (N=3,321)

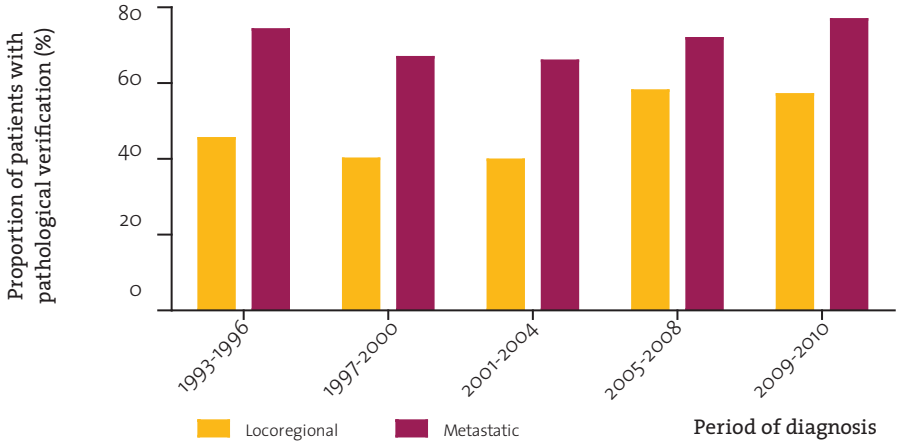
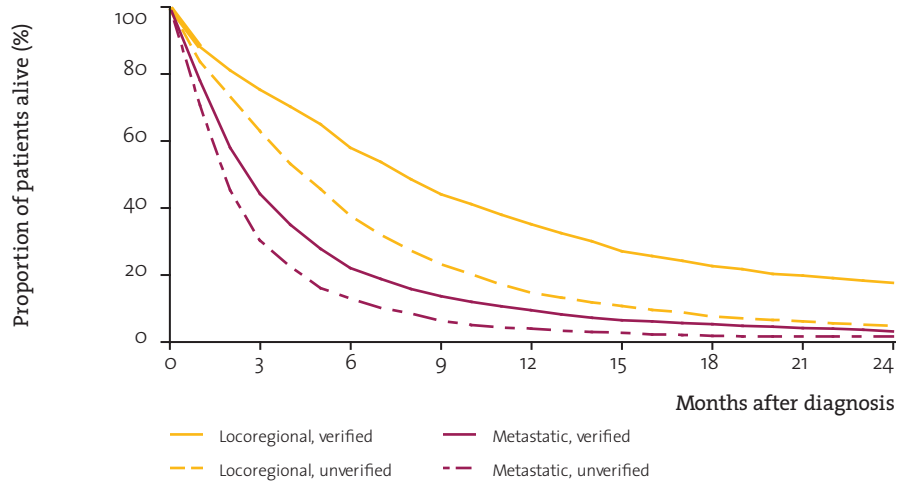


Figure 2 Overall survival according to pathological verification and disease extension, in patients diagnosed with a neoplasm of the pancreas, in the southern Netherlands, between 1993 and 2010 (N=3,321)



Discussion

In our study we found that in 59% of the patients with suspected pancreatic cancer, pathological verification was obtained. The rate of pathological verification in our study seems in line with other population-based studies. In the EUROCARE 4 study a comparable overall verification rate of 63% (range 30-91%) was found. The verification rate was established as one of the quality indicators for participating registries.[4] In the United states pancreatic cancer cases without microscopic verification represent one fourth of the total number of pancreatic cancer cases.[6,7] The validity of diagnostic information from registries with low rates of verification is obviously questionable. However, high rates of pathological verification do not simply mean that the validity of the data is excellent. Instead, exceptionally high proportions of verification might suggests over-reliance on the pathology laboratory as source of information, and failure to find cases without pathological verification.[7] However, the wide range of verification worldwide, may hamper the comparability across studies, countries and contents.

The rate of pathological verification was higher in patients with metastatic disease compared to patients with non-metastatic disease. However, in this latter group of patients the rate of verification increased significantly over time from 45% to 57%. This can be partially explained by the increased resection rate after the introduction of high-volume centers in the southern Netherlands.[8,9] Furthermore, the diagnostic advances that have been made in pancreatic cancer played an important role, especially the introduction of endoscopic ultrasonography (EUS) in the early nineties. EUS rapidly evolved to a diagnostic imaging modality by which fine needle biopsies could be guided into small or encased pancreatic lesions. Eventually, endoscopic ultrasound combined with fine needle aspiration became the primary modality for tissue verification with a sensitivity of 85% and a specificity of 98%.[10]

In this study, the highest rate of verification was found in pancreatic tail tumors (70%). Due to a lack of symptoms, tumors at this location are usually larger at the time of diagnosis making them more accessible for diagnostic procedures.[11] In addition, given anatomical circumstances localized pancreatic tail tumors are more often resected as compared to tumors located in the head of the pancreas in spite of a larger tumor size.[12]

In 75% of the patients with metastatic pancreatic cancer, the diagnosis was microscopically verified. High rates of verification were especially found in

patients with metastases limited to the peritoneum or to extra regional lymph nodes. One reason for the high verification rate found in patients with peritoneal dissemination might be the inability to detect small volume peritoneal implants on imaging studies.[13,14] These small volume peritoneal implants might be identified by coincidence during surgery with an initially curative intent. In patients who are not eligible for surgery there must be an underestimation of the peritoneal disease burden.[14] The identified large volume implants or moderate to high-volumes of ascites are easily accessible for diagnostic procedures. For patients with suspected extra regional lymph node involvement, it can be hypothesized that the high verification rate is a result of the major therapeutic implications which extra regional nodal involvement has on the treatment choice.

Patient characteristics such as age and socioeconomic status influenced the rate of verification as well. Although younger patients and those with a higher socioeconomic status more often underwent resection or received chemotherapy with upfront verification, this effect was not only treatment-related. Possibly, younger patients and patients with a higher socioeconomic status are more eager to have their diagnosis established.[9] Not only patient characteristics differed between patients with and without pathological verification, previous population-based studies showed an association with etiological factors as well, such as cigarette smoking and body mass index.[6,15,16]

Our finding that 90% of the patients with a tissue diagnosis had an adenocarcinoma is in agreement with the already published literature.[17] The not otherwise specified large cell carcinomas of the pancreas could have been adenocarcinomas as well, poorly or undifferentiated. The proportion of neuroendocrine tumors that we found is slightly higher compared to the proportion found in several more dated studies.[18,19] A possible explanation might be the growing interest in neuroendocrine malignancies.[20]

Median overall survival in all patients with pancreatic cancer is dismal (3,5 months). Crude survival curves showed that patients with pathologically verified pancreatic cancer carried a more favorable prognosis, regardless of the extent of disease, with the best prognosis found in patients with verified locoregional disease. These patients had a median overall survival of 7.6 months which is comparable to the median overall survival found in a large population-based study using data from the SEER registry.[21] The prognosis of patients with pathologically unverified locoregional disease was only 4.4 months. The

difference in overall survival between these subgroups was mainly explained by treatment, in particular surgical resection. After adjusting for the effect of treatment in a multivariable model, the risk of death between subgroups was comparable. Moreover, 5% percent of the patients with unverified locoregional disease had an overall survival exceeding two years. Since long-term survival in patients with pancreatic cancer is extremely rare, especially if the primary tumor has not been resected, it is likely that these patients suffered from a more indolent tumor of the pancreas or even a benign disease. It could be informative to collect additional data in long-term survivors to investigate whether the initial diagnosis has been revised by the treating physician. Even in long-term survivors with pathologically verified disease re-evaluation showed false diagnosis.[22]

For patients with metastatic disease, those with verified cancer had a median overall survival of 2.5 months compared to 1.7 months in patients without pathologically verified metastatic disease. These differences in survival seem at least partly a result of selection bias and treatment-related differences as well, especially the prescription of chemotherapy. Patient with verified cancer were more frequently treated with chemotherapy since the guidelines recommend upfront pathological confirmation. And biopsies might be omitted in patients who are not candidates for palliative treatment, the patients that have a worse overall survival in advance.

In selected patients, an elevated level of the serum marker CA 19-9 in combination with a pancreatic mass on imaging studies might be enough to establish the diagnosis pancreatic cancer. Previous research found significantly higher concentrations of CA 19-9 in patients with a pancreatic adenocarcinoma compared to patients without a malignancy and those with a tumor of neuroendocrine origin. The sensitivity and specificity of elevated serum 19-9 concentrations in symptomatic patients were respectively between 79-81% and 82-90%.[23] However, the predictive value of CA 19-9 was especially high in patients with a pancreatic mass on imaging studies. The combination of a suspected mass, weight loss, elevated bilirubin levels and elevated serum concentrations of CA 19-9 provided an almost 100% specificity and positive predictive value for pancreatic cancer.[23,24]

Limitations

We would like to acknowledge the limitations inherent to this population-based nature of our study. First and foremost, the proportion of patients without verified pancreatic cancer found in our study seems to be an underestimation. However, the completeness of our registry is estimated to be at least 95%.[5] Second, detailed information on serum CA 19-9 levels, imaging studies or diagnostic procedures are lacking.

Conclusion

In conclusion, both patients with and without pathologic verification of a pancreatic mass have a dismal prognosis. The survival data as obtained in the current study suggest that all patients, including those without verification, suffered from true invasive pancreatic cancer. Before starting palliative treatment including chemotherapy and radiotherapy pathological verification remains preferable and desirable. However, in selected patients, a high clinical suspicion of pancreatic cancer, may justify treatment even in the absence of pathological verification.

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Chapter 5.3
Does long-term survival exist in pancreatic adenocarcinoma?

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Abstract

Background: We conducted a population-based study to investigate long-term survival in patients diagnosed with a (suspected) pancreatic adenocarcinoma.

Methods: All patients diagnosed with a pancreatic adenocarcinoma or with a pathologically unverified tumor of the pancreas between 1993 and 2008 in the south of the Netherlands were selected from the Netherlands Cancer Registry (NCR). Medical charts of patients who were alive five years or longer after diagnosis were reviewed.

Results: A total of 2,564 patients were included, of whom 1,365 had a pancreatic adenocarcinoma and 1,199 had a pathologically unverified pancreatic tumor. The five-year survival rate of patients with pathologically verified adenocarcinomas was 1.7% (24 of 1,365 patients). Twenty-one of these 24 long-term survivors were among the 207 cases that underwent surgical resection as initial treatment; five-year survival rate after resection thus being 10.1%. Half of the long-term survivors who underwent surgical resection eventually died of recurrent disease. The five-year survival rate among patients with clinically suspected but microscopically unverified pancreatic tumors was 1.3% (16 of 1,199 patients). In 15 of these 16 long-term survivors the initial clinical diagnosis was revised: 14 had benign disease and one a premalignant tumor.

Conclusion: Long-term survival among patients with pancreatic adenocarcinoma is extremely rare. As long-term survival in clinically suspected but pathologically unverified cancer is very unlikely, repeated fine needle

aspiration or, preferably, histological biopsy is recommended in order to establish an alternative diagnosis in patients who survive longer than expected (more than 6–12 months).

Introduction

Survival after a diagnosis of pancreatic cancer is often short, with a five-year survival rate reported as low as 7% in Europe.[1] The only potentially curative treatment is radical surgery, which is, together with adjuvant chemotherapy standard of care in patients with a resectable pancreatic adenocarcinoma.[2] Nevertheless, the majority of patients is diagnosed with inoperable locally advanced or metastatic disease, therapeutic options in these stages are limited.

In Europe, the overall microscopic verification rate for pancreatic tumors is 63%.[3]The major histological type of pancreatic tumors is ductal adenocarcinoma, which represents about 85% of all pancreatic neoplasms and is associated with poor survival rates. Other types of pancreatic cancer, such as neuroendocrine tumors, may exhibit a less aggressive behavior. A recent population-based Dutch study showed a poor prognosis in patients with pancreatic tumors both with and without pathological verification, suggesting that virtually all patients, including those without verification, suffered from true pancreatic adenocarcinoma.[4] Only a small proportion of the patients had an overall survival exceeding two years. Considering these results, one might question if long-term survival exists in pancreatic cancer. We conducted a population-based study in order to investigate long-term survival in all patients diagnosed with pancreatic cancer in the south of the Netherlands in the years 1993–2008. Long-term survival was defined as an overall survival exceeding five years.

Methods

Data collection

We used data from the Netherlands Cancer Registry (NCR), maintained by the Comprehensive Cancer Centre Netherlands. The registry collects data on all patients with newly diagnosed cancer in the Netherlands. We limited our study to the area of the previous Eindhoven Cancer Registry (ECR), in order to be able

to perform a medical chart review. This area hosts 2.4 million inhabitants (~15% of the Dutch Population) and is served by 10 general hospitals, two large radiotherapy institutes and six pathology laboratories. The pathology laboratories all participate in the nationwide automated pathology archive (PALGA) which notifies the cancer registry. Additional sources responsible for notification are the national registry of hospital discharge (LMR), multidisciplinary team reports and diagnosis-therapy combinations (specific codes used for reimbursement purposes). The completeness of the registry exceeds 95%. After notification, information on patient characteristics, tumor characteristics and initial treatment is routinely extracted from medical records by trained administrators within 6–9 months after diagnosis. For the present study we selected patients with a malignancy of the pancreas diagnosed between 1 January 1993 and 31 December 2008. We decided to restrict our inclusion to adenocarcinomas (ICD-O morphology codes 8140, 8141, 8260, 8440, 8453, 8470, 8471, 8480, 8481, 8490, 8500) and pancreatic neoplasms without pathological verification (ICD-O morphology code 8000).

Vital status of patients was assessed at 1 January 2014 through linkage with civil municipal registries and the central bureau for genealogy. The latter is an institution that collects data on all deceased Dutch citizens. The survival was calculated based on all-cause mortality. We defined patients with an overall survival of more than five years as long-term survivors. Additional data were retrospectively extracted from the medical records of long-term survivors by two experienced researchers with the approval and under supervision of the treating physicians. The additional data concerned letters and pathology reports to investigate if the initial clinical or pathological diagnosis had been re-evaluated.

Statistical analyses

We performed all statistical analyses using SAS statistical software (version 9.3, SAS institute, Cary, NC, USA). Survival time was defined as the time from diagnosis to death or 1 January 2014, for patients who were still alive. The crude survival was calculated with the life test, a log rank test was carried out to compare survival curves between different subgroups.

Results

Between 1 January 1993 and 31 December 2008 a total of 2,796 patients were diagnosed with a neoplasm of the pancreas of whom 1,365 (48.8%) patients had an adenocarcinoma, and 1,199 (42.9%) patients had a pathologically unverified tumor of the pancreas. Two hundred and thirty-two patients were excluded from further analyses: 68 (2.4%) patients with a neuroendocrine tumor and 164 (5.9%) patients with other types of pancreatic malignancies (figure 1).

General characteristics of the remaining 2,564 patients are depicted in table 1. Fifty-two percent of our study population was male and the median age at time of diagnosis was 70 years (range 32–100) and 45.1% had metastases at time of diagnosis. The proportion of patients presenting with metastatic disease increased from 34.7% in 1993–1996 to 52.8% in 2005–2008 ($p<0.0001$). Eight percent (N=207) of the total study population was eligible for surgery with a curative intent. The resection rate did not change over time ($p=0.08$). However, an increasing proportion ($p<0.0001$) of the surgically treated patients received adjuvant chemotherapy. In 2008, 50.0% of the surgically treated patients received adjuvant chemotherapy.

Forty-seven percent of the patients (N=1,201) had non-metastatic unresected pancreatic cancer, of whom 32.8% had their diagnosis pathologically confirmed. Eight percent (N=100) of these patients received treatment within six months after diagnosis. The treatment rate was higher in patients with a microscopically verified pancreatic adenocarcinoma compared to patients with a non-microscopically verified pancreatic tumor (16.5% vs. 4.3%, $p<0.0001$). Fifty-nine patients (59.0%) received palliative chemotherapy and 24 patients (24.0%) were treated with chemoradiotherapy.

The remaining 45.1% of the patients (N=1,156) had metastases at time of diagnosis, the verification rate in these patients was 66.1%. Sixteen percent of the patients with metastatic pancreatic cancer received chemotherapy, the prescription of chemotherapy increased significantly over time (8.8% in 1993–1996 to 20.4% in 2005–2008, $p<0.0001$) and was significantly higher in patients with microscopically verified disease (20.9% vs. 6.1%, $p<0.0001$).

The median overall survival of surgically treated patients was 13.7 months (95% CI 11.3–16.1) with a one-year survival rate of 55.8% (figure 2). The outcome of these patients significantly improved over time from a median survival of 7.1 months (95% CI 4.7–13.8) in 1993–1996 to 17.4 months (95% CI 13.6–25.0) in 2005–2008 (log rank for these periods $p=0.004$). The outcome of patients with

Table 1 General characteristics of patients diagnosed with a neoplasm of the pancreas, in the southern Netherlands between 1993 and 2008 (N=2,564)

	N	%
Sex		
Male	1,327	51.8
Female	1,237	48.2
Age (yrs)		
< 50	140	5.5
50-59	353	13.8
60-69	751	29.3
70-79	904	35.3
≥ 80	416	16.2
Socioeconomic status (SES)		
Low	737	28.7
Intermediate	964	37.6
High	667	26.0
Institutionalised	156	6.1
Unknown	40	1.6
Number of comorbid conditions		
0	1,210	47.2
1	767	29.9
≥2	301	11.7
Unknown	286	11.2
Histologic subtype		
Adenocarcinoma	1,365	53.2
Unknown	1,199	46.8
Extent of disease		
Resected	207	8.1
Unresected locoregional	1,201	46.8
Metastatic	1,156	45.1
Period of diagnosis		
1993-1996	522	20.4
1997-2000	653	25.5
2001-2004	601	23.4
2005-2008	788	30.7
Chemotherapy		
Adjuvant	23	0.9
Palliative	245	9.6
No	2,296	89.5

Figure 1 Study flow chart

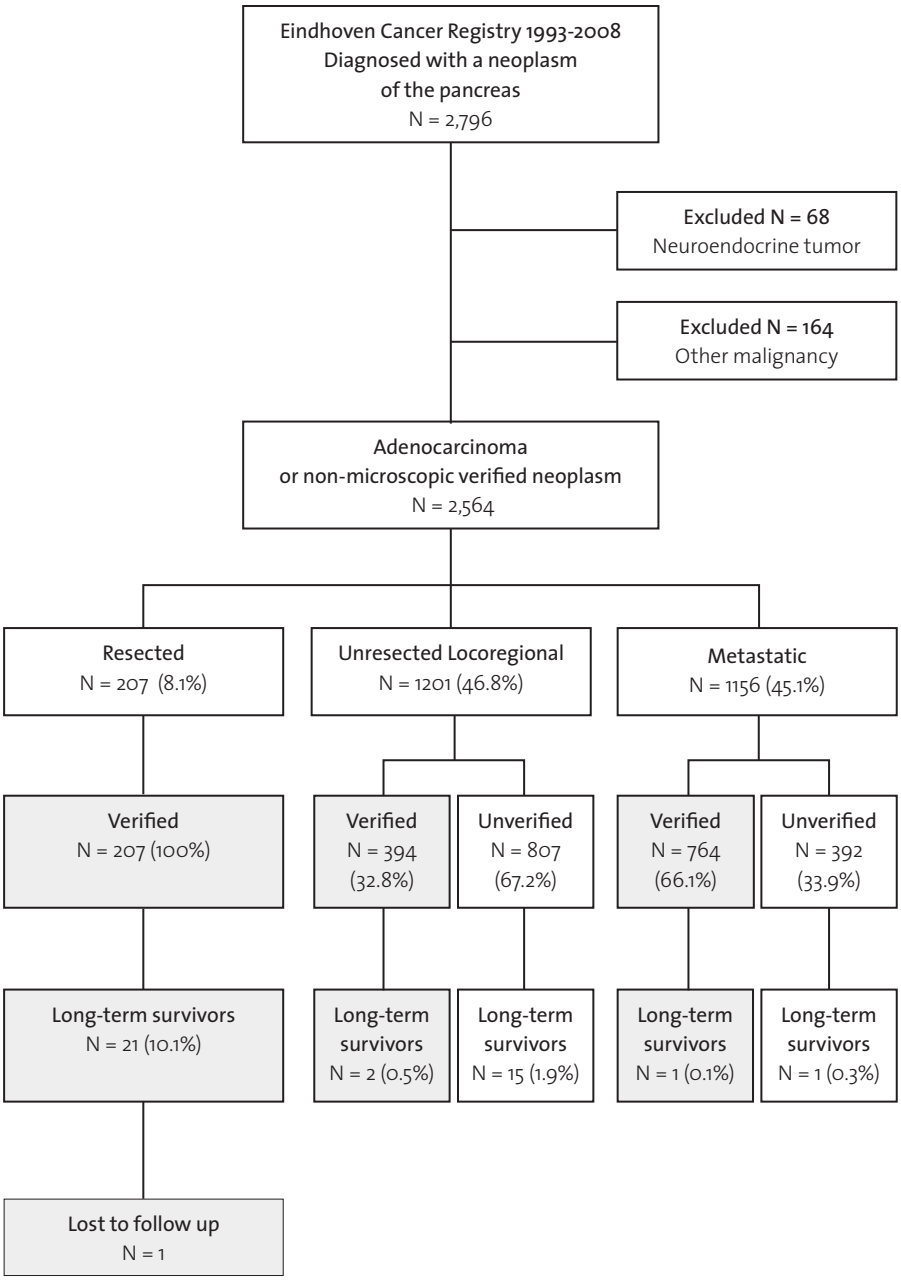
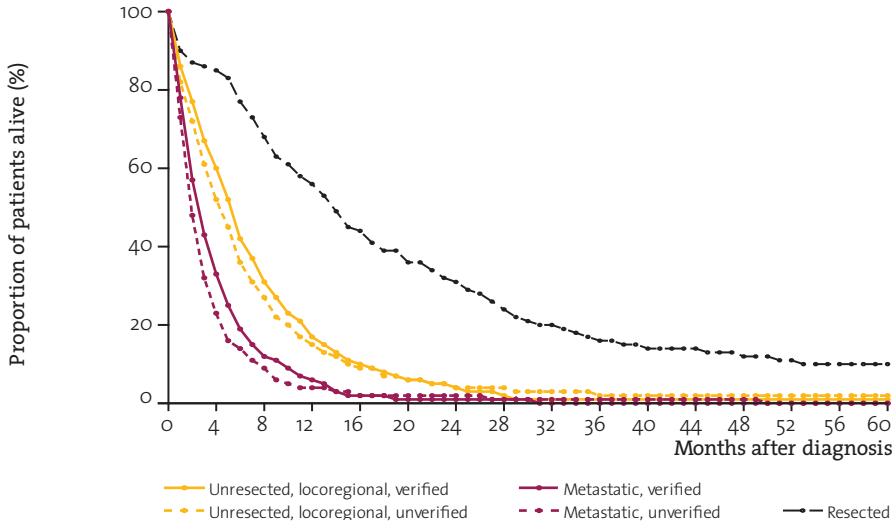


Figure 2 Overall survival of patients diagnosed with pancreatic cancer in the southern Netherlands between 1993 and 2008, according to extent of disease (N=2,564)



unresected and metastatic pancreatic cancer remained unchanged over time. The median survival for patients with unresected localized pancreatic cancer was 4.6 months (95% CI 4.2–5.0) with a one-year survival rate of 15.4%. Patients with metastatic pancreatic cancer carried the poorest prognosis of only 2.2 months (95% CI 2.1–2.4) with a one-year survival rate of 5.2%. There were small but significant differences in survival between patients with metastatic microscopically verified pancreatic cancer and patients with non-verified metastatic disease.

Only 40 patients (1.6%) of our total study population had an overall survival exceeding five years. Of the long-term survivors, 21 patients underwent surgical resection as initial treatment which represented 10.1% of the total of 207 surgically resected patients. The general characteristics of this group of patients are depicted in Table 2. Additional data collection of this group of 21 long-term survivors showed that despite surgery, three patients developed locoregional recurrence or metastases within five years, and seven patients more than five years after initial diagnosis. Nine of these 10 patients with recurrent disease died between five and 10 years after initial diagnosis.

Table 2 General characteristics of 21 long-term survivors with surgically resected pancreatic cancer, diagnosed in the southern Netherlands between 1993 and 2008

	N
Sex	
Male	12
Female	9
Age (yrs)	
< 50	2
50-59	3
60-69	11
70-79	5
≥ 80	0
Socioeconomic status (SES)	
Low	6
Intermediate	6
High	7
Institutionalised	1
Unknown	1
Number of comorbid conditions	
0	
1	13
≥2	4
Unknown	2
	2
Tumour grade	
Good/moderate	14
Poor/undifferentiated	2
Unknown	5

	N
T stage	
1	7
2	5
3	6
4	1
X	2
N stage	
0	8
1	7
X	6
TNM Stage	
1	9
2	6
3	4
X	2
Period of diagnosis	
1993-1996	1
1997-2000	7
2001-2004	4
2005-2008	9
Adjuvant chemotherapy	
Yes	6
No	15

Seventeen long-term survivors had non-metastatic unresected cancer, of whom 15 patients had non-microscopically verified disease at time of diagnosis. In 14 of these 15 patients the diagnosis was revised by the treating physician. The majority of these patients had a pancreatitis (focal or auto-immune), one patient had an intraductal papillary mucinous neoplasm (IPMN), one patient had a cystic adenoma, and one patient sclerosing cholangitis. The patient without revision of the diagnosis died 5.1 years after the initial diagnosis.

Two long-term survivors with unresected disease had a histologically verified adenocarcinoma at time of diagnosis. One of these patients only received a palliative bypass, the other patient was treated with palliative chemotherapy. Both tumors showed a remarkable indolent disease course.

Two long-term survivors had metastatic disease at time of diagnosis. One of them had a pathologically verified metastatic adenocarcinoma of the pancreas and was treated with palliative chemotherapy as well. The other one had metastatic disease without microscopic verification. In this patient the diagnosis was revised. Additional biopsies revealed a Wegener's granulomatosis/ANCA associated vasculitis and after correct immunosuppressive treatment the imaging studies normalized within a couple of months.

Discussion

In this population-based study including all patients with pathologically verified (adenocarcinoma) pancreatic cancer or clinically suspected pancreatic cancer in the period 1993 until 2008 we found that only 40 of 2,564 patients (1.6%) survived for more than five years.

The recently published Eurocare-5 data, reported a remarkably high five-year survival rate of 7% for patients diagnosed between 2000 and 2007 throughout Europe with any type of pancreatic tumor.[1] The authors suggest that difficulties with ascertainment of vital status in some countries might have biased their long-term survival estimates. More in line with our results are the five-year survival rates reported in population-based studies in Norway (1965–2007), Finland (1990–1996) and Australia (2002–2003) of <3%, 1.8% and 2.6%, respectively, in patients with pancreatic cancer. The Norwegian cohort included all registered pancreatic cancer patients, both pathologically verified and unverified. At five years of diagnosis, relative survival was 5.3% in men and 2.6%. in women. Five-year survival rate in patients with pancreatic cancer diagnosed in 1990–2006 was less than 3%.[5] In the Finnish study, all types of pancreatic

cancer were included. Re-evaluation of histological specimens of the long-term survivors initially recorded as having histologically proven pancreatic adenocarcinoma, confirmed pancreatic adenocarcinoma in only 10 of 26 patients, representing 11.2% of all long-term survivors (10 of 89 patients).[6] In the Australian study, neuroendocrine and ampullary tumors were excluded and, similar to our results, half of the long-term survivors had undergone surgical resection. As the other half of the long-term survivors had no pathologically confirmed diagnosis, true pancreatic cancer in these patients may be doubted because long-term survival in patients with pancreatic cancer, especially if the primary tumor has not been resected, is extremely rare and a more indolent or benign disease seems a more likely cause.[7]

In our study the five-year survival among patients with clinically suspected but microscopically unverified pancreatic cancer was 1.3% (16 of 1,199 patients). However, in 15 of the 16 long-term survivors without initial pathological verification, the diagnosis was revised: 14 patients had a benign disease and one a premalignant tumor. As data collection by the registry occurred within 6–9 months after initial diagnosis, revision of the primary diagnosis had taken place after this period of time. None of the long-term survivors with pathologically unverified metastatic or unresected pancreatic cancer were diagnosed with pancreatic malignancies that exhibited a more indolent clinical course, such as neuroendocrine tumors. Several explanations could be proposed for this finding. First of all, pancreatic neuroendocrine tumors are rare, representing only 1–3% of all pancreatic tumors.[8,9] Second, computed tomography technology, the imaging modality that is most commonly used to investigate known or suspected pancreatic tumors, has improved. As a result, we succeed to differentiate better between pancreatic neuroendocrine tumors and other malignancies of the pancreas. Detection rate of neuroendocrine tumors with CT scan exceeds 80%.[10] Finally, although overall survival for patients with pancreatic neuroendocrine tumors is more favorable than for patients with pancreatic adenocarcinomas, the median overall survival in metastatic disease does not exceed 2-5.8.[11,12]

The five-year survival of patients with pathologically verified pancreatic cancer in our study was 1.7% (24 of 1,365 patients). The majority of these long-term survivors with a verified adenocarcinoma had undergone surgical resection (21 of 24 patients), comprising 10.1% of all surgically treated patients (N=207). The five-year survival rate of surgically treated patients in our study

is comparable with the five-year survival rate of 12.2%, found in a recently published large cohort study, including 11,081 patients with surgically resected invasive pancreatic adenocarcinoma.[13] By contrast, our results seem inferior to the results found in the phase III CONKO-001 trial, in which patients who underwent surgical resection had a five-year survival of 15.0%.[14] However, this trial was performed in a selected group of patients. Another explanation for the lower five-year survival of surgically treated patients in our study might be that adjuvant chemotherapy was not part of standard care during the first period of this study. Significant survival differences were found in the CONKO-001 trial between patients treated with surgery alone and those who received adjuvant chemotherapy, five-year survival rates were, respectively, 9.1% and 20.7%.[14]

In our study, we tried to identify prognostic factors predicting long-term survival, however, the small number of five-year survivors among the surgically treated patients was not suitable for testing in a multivariate model. In a recently published large cohort study, Paniccia et al. identified pathologic T stage, lymph node ratio and administration of adjuvant chemotherapy as variables associated with long-term survival in surgically treated pancreatic adenocarcinomas.[13] In our study, the surgically treated long-term survivors had very different tumor characteristics. It is noteworthy that approximately half of surgically treated long-term survivors (9 of 21 patients) eventually died from metastatic or locoregional recurrence, further emphasizing the largely palliative nature of surgery in pancreatic cancer.

Several studies have shown that surgical resection is performed in 8–15% of all pancreatic carcinomas.[7,14-16] In the present study, 8.1% of the patients underwent surgical resection. Whilst the resection rate did not change over time, some important surgery-related improvements were made, including the implementation of centralization of pancreatic cancer surgery from 2005 onwards and the standard use of adjuvant chemotherapy, improving disease-free and overall survival through the administration of adjuvant gemcitabine during six months.[17-19] Our population-based data showed an increase in median overall survival of surgically treated patients from seven months in the early period to 17 months in the period 2005–2008, which is consistent with median survival rates demonstrated in several other population-based studies.[16,20,21]

In contrast to the surgically treated patients, the median overall survival of patients with unresected and metastatic pancreatic cancer remained unchanged over time. Whilst the proportion of patients presenting with

metastatic disease increased due to improved and more accurate diagnostic imaging techniques, no beneficial effect on survival as a result of stage migration could be observed. Unfortunately, in this population-based study we have no information as to why surgical resection could not be performed in patients referred to as having irresectable non-metastatic pancreatic cancer. Among unresected patients (locally advanced unresected + metastatic disease), 10.3% received chemotherapy. During the course of the study, no substantial progress had been made in chemotherapeutic treatment of advanced pancreatic cancer. However, the prescription of chemotherapy in metastatic disease had more than doubled, from 8.8% in 1993–1996 to 20.4% in 2005–2008, possibly because physicians gained more experience with the use of chemotherapy in the adjuvant setting. Since 2011, new treatment options for metastatic pancreatic cancer have emerged, demonstrating an overall survival benefit by using combination chemotherapy.[22,23] The FOLFIRINOX regimen is currently the most effective treatment in metastatic disease, but due to toxicity, its use is restricted to a select group of patients.

Conclusion

In conclusion, long-term survival in patients suffering from pancreatic cancer is extremely rare. We found that only 1.6% of all patients survived for more than five years. Of the patients who were eligible for surgical resection, 10.1% survived for at least five years. Perhaps the number of long-term survivors may further increase in the future, by optimizing centralization, more extensive surgery, and increased use of possibly better (neo) adjuvant strategies. However, unresectable and metastatic disease at presentation remains a key problem, stressing the need for better understanding of the disease and better systemic treatment options. Survival in patients with pathologically verified (adenocarcinoma) pancreatic cancer and clinically suspected but microscopically unverified pancreatic cancer was very similar, demonstrating the reliability of the clinical and radiological judgement. However, if a patient with pathologically unverified pancreatic cancer survives longer than expected (more than 6–12 months depending on the extent of the disease at the time of primary diagnosis), we recommend to perform fine needle aspiration or, preferably, histological biopsy in order to obtain pathological confirmation of the diagnosis.

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Chapter 5.4

Volume matters in the systemic treatment of metastatic pancreatic cancer: a population-based study in the Netherlands

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Abstract

Background: In pancreatic cancer surgery, a relationship between surgical volume and postoperative mortality and overall survival has been established. As a result, high-volume centers report significantly better survival rates. In this population-based study, we aimed to explore the influence of incidence and treatment volume on the outcome of patients with metastatic pancreatic cancer diagnosed in the Netherlands.

Methods: All patients diagnosed with metastatic pancreatic cancer in the Netherlands between 2007 and 2011 were included. We defined three types of high-volume centers: high volume incidence center based on the number of patients diagnosed with metastatic disease, high-volume treatment center based on number of patients diagnosed with metastatic disease and started on palliative chemotherapy and high volume surgical center based on the number of resections with a curative intent performed in patients with non-metastatic pancreatic cancer.
Independent predictors of administration of palliative chemotherapy were evaluated by means of logistic regression analysis. The multivariable Cox proportional hazard model was used to assess the impact of being diagnosed or treated in a high-volume centers on survival.

Results: 5,385 patients presented with metastatic pancreatic cancer of which 24% received palliative chemotherapy. Being treated with chemotherapy in a high-volume treatment center was associated with improved survival (HR 0.76 95% CI 0.67-0.87). Also, in patients with metastatic

pancreatic cancer, being diagnosed in a high-volume surgical center was associated with improved survival (HR 0.74 95% CI 0.66-0.83).

Conclusion: Being treated with chemotherapy in a high volume treatment center was associated with an improved overall survival compared to being treated in a non-high volume treatment center. This suggests that a volume-outcome relationship, as previously described in resectable pancreatic cancer, might also be present in systemically treated patients with metastatic disease.

Introduction

The incidence of pancreatic cancer is rising in developed countries. In 2012, pancreatic cancer was the fifth leading cause of cancer related-mortality in Europe.[1] By 2030, pancreatic cancer is expected to become the second leading cause of cancer-related death.[2]

The only potential curative treatment for pancreatic cancer is surgical resection. Unfortunately, only 20% of the pancreatic cancer patients present with resectable disease. Patients not fit enough to undergo surgery or those with irresectable or metastatic tumors have a poor prognosis with a median overall survival of approximately three months.[3] In 1997, gemcitabine monotherapy became the first-line palliative treatment for this subgroup of patients. In numerous trials over the years, different drug regimens have been tested. None of these trials demonstrated a statistically significant survival benefit, except for gemcitabine plus erlotinib which was associated with a very modest survival benefit of only 2 weeks.[4] Fortunately, two encouraging trials have been published recently showing a significant survival benefit for patients treated with gemcitabine plus nab-paclitaxel or FOLFIRINOX in comparison with gemcitabine monotherapy.[5-7]

Limited treatment options in pancreatic cancer might have led to reserved prescription and heterogeneity in administration of palliative chemotherapy. A recently published population-based study investigating the use of palliative chemotherapy in patients with metastatic pancreatic cancer showed a large variation in prescription rate between ten community hospitals, varying from

5-34%.[8] Reasons for not offering palliative chemotherapy were age and socio-economic status of the patient.[9,10] However, preference and experience of the treating physician might have played an important role as well.[11]

In pancreatic cancer surgery, a relationship between the number of surgically treated patients in a hospital and postoperative outcome has been established, with a lower postoperative mortality in high-volume treatment centers.[12-15] Interestingly, the number of resections per hospital had a greater impact on the post operative mortality than the surgeons caseload, indicating the importance of a specialized medical infrastructure for this specific group of patients.[16] It might be hypothesized that the outcome of systemically treated patients is positively influenced by the experience of a medical oncologist, defined by the number of treated patients. Moreover, the combined experience of the multidisciplinary team providing pancreatic cancer care may be a relevant factor determining patient outcome as well.

In 245 patients with resectable pancreatic cancer, a superior survival was found for patients treated with adjuvant chemotherapy in a high-volume treatment hospital compared to patients treated in a low-volume hospital.[17] These data were presented at ASCO Gastrointestinal Cancers Symposium 2016 and underline that further elaboration is necessary on differences in patterns of care and their impact on survival.

To our knowledge, no information is available on the relationship between volume and outcome of patients with metastatic pancreatic cancer. Therefore, we conducted a nationwide population-based study in patients with metastatic pancreatic cancer and assessed whether volume influenced the prescription of palliative chemotherapy and impacted the median overall survival.

Methods

Data collection

Data were obtained from the Netherlands Cancer Registry (NCR). This is a population-based database which collects information on all patients newly diagnosed with a malignancy in the Netherlands. The registry area includes about 16.7 million inhabitants and encompasses 91 hospitals, of which 8 academic centers. The NCR is notified by the national automated pathological archive (PALGA), if the newly diagnosed cancer is microscopically verified. In the absence of verification, notification occurs by additional sources, such as

the national registry of hospital discharge, multidisciplinary team reports and diagnosis therapy combinations (specific codes for reimbursement purposes). Within 6-9 months after notification, trained registration clerks operating on behalf of the NCR extract patient and tumor characteristics from medical records. Data are coded according to a national manual and cancer topography and morphology are classified according to the International Classification of Disease for Oncology (ICD-O) second or third edition.

Our inclusion was limited to patients diagnosed with an adenocarcinoma, a not otherwise specified carcinoma (ICD-O morphology codes 8010, 8012, 8020, 8140,8141, 8260, 8310, 8440, 8470, 8480, 8481, 8490, 8500, 8560) or a non-microscopic verified neoplasm of the pancreas between January 2007 and December 2011. Other morphology codes were excluded or did not occur during the study period. Patients diagnosed at autopsy were excluded. Carcinomas were classified according to the Tumor Lymph Node Metastases classification and staged according to the recommendations of the international Union against Cancer (UICC) TNM classification in the respective period. For staging of neoplasms without microscopic verification the clinical Extent of Disease (cEOD) was used.

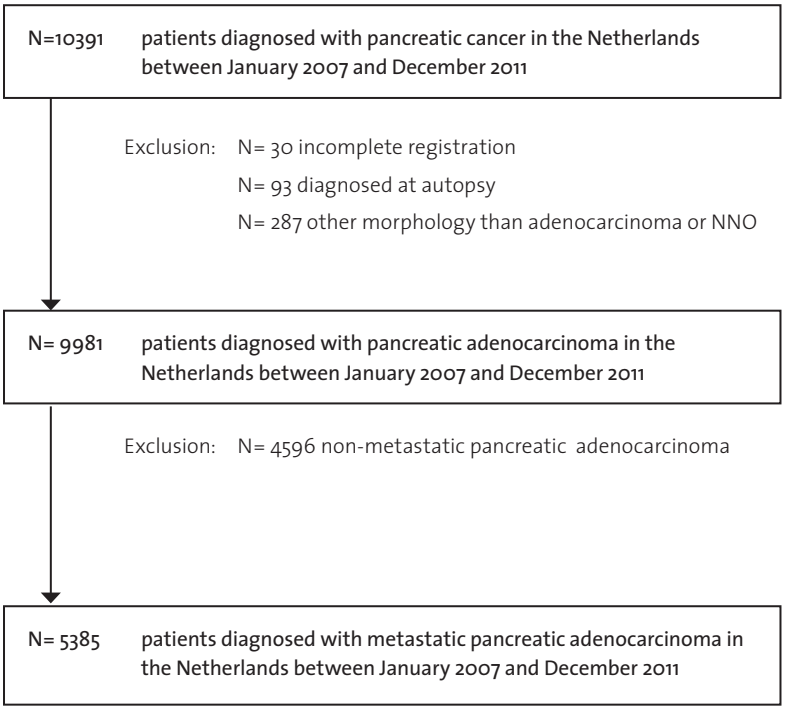
To assess the influence of hospital volume on outcome, we defined high-volume centers based on the upper quartile (Q3/75th percentile). Each volume threshold dichotomized the data and created two categories for comparison: hospitals with volume greater or equal to the cutoff value and hospitals with volume less than the cut-off value. We defined three different types of high-volume centers.

1) High-volume incidence center: a hospital volume that refers to the number of patients diagnosed with metastatic pancreatic cancer. This may be regarded the most straightforward hospital volume. ≥101 patients diagnosed in 5 years (range 14 -183) However, as pancreatic cancer treatment may be an important determinant of outcome of pancreatic cancer patients and a high volume incidence center does not necessarily treat a high volume of patients, we also identified high volume treatment center.
2) High-volume treatment center: a hospital volume that refers to the number of metastatic pancreatic cancer patients treated with chemotherapy. This may be regarded as a proxy for the experience of a hospital to deliver care to this patient population that may develop specific complications in this disease stage. ≥28 patients treated in 5 years (range 1-116);
3) High-volume surgical center: a hospital volume which refers to the number

of surgical procedures in pancreatic cancer, which may be regarded as a proxy for the presence of a well-developed infrastructure to deliver complex care to pancreatic cancer patients; ≥ 68 resections with curative intent treated in 5 years (range 1-123).

Vital status of all patients on 1st of January 2014 was assessed through linkage with civil municipal registries and the Central bureau for genealogy, which collects data on all citizens who die.

Figure 1 Flow diagram of included patients



** NNO not otherwise specified*

Statistical analysis

We performed all statistical analyses using SAS statistical software (version 9.4, SAS institute, Cary, NC, U.S.A.). Two sided p-values of <0.05 were considered statistically significant.

The proportion of patients treated with chemotherapy was described for different subgroups and high-volume centers. Differences between subgroups were tested by means of a χ^2 test and trends over time were analyzed by means of a Cochran-Armitage trend test. Independent influences on prescription of palliative chemotherapy were evaluated by means of a logistic regression analysis. The different types of high-volume centers were added separately to the model. Survival time was defined as the time from diagnosis to death or 1 January 2014, for patients who were still alive. The crude survival was calculated with the life test and differences between survival curves were evaluated by means of a log rank test. The independent prognostic effect of being diagnosed or treated in a high-volume center was estimated using Cox regression analyses;

The hazard ratios for death were adjusted for gender, age, extent of disease and period of diagnosis. The influence of being diagnosed in a high-volume treatment center was investigated in patients treated with chemotherapy only; untreated patients were excluded from this analysis. In the other models chemotherapy was added separately to investigate the effect of treatment on the hazard ratio of death.

Results

Between 1 January 2007 and 31 December 2011 9,981 patients were diagnosed with pancreatic cancer in the Netherlands, of whom 5,385 (54%) patients presented with metastatic disease. The patient selection is shown in figure 1. Fifty-two percent of the patients with metastatic disease were male, the median age at time of diagnosis was 69 years (range 21-100) and in 68% of the cases the diagnosis was microscopically confirmed. The general characteristics of patients treated in high-volume centers are shown in table 1.

We defined high-volume centers, based on three different volume thresholds. In total, 17 hospitals were classified as a high-volume center. Thirteen hospitals were classified as high-volume incidence center, seven hospitals as high-volume treatment center and four hospitals as high-volume surgical center. Only one hospital qualified for all three high-volume definitions. Another four

Table 1 General characteristics of patients diagnosed with a neoplasm of the pancreas in the Netherlands between 2007 and 2011, stratified according to high volume center (N=5,385)

	Total		High-volume incidence center		High-volume treatment center		High-volume surgical center	
	N	(%)	N	(%)	N	(%)	N	(%)
Sex								
Male	2796	(52)	825	(54)	455	(55)	215	(59)
Female	2589	(48)	707	(46)	380	(46)	148	(41)
Age (yrs)								
<50	239	(4)	68	(4)	47	(6)	29	(8)
50-59	817	(15)	228	(15)	140	(17)	83	(23)
60-69	1671	(31)	505	(33)	302	(36)	131	(36)
70-79	1731	(32)	471	(31)	250	(30)	97	(27)
≥80	927	(17)	260	(17)	96	(12)	23	(6)
Histologic subtype								
Adenocarcinoma	3640	(68)	1082	(71)	659	(79)	312	(86)
Non-microscopic verified	1745	(32)	450	(29)	176	(21)	51	(14)
Location of metastase								
Liver	2770	(51)	775	(51)	407	(49)	168	(46)
Peritoneum	425	(8)	110	(7)	54	(7)	36	(10)
Lung	244	(5)	66	(4)	36	(4)	14	(4)
Extra regional lymphnodes	179	(3)	61	(4)	38	(5)	27	(7)
Other	100	(2)	25	(2)	18	(2)	7	(2)
2 organs	1190	(22)	340	(22)	199	(24)	84	(23)
3 or more organs	431	(8)	131	(9)	73	(9)	23	(6)
Chemotherapy								
Yes	1274	(24)	400	(26)	329	(39)	100	(28)
No	4111	(76)	1132	(74)	506	(61)	263	(73)
Total	5385	(100)	1532	(28)	835	(16)	363	(7)

Table 2 Crude percentages and adjusted odds for receiving chemotherapy among patients diagnosed with metastatic pancreatic cancer in the Netherlands between 2007 and 2011 (N=5,385)

	Crude percentage %	Multivariate Odds ratio (95% CI)
Diagnosed in high-volume incidence center *		
Yes	26	1.14 (0.98-1.32)
No	23	1.00 (reference)
Treated in high-volume treatment center *		
Yes	39	2.20 (1.85-2.61)
No	21	1.00 (reference)
Diagnosed in high-volume surgical center *		
Yes	28	0.82 (0.64-1.07)
No	23	1.00 (reference)

** Different types of high volume centers were added separately to the model adjusted for tumor and patient characteristics*

high-volume incidence centers were high-volume treatment centers as well.

Twenty-four percent (N=1,274) of the patients with metastatic pancreatic cancer received palliative chemotherapy. Table 2 shows the crude proportions of patients treated with chemotherapy in the different high-volume centers. The odds of receiving palliative chemotherapy were higher in high-volume treatment centers. Whereas palliative chemotherapy was not administered more frequently in high-volume incidence centers or high-volume surgical centers. Other predictive factors for prescription of chemotherapy were younger age at time of diagnosis, the presence of microscopic verification (OR 3.13 (2.63-3.85), two sites of metastases (OR 0.73 (0.57-0.94) and a more recent year of diagnosis. (OR for 2011, 2007 reference 1.55 (1.24-1.94))

We found that patients diagnosed in the hospital that qualified for all three high-volume definitions had pathological verification more often compared to patients who were diagnosed in a hospital that was only one type of high

Table 3 Crude median overall survival, crude 1-year survival and adjusted hazard ratios for patients diagnosed with metastatic pancreatic cancer between 2007 and 2011 in the Netherlands (N=5,385)

	Crude Median survival (weeks)	Crude 1-year survival (%)	Multivariable HR (95% CI)
Diagnosed in high-volume incidence center *			
Yes	9.9	6.7	0.86 (0.94-1.06)
No	9.4	5.5	1.00 (reference)
Treated in high-volume treatment center * **			
Yes	28.4	21.3	0.76 (0.67-0.87)
No	22.9	11.6	1.00 (reference)
Diagnosed in high-volume surgical center *			
Yes	14.7	11.9	0.74 (0.66-0.83)
No	9.3	5.4	1.00 (reference)

** Different types of high volume centers were added separately to the model adjusted for all the above listed variables.*

*** Only patients treated with palliative chemotherapy were included in the analysis (N = 1,274)*

volume center. However, patients in that specific hospital were not treated with palliative chemotherapy more frequently compared to other high-volume hospitals.

The median overall survival of patients with metastatic pancreatic cancer was 9.6 weeks (1-year survival rate 6%). Table 3 shows the results of a multivariable proportional hazards regression analysis modeling the risk of death for patients with metastatic pancreatic cancer. Factors that were associated with poor survival were older age (≥80 years), absence of microscopic verification and metastases in multiple organs. Beneficial prognostic factors were metastases limited to the lungs or limited to extra-regional lymph nodes, treatment with palliative chemotherapy and treatment in a high-volume surgical center. By excluding treatment with chemotherapy from the model (result not shown) the beneficial effect of younger age was statistically significant.

The median overall survival in patients treated with palliative chemotherapy

was 24 weeks (1-year survival rate 14%). Multivariable hazard regression analysis in patients treated with palliative chemotherapy revealed that being treated in a high-volume treatment center was associated with improved survival (HR 0.76, 95CI 0,67-0,87).

Discussion

To our best knowledge, this is the first study showing a positive association between hospital volume and overall survival in patients with metastatic pancreatic cancer. This population-based study demonstrated that being diagnosed in a high-volume surgical center and being treated with palliative chemotherapy in a high-volume treatment center was associated with an improved overall survival.

The presence of microscopic verification as well as younger age are well-known and established predictors for starting palliative chemotherapy.[10] In this study, we did not find any relationship between the volume of incidence and the prescription of palliative chemotherapy in a multivariate regression analysis. Being diagnosed in a high volume incidence center neither seemed to influence the survival of patients with metastatic pancreatic cancer. Remarkably, being treated with palliative chemotherapy in a high-volume treatment center positively influenced the survival of patients with metastatic pancreatic cancer. This may be explained by the experience of physicians in high-volume treatment centers with the specific patient population and adverse events of prescribed chemotherapeutic agents. As early as 1979, Luft et al. described an inverse relation between surgical volume and mortality in patients with resectable pancreatic cancer.[18] High-volume surgical centers reported significantly better survival rates.[14,19,20]

In metastatic disease, the medical oncologist has to weigh patients' prognosis, treatment toxicity and the possible positive impact on quality or quantity of life. Together with the patient, the physician has to decide to start palliative chemotherapy or to provide supportive care only. Given the often poor clinical condition of pancreatic cancer patients which may deteriorate rapidly, this decision making process is complex. Moreover, when starting palliative chemotherapy, toxicity has to be managed adequately. This includes appropriate reductions in chemotherapy dosage, and deciding when to stop or to continue therapy. Therefore, experience with the treatment of this specific patient population,

gained by treating a relatively high number of patients, may be of paramount importance for the outcome of these patients. Furthermore, we hypothesize that not only the expertise of an individual medical oncologist, but also the complete infrastructure of the hospital may relate to patient outcome.[21] The specific tumor and treatment-related complications such as pain management, nutritional care and biliary drainage, request comprehensive care. For example, cholangitis due to compression of the bile ducts and duodenal obstruction by a primary tumor in the head of the pancreas is common in patients with metastatic pancreatic cancer. Decompression has shown to improve the quality of life of these patients and may improve survival.[22,23] A yearly volume of ≥50 endoscopic retrograde cholangiopancreatographies per endoscopist was associated with a lower risk of procedural failure.[24] Our finding that patients being diagnosed with metastatic pancreatic cancer in a high-volume surgical center exhibited an improved survival, suggests that an experienced multidisciplinary team and an adequate infrastructure of a hospital may contribute to improved survival as well.

The prognosis of patients with pancreatic cancer remains poor with a median overall survival of 9.6 weeks. It is difficult to compare our results with the outcome of randomized controlled trials, which show higher survival rates due to inclusion of relatively young patients with a good performance status. However, we found that the median overall survival was comparable to the median overall survival found in other population-based studies.[25-27] In contrast to other population-based studies we also included patients with pathologically unverified neoplasms of the pancreas. We found that a significant proportion of pancreatic cancer patients did not have their diagnosis confirmed by pathological examination. Possibly, because these patients were considered unfit for palliative chemotherapy and pathological confirmation would not have had therapeutic consequences. The overall survival of these patients was only 7 weeks and, so the likelihood that these patients suffered from pancreatic cancer as well is high.

In our series, 24% of the patients with metastatic pancreatic cancer was treated with palliative chemotherapy. The reported percentage in previous population-based studies including patients with metastatic pancreatic cancer was highly variable. Moreover, the presented specific subsets of patients treated with palliative chemotherapy were inconsistent. David et al. found that 30% of the patients with advanced pancreatic cancer received palliative

chemotherapy after palliative surgery, in patients who did not undergo resection the percentage was only 17%.[28] Sharp et al. found a similar percentage in patients with locally advanced and metastatic pancreatic cancer.[29] In an Australian cohort study including patients with locally advanced and metastatic pancreatic cancer, 43% of the patients received palliative chemotherapy, however this was a smaller study with 1863 patients and selection bias may have occurred.[30] A second Australian study by Jefford et al. reported 54% chemotherapy prescriptions, but analyzed both resectable and irresectable tumors.[31] A recent study by Oberstein et al. seems to report a considerably higher percentage of patients treated with palliative chemotherapy (54%). However, patients who died within 30 days (22%) were excluded from the analysis.[32] Median survival in patients treated with palliative chemotherapy was 24 weeks. This corresponds well with previously published data from the south of the Netherlands.[8] Similar to previous studies, we found that younger age and limited metastases were related to better survival.[25,33]

It should be noted that this analysis was conducted in the era before FOLFIRINOX and nab-paclitaxel with gemcitabine. With the introduction of these new regimens, experience of the medical oncologist might become even more important. The combination therapies have different efficacies, different side effects, and different routes of administration.[6,7,34] As there are no direct data comparing FOLFIRINOX with the combination nab-paclitaxel and gemcitabine, experience with all known palliative treatment options is of utmost importance to select the appropriate treatment for each individual patient. Because of the higher toxicity of these therapies, less patients will be considered fit enough and as a consequence the experience per center with a specific regimen might decrease. Thus, concentration of medical oncological care for patients with metastatic pancreatic cancer may become even more important.

It should be acknowledged that even with very careful analysis of population-based data it cannot be excluded that part of our results are explained by selection bias. Patients treated in high-volume surgical centers may be a selection of fit patients with limited metastatic tumor load. Part of these patients may initially have been considered resectable while explorative laparotomy revealed irresectable disease, for instance due to small peritoneal metastases. Furthermore, it may be argued that younger, fitter patients select high-volume hospitals. To minimize the confounding effect of palliative chemotherapy itself, only patients were analyzed that were treated with palliative chemotherapy.

Yet, other confounders related with usage of palliative chemotherapy cannot be ruled out. However, after adjustment for patient and tumor characteristics, we showed that survival was better in high-volume treatment centers. Unfortunately, we did not have information on performance status available in our dataset.[35] This lack of information on performance status is a significant limitation to our study. Furthermore, the hospital volumes that we defined in our study need validation and from these data no definite conclusions can be drawn on whether a specific type of high-volume center should be the norm for best clinical practice.

Conclusion

In conclusion, in this nationwide database, hospital volume of palliative chemotherapy was associated with improved survival demonstrating that a volume-outcome relationship, as described for pancreatic surgery, may also exist for pancreatic medical oncology.

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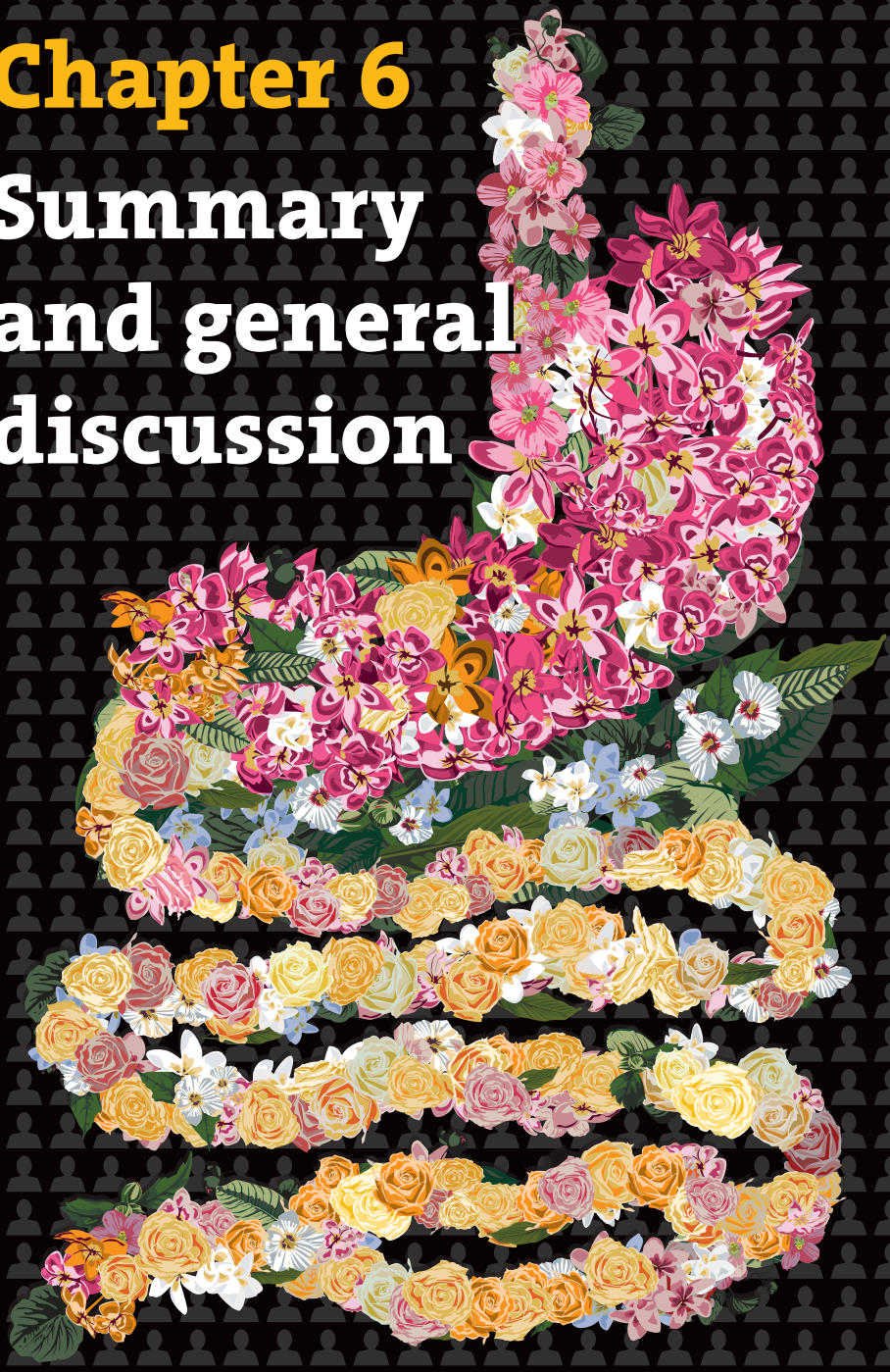
Chapter 6
Summary and general discussion



Summary and General Discussion

This thesis revealed trends in absolute incidence, treatment and overall survival of patients diagnosed with metastatic upper gastrointestinal cancers in the Netherlands.

Summary

Among patients with esophageal cancer the proportional incidence of metastatic disease increased from 22% in 1994-1998 to 32% in 2009-2013. In chapter 2.1, we investigated the use of external beam radiotherapy, chemoradiotherapy, brachytherapy and chemotherapy in these metastatic esophageal cancer patients in the South of the Netherlands, diagnosed between 1 January 1994 and 31 December 2013 (N=1,020). Major changes in treatment strategies took place. We demonstrated that patients were increasingly treated with one or more of the above mentioned modalities. Seventy percent of the patients diagnosed between 2009 and 2013 received treatment, compared to 56% between 1994 and 1998. The prescription rates of chemoradiotherapy and chemotherapy increased drastically, whereas the use of external beam radiotherapy and brachytherapy decreased. These altered treatment strategies, together with a more appropriate patient selection and stage migration, ultimately led to an improvement of overall survival from 18 weeks in 1994-1998 to 25 weeks in 2009-2013.

In gastric cancer, the proportional incidence of metastatic disease increased as well, presumably as a result of stage migration (chapter 3.1). Again we noticed a marked increase in the prescription rate of palliative chemotherapy, from 5% in 1990 to 36% in 2011. After adjustment for patient and tumor characteristics, a large inter-hospital variation was observed in the prescription rates of palliative chemotherapy. Unfortunately, the substantial increase in the prescription rate of palliative chemotherapy did not impact the median overall survival of patients with metastatic gastric cancer, which remained poor between 15 and 17 weeks.

The most common metastatic site in gastric cancer was the peritoneal cavity, in chapter 3.2 we focused on this subgroup of patients with

peritoneal carcinomatosis. Although the efficacy of palliative chemotherapy in this subgroup has not been proven in terms of overall survival benefit, prescription rates increased drastically. Once more, no improvement in median overall survival was observed.

In chapter 4, we showed the results of one of the largest population-based studies in adenocarcinomas of the small bowel conducted so far. The study confirmed previously published data on the rising incidence, which is mainly caused by a twofold increase in the incidence of duodenal adenocarcinomas. During the study period, the proportional incidence of metastatic disease increased from 27% in 1999-2003 to 38% in 2009-2013. The most common metastatic sites were the liver (46%) and the peritoneal cavity (29%). The location of the primary tumor was associated with the metastatic site. A part of our study focused on patients with locoregional disease. One of the most notable findings was the use of chemotherapy in 15% of these patients. A significant increase in median overall survival was found in the subset of patients treated with adjuvant chemotherapy. The prescription rate of palliative chemotherapy increased from 19% to 37% in patients with metastatic small bowel adenocarcinomas. Although patients treated with palliative chemotherapy exhibited an improved median overall survival compared to patients receiving supportive care only, the increased prescription rate did not influence the median overall survival of the total population with metastatic disease, which remained between 4-5 months.

This thesis had a special focus on pancreatic malignancies, one of the leading causes of cancer-related deaths worldwide. The disease is often detected in an advanced stage: in chapter 5.1 we investigated trends in treatment and overall survival in patients with metastatic pancreatic cancer. Although gemcitabine monotherapy has been the reference regimen since 1995, the prescription rate of palliative chemotherapy increased almost threefold from 10% in 1993-1996 to 27% in 2009-2010. As in metastatic gastric cancer, large inter-hospital variations were observed in the prescription of palliative chemotherapy. Unfortunately, increased use of palliative chemotherapy did not impact the median overall survival of patients with metastatic pancreatic cancer which remained 10 weeks, with a 1-year survival rate of only 6%. In this study we also noticed that a significant proportion of the patients diagnosed with a malignancy of the pancreas did not have a pathologically verified tumor.

Therefore, in chapter 5.2 we investigated the relevance of pathological

verification in suspected pancreatic cancer. Although obtaining tissue to establish the diagnosis can be notoriously difficult in patients with suspected pancreatic cancer, the current guidelines strongly recommend pathological verification, especially in patients with locally advanced or metastatic disease prior to treatment. Our data showed that the prognosis of patients without pathological verification was comparable to the prognosis of patients with pathologically verified malignancies of the pancreas. This suggests that they suffered from true pancreatic cancer. Therefore, in our opinion verification still remains desirable in patients with suspected locally advanced or metastatic pancreatic cancer. However, if a biopsy cannot be obtained, a high clinical suspicion should justify treatment even in the absence of pathological verification.

The very poor prognosis associated with locoregional and metastatic pancreatic cancer led to the research question "does long-term survival exist in pancreatic cancer?" (Chapter 5.3). In a population-based study including 2,564 patients with adenocarcinomas or microscopic unverified cancers of the pancreas, we found that only 40 patients (1.6%) survived for more than five-years. Twenty-one long-term survivors had received a curative resection of the primary tumor, with a five year survival rate of 10%. Additional data collection in these 21 long-term survivors revealed that locoregional or distant recurrence had occurred in 10 patients, so the disease-free survival after curative resection after five years was only 5%. Of the remaining 19 long-term survivors, 16 had a non-microscopically verified neoplasm at time of diagnosis. The diagnosis was revised to a more benign one in 15 patients, the majority of these patients were later diagnosed with a focal or auto-immune pancreatitis.

In an attempt to improve the poor prognosis of patients with resectable pancreatic cancer, surgical care has been centralized. Morbidity and mortality were significantly lower in these high volume surgery centers. In chapter 5.4 we investigated whether there was a volume-outcome relationship in metastatic pancreatic cancer as well. We defined three types of high-volume centers, high-volume incidence center, a volume which refers to the number of patients diagnosed with metastatic pancreatic cancer. High-volume treatment center refers to the number of metastatic pancreatic cancer patients receiving palliative chemotherapy and a high-volume surgical center refers to the number of curative surgical procedures in a hospital. In total, 17 hospitals of the 91 were classified as high-volume centers. Of the 9,981 included patients 24% received palliative chemotherapy. The results of a multivariable regression analysis

showed that chemotherapy was not administered more frequently in high volume incidence centers. The median overall survival found in this nationwide study was comparable to the survival found in chapter 5.2. Palliative chemotherapy was associated with a better overall survival in comparison to patients receiving supportive care only. Surprisingly, being treated in a high-volume treatment center was associated with an improved overall survival compared to being treated in a non high-volume treatment center, respectively 28 weeks and 23 weeks. Being diagnosed in a high-volume surgical center positively impacted overall survival as well, which might suggest that the infrastructure in these hospitals is better suited to treat this complex disease.

General discussion

This thesis reported trends in incidence, treatment and survival of patients diagnosed with metastatic malignancies of the esophagus, stomach, small bowel and pancreas. In this chapter the results observed in this thesis will be discussed in a broader context.

Trends in incidence of metastatic upper gastrointestinal cancer

The absolute number of new patients with esophageal adenocarcinoma, small bowel adenocarcinoma and pancreatic cancer increased. In contrast, there has been a decrease in the absolute number of patients presenting with gastric cancer.[1]

Throughout the studies in this thesis an increase in the proportional incidence of metastatic disease was observed. The most notable increase, from 35% in 1993-1996 to 59% in 2009-2010 was seen in patients diagnosed with pancreatic cancer. The increases seem to reflect stage migration. Evolution of diagnostic imaging techniques, such as the improvement of computed tomography scans, introduction of FDG positron emission tomography and endoscopic ultrasonography, have led to detection of small metastases that previously remained unidentified.[2]

Besides the improved diagnostic accuracy, altered tumor biology might have played a role as well, especially in esophageal and gastric cancer. In esophageal cancer the histologic distribution changed drastically. During the last two decades adenocarcinomas became the predominant histologic subtype in

most developed countries.[3,4] Patients diagnosed with adenocarcinomas of the esophagus more frequently had metastases at time of diagnosis in comparison to patients with squamous cell cancers of the esophagus, respectively 34% and 24%. Therefore the altered histologic distribution in esophageal cancer might have attributed to the increase in proportional incidence of metastatic disease. In gastric cancer an altered histologic distribution might have played a role as well. Gastric cancer can be classified according to the Lauren classification, which distinguishes intestinal type gastric cancer and diffuse type gastric cancer. In intestinal gastric cancer the glandular appearance of the stomach remains preserved, whereas in diffuse type gastric cancer the glandular architecture is lost completely and tumor cells diffusely infiltrate the stomach.[5,6] Multiple population-based studies showed that the incidence of intestinal type gastric cancer decreased more sharply compared to the more aggressive diffuse type.[7,8] This change in histologic distribution could be an explanation for the increase in proportional incidence of metastatic gastric cancer. In small bowel adenocarcinomas and pancreatic cancer there is no evidence for an altered, more aggressive tumor biology.

Trends in systemic treatment of metastatic upper gastrointestinal cancer

In patients diagnosed with metastatic esophageal cancer, gastric cancer, small bowel cancer and pancreatic cancer prescription rates of palliative chemotherapy increased significantly.

In metastatic gastroesophageal cancer, chemotherapy has proven to be superior to 'best supportive care'.[9,10] Several agents have shown to be active in gastroesophageal cancer, for instance fluoropyrimidines, platinum-derivates, taxanes, anthracyclines and irinotecan. A meta-analysis by Wagner et al. showed that combination regimens were more effective than single-agents, survival increased from 6.7 months to 8.3 months.[10]

Initial regimens were based on infusional fluorouracil and an anthracycline (e.g. epirubicin), later cisplatin was added. For years, this combination was the first line treatment in patients with a good clinical condition. One of the major disadvantages of this regimen was the need for a central venous access and an ambulatory infusion pump to administer the fluorouracil. Furthermore, the highly nephrotoxic cisplatin needed a long intravenous hydration scheme and required an overnight hospital admission.

The REAL2 trial evaluated whether infusional fluorouracil and cisplatin, could be replaced by capecitabine and oxaliplatin, respectively. They randomly assigned 1002 patients with untreated locally advanced or metastatic gastro-esophageal cancer to four different triplet therapies: epirubicin and cisplatin plus fluorouracil (ECF) or capecitabin (ECX) or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX). Results showed that capecitabine and oxaliplatin were at least as effective as fluorouracil and cisplatin. The fluoropyrimidine-related adverse events were similar in the capecitabine groups and the fluorouracil groups and oxaliplatin showed a more favourable toxicity profile in comparison to cisplatin, with lower incidence of grade 3 and 4 neutropenia and renal toxicity.[11] More important, capecitabine and oxaliplatin were more patient convenient, a central venous access and a long intravenous hydration scheme were no longer needed. The introduction of these agents might have led to increased prescription of palliative chemotherapy in patients with metastatic gastroesophageal cancer.

Due to the rarity of small bowel adenocarcinoma, no randomized controlled trials have addressed the role of palliative chemotherapy. Some small retrospective studies showed that chemotherapy improved survival compared to best supportive care. Most of the studied regimens were based on fluorouracil combined with a platinum-based derivative. The largest study, including 80 patients with metastatic small bowel adenocarcinoma, found that platinum-based regimens were superior to non-platinum based regimens in terms of response rates and overall survival.[12] This might suggest that platinum-based regimens should be the standard of care in metastatic small bowel adenocarcinoma, however larger prospective studies are needed. Although these studies are currently lacking, the prescription rate of palliative chemotherapy in patients with metastatic small bowel adenocarcinomas increased from 19% in 1999-2003 to 37% in 2009-2013.

In metastatic pancreatic cancer, gemcitabine monotherapy has been the reference regimen for two decades. Guidelines were based on a publication of Burris et al. in 1995. The study, including 126 patients with advanced pancreatic cancer, compared the effectiveness of gemcitabine and fluorouracil in advanced pancreatic cancer. Patients were randomly assigned to treatment with gemcitabine 1,000 mg/m2 weekly during 7 weeks followed by 1 week of rest, after which gemcitabine was administered weekly during three weeks followed by 1 week of rest, or to fluorouracil 600 mg/m2 once weekly. The primary outcome

was clinical benefit, which was measured in terms of pain, performance score and weight. In 24% of the patients treated with gemcitabine there was an improvement of clinical condition compared to 4.8% of the patients treated with fluorouracil. The median overall survival improved from 4.4 months to 5.7 months (p = 0.0022).[13] Until 2011, gemcitabine monotherapy remained the reference regimen, since all studies conducted in advanced pancreatic cancer yielded disappointing results. The majority of these studies compared gemcitabine with a gemcitabine based combination. None of them, demonstrated a statistically significant survival benefit, except for gemcitabine plus erlotinib, which improved the median overall survival with two weeks.[14] Although no progress has been made for the treatment of pancreatic cancer during the studied periods, the prescription rate of palliative chemotherapy almost tripled from 10% in 1993-1996 to 27% 2009-2010.

The marked increases in the prescription rates of palliative chemotherapy are probably not only the result of the ongoing introduction of new cytotoxic agents. The fact that phycisians became more familiar with the use of certain agents might be a contributory factor as well. More experience with for instance epirubicin, cisplatin and fluorouracil (ECF) in the treatment of gastroesophageal cancer was gained after publication of the MAGIC trial in 2006. This trial showed that perioperative ECF in patients with resectable gastroesophageal cancer reduced tumor size, tumor stage and improved the overall survival. [15] The trial drastically changed the treatment of resectable gastric cancer, but might also have influenced the prescription rates in metastatic gastroesophageal cancer. Increases in prescription rates of palliative chemotherapy in metastatic pancreatic cancer were observed after introduction of gemcitabine in the adjuvant setting. In 2007, Oettle et al. presented the first results of the CONKO-001 trial which showed that gemcitabine was well tolerated and significantly delayed the development of recurrent disease.[16] Final results of this study presented one year later at the 44th ASCO annual meeting, showed that adjuvant treatment with gemcitabine also improved median overall survival. [17,18]

Furthermore reduced skepticism towards systemic therapies could have played a role as well. Great improvements in the palliative systemic treatment of for instance metastatic colorectal cancer might have reduced the skepticism and increased expectations among physicians and patients towards systemic therapies for other indications. Multiple studies have shown that patients nowadays would choose chemotherapy, even for small gains. They value the

small benefits greatly and believe that toxicity is of minor importance.[19]

Another contributing factor might be the improved management of treatment-related toxicity. More effective agents became available to prevent chemotherapy-induced nausea, such as selective 5-HT3 antagonists, neurokinin-1 antagonists and corticosteroids. The majority of patients experience complete protection with these agents.[20] The incidence of treatment-related neutropenic fever has also been reduced after the introduction of granulocyte colony-stimulating factors (GCSF). Administration of granulocyte colony-stimulating factors is recommended when the anticipated incidence of neutropenic fever is 20% or after neutropenic fever has occurred in one of the prior cycles.[21]

Some end of life studies suggest that we continue palliative systemic treatment too long. An increasing number of new regimens are initiated in the last weeks of life, despite the fact that it seems to negatively impact the quality of life.[22-24] In light of this, there are serious concerns about the financial consequences of these (palliative) systemic treatments, with rapidly escalating health care costs. The cancer-drug industry has become major, hundreds of biotech companies try to develop new drugs based on molecular targets.[25] The newly introduced agents are often costly, with prices exceeding 4,000 euro a month.[26] Between 2003 and 2011 the annual direct costs for cancer care in the Netherlands doubled from 2.4 billion euro to 4.8 billion euro.[27] This trend is no longer sustainable. We must find ways to reduce the costs. Smith et al. suggest to limit second-line and third-line treatments to sequential monotherapies. This might reduce the prescription of palliative chemotherapy and toxicity related hospitalizations.[26]

Hospital variation in the prescription of palliative chemotherapy

Among patients with metastatic gastric and pancreatic cancer this thesis showed inter-hospital variation in the prescription of palliative chemotherapy. Large differences in prescription rates between community hospitals existed, varying from 9% to 27% in patients with metastatic gastric cancer and from 5% to 34% in patients with metastatic pancreatic cancer. These differences persisted after adjustment for case-mix in multivariable logistic regression analysis.

A partial explanation for the large inter-hospital variation in patients with metastatic malignancies, might be the vague and unclear national guidelines which state that “palliative chemotherapy should be considered in patients

with a good clinical condition". The definition of "good clinical condition" is a sum of many subjective variables. In an attempt for a more objective definition, two rating scales have been developed around the 1950s: the Eastern Cooperative Oncology Group Performance status (ECOG) and the Karnofsky Performance status scales (KPS). Both scales are based on a patients ability to perform daily activities and have shown to correlate with survival and treatment-related toxicity. However, these simple and useful scales are subject to bias.[28] Different studies have shown that inter-observer agreement rates using this scales were very low.[28,29] Since the 1950s, no new tools have been adapted in clinical practice. A great need remains for a more objective tool to select patients eligible for treatment more accurately. Introduction of such a tool might reduce inter-hospital variation in the prescription of palliative chemotherapy.

Furthermore, we hypothesize that there are other patient, physician or institutional related factors that influenced prescription of palliative chemotherapy. Due to the population-based nature of our data, we were unable to capture these factors. Patient-related factors that might have influenced the prescription rates besides performance status were nutritional status and disease-related symptoms. However, one could assume that these patient factors were roughly comparable between the community hospitals included in our studies. Probably physician-related factors and institutional related factors might have played a role too. A population-based study in elderly women diagnosed with breast cancer, showed that the administration of chemotherapy was influenced by practice settings. Chemotherapy was prescribed more frequently in private practices compared to non-private practices. In addition, physician-related factors such as graduation year and sex of the physician influenced the odds of receiving chemotherapy. Physicians graduated after 1975 prescribed chemotherapy more frequently compared to physicians graduated before 1975 and male physicians were more likely to prescribe chemotherapy compared to female physicians.[30] Besides these factors, we hypothesize that experience, clinical traditions, presence of a dedicated multidisciplinary team, involvement of medical specialists in scientific research and teaching status of a hospital also play a role.[31]

Survival of patients with metastatic upper gastrointestinal cancer

The increased prescription rates of palliative chemotherapy in upper gastrointestinal cancers only impacted median overall survival of patients with metastatic esophageal cancer, which increased from 18 to 25 weeks.[4] To assess if this was a true effect of treatment, we first developed a multivariable hazard regression model without a treatment variable and later added the variable separately. After adjusting for treatment, the hazard ratio of dying according to period of diagnosis attenuated, which suggests that altered treatment strategies contributed to the reduced mortality over time.[32] Other population-based studies hypothesized that stage migration played a role as well.[2] Although the effect of stage migration might be expected in patients with metastatic gastric cancer, small bowel cancer, and pancreatic cancer, the median overall survival in these patients remained stable last two decades.[33-35]

Although the increased prescription rates of palliative chemotherapy did not impact overall survival of the entire group of patients presenting with metastatic upper gastrointestinal malignancies, this does not imply that these patients should not be treated with palliative chemotherapy. Individual patients might benefit from systemic treatment. In all studies, patients treated with chemotherapy had a significantly better overall survival compared to patients treated with supportive care only.[4,33-35] Partially, the better overall survival observed in treated patients is very likely to be explained by the observational character of our studies. The observational character might have led to selection bias: fitter patients, those with a better overall survival beforehand, had higher odds receiving chemotherapy. Unfortunately, it has been impossible to adjust fully for selection bias, since important confounders such as the previously mentioned performance status, nutritional status and disease-related symptoms were lacking in our database at the time of studies. Furthermore, it is very likely that the gains achieved with systemic treatments in the treated patients are too little to impact the overall survival of the entire population with metastatic upper gastrointestinal cancer. Hopefully, future regimens that will be discussed later, will be able to achieve this.

Volume-outcome and centralization

Volume-outcome effects have been widely studied for surgical procedures. In this thesis, we were the first to describe a non-surgical volume-outcome effect.

We found that patients with metastatic pancreatic cancer treated in a high-volume center, based on the number of patients receiving palliative chemotherapy, had a better overall survival compared to patients treated in a non high-volume center.[36] This could be explained by a better ability of physicians in high-volume treatment centers to manage treatment related toxicity.

Although this was the first study to show a volume-outcome relation, some systemic treatments are already centralized in the Netherlands. One example is the systemic treatment with ipilimumab, a monoclonal antibody that induces an antitumor response in metastatic melanomas. Ipilimumab can cause some serious side effects, for which early recognition is of utmost importance. Therefore treatment with this targeted agent is performed in specialized centers only.[37]

Second, patients with metastatic testicular cancer seem to benefit from centralization. Verhoeven et al. showed that centralization in patients with metastatic testicular cancer positively impacted the overall survival. After centralization the overall survival increased from 73% to 88% in patients with metastatic seminomas and from 79% to 85% in patients with metastatic non-seminomas.[38]

It is unclear whether systemic treatments of other metastatic malignancies such as pancreatic cancer should be centralized. Advantages of centralization are more experience with the prescribed chemotherapeutic and targeted therapies in high volume centers. This might lead to earlier recognition of treatment-related toxicity. Furthermore, centralization will boost the participation of patients in clinical research, which is of utmost importance for the treatment of metastatic upper gastrointestinal cancer. Disadvantages of centralization might be, that referral to expertise centers, increases the travelling time for patients with a limited life expectancy. In addition, specialized centers might not necessarily be better equipped for the treatment of elderly patients with comorbidity than community hospitals.

If we decide to centralize care for patients with metastatic malignancies, an unresolved question is where to set the bar. In future studies different volume thresholds should be investigated, to establish acceptable minimum volume standards.

Future perspectives

Last decades, new insights in the molecular basis of malignancies led to the introduction of targeted therapies. These therapies are directed against specific target molecules in or on cancer cells. Despite promising results in preclinical trials, the majority of investigated targeted agents in upper gastrointestinal cancers failed in clinical trials.

Currently, there are two targeted therapies approved for the treatment of advanced gastroesophageal cancer: trastuzumab, a monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2), and ramucirumab, a vascular endothelial growth factor receptor-2 (VEGF-2) inhibitor. Trastuzumab was approved after the publication of the ToGA trial in 2010, which demonstrated that trastuzumab in combination with chemotherapy improved the median overall survival of patients with advanced HER-2 positive gastroesophageal cancers.[39] Approximately 10-15% of esophagogastric adenocarcinomas overexpress HER-2.[39] Novel approaches to target HER2 positive disease are studied, such as pertuzumab, a monoclonal antibody directed against the extracellulair domain of HER2.[40]

Ramucirumab was approved in 2014 after publication of the REGARD trial. In this trial, ramucirumab exhibited a small but significant survival benefit, as single agent in patients with advanced gastroesophageal cancer progressing after first-line chemotherapy.[41] The RAINBOW trial showed a survival benefit as well, comparing weekly paclitaxel plus ramucirumab with weekly paclitaxel plus placebo.[42] Based on these studies, the recently introduced Dutch guideline states that second-line treatment with paclitaxel and ramucirumab should be considered in patients with advanced gastroesophageal cancer. Another promising targeted agent directed against the vascular endothelial growth factor receptor might be the tyrosine kinase inhibitor (TKI) apatinib. In a large Chinese phase III trial where apatinib was administered in third line, the median overall survival of patients with advanced or metastatic gastroesophageal cancer improved with 1.8 months. However, there is no clinical experience with this agent outside of China, and it is not clear whether these results are applicable to a global population.[43]

Immunotherapeutic approaches like antibodies directed against programmed cell death 1 (PD-1) have demonstrated efficacy in a variety of solid tumors. This programmed death 1 protein is a key immune checkpoint receptor

expressed by activated T cells. Binding of PD-1 to its ligand, leads to immunosuppression and prevents rejection by the immune system. In a phase IB trial in advanced gastric cancer, antibodies directed against PD1 showed promising results, with a manageable toxicity profile and promising antitumor activity, warranting further research in phase II and phase III trials.[44]

For the treatment of metastatic pancreatic cancer, major improvement came with the introduction of triplet chemotherapy including fluorouracil, oxaliplatin and irinotecan (FOLFIRINOX). This combination has proven to be superior to gemcitabine monotherapy. However, significantly more adverse events were observed in the FOLFIRINOX group, therefore this combination should be preserved for the selected group of patients with a good performance status (ECOG 0-1).[14] In patients with a lower performance status (ECOG 2), treatment with the nab-paclitaxel plus gemcitabine could be considered especially if they have a heavy tumor load. [45] Recently, the results of the NAPOLI-1 trial were published which investigated the efficacy of adding nanoliposomal irinotecan to fluorouracil plus folinic acid in gemcitabine pretreated patients with adenocarcinoma of the pancreas. The authors concluded that nanoliposomal irinotecan represents a new treatment option for patients with pancreatic cancer, it improved survival and had a manageable toxicity profile.[46]

Despite numerous attempts, most targeted therapies have failed to demonstrate a significant improvement in overall survival. The only exception was gemcitabine plus erlotinib, which has demonstrated a statistically significant but clinically modest benefit.[47,48] A problem in treating pancreatic cancer is its genetic diversity. Until now, the targetable mutations have been targeted in an unselected patient population.[49] Possibly results of targeted agents will improve if patient selection is refined based on the molecular phenotype of the tumor.

Pancreatic cancer is characterized by a dense desmoplastic stroma, surrounding the tumor cells. It has been hypothesized that this microenvironment represents a barrier that prevents effective penetration of chemotherapeutic and targeted agents to reach cancer cells. Currently, therapeutic agents targeting this tumor-associated stroma are subject of great interest. [50] Moreover, researchers found that the immune system also plays an important role in shaping the tumor microenvironment. Most cancers exploit multiple mechanisms in order to escape immune cell recognition and antitumor effector functions. In pancreatic cancer chemokine pathways are found

to recruit myeloid cells to the tumor microenvironment, which modulate it in such a way that it promotes tumor growth. Different types of immunotherapy are currently tested in patients with advanced pancreatic cancers.[50,51]
Hopefully the advances in the systemic treatments of upper gastrointestinal cancer will be able to impact the overall survival of these subgroups of patients in the future. However, it should be noted that most treatments will be for highly selected patients, which will be the minority of the population. Furthermore, the impact of the introduced agents on median overall survival of the individual patients might be too little to impact the overall survival of the entire population.[34] However, population-based studies presenting real-word data remain of importance to monitor the effect of the introduction of new treatment regimens on the outcome of cancer.

Strengths and limitations of register-based studies

The studies included in this thesis were based on data from the Netherlands Cancer Registry (NCR). Trained datamanagers operating on behalf of this registry routinely collected patient, tumor and treatment characteristics from medical records 6-9 months after initial diagnosis.
Register-based observational studies as included in this thesis have several strengths. First of all they often have large sample sizes and great statistical power.[52] This makes it possible to study rare diseases such as small bowel adenocarcinomas. Second, the registry covers virtually all cases. If a tumor is pathologically verified, the Dutch cancer registry is notified by the national automated pathological archive PALGA. If this pathological verification is lacking, notification occurs by additional sources as the national registry of hospital discharge (LMR), multidisciplinary team reports and diagnosis-therapy combinations (specific codes used for reimbursement purposes). The completeness of the Dutch cancer registry is estimated to be at least 95%. Other forms of research such as surveys and/or clinical studies might be influenced by suboptimal participation rates.
However, register-based observational studies also have limitations. The data are collected independent of the research question, as a result important information might be lacking.[52] In the dataset used, for instance, additional information on performance status, nutritional status, disease related symptoms, number and size of the metastases, used chemotherapeutic agents and treatment-related toxicity was lacking. Therefore differences in baseline

characteristics between patients treated with chemotherapy and patients receiving supportive care only cannot be ruled out. This might have led to selection-bias, patients in a good clinical condition with limited disease related symptoms, those with a better overall survival beforehand, presumably had higher odds receiving chemotherapy.

Concluding remarks

The studies included in this thesis investigated trends in treatment and overall survival of patients diagnosed with metastatic upper gastrointestinal malignancies. Over time, increasing proportions of patients were treated with palliative chemotherapy. Only in patients with metastatic esophageal cancer the increased prescription rate led to an increase in median overall survival. The median overall survival of patients with metastatic gastric cancer, small bowel adenocarcinomas and pancreatic cancer remained unchanged. However, this does not alter the fact that individual patients might benefit from palliative treatment. Adequate patient selection is of utmost importance. The large inter-hospital variation in prescription rates suggests that there is still room for improvement.

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Chapter 7
Appendix

Nederlandse samenvatting

Door vergrijzing van de bevolking neemt het aantal nieuwe kankerpatiënten in Nederland toe. Een aanzienlijk deel hiervan heeft een tumor gelokaliseerd in het maag-darmkanaal. Darmkanker is momenteel de meest voorkomende soort kanker in Nederland. Ook maagkanker is een groot probleem, wereldwijd is het de vierde meest voorkomende vorm van kanker en het is de tweede belangrijkste oorzaak van sterfte door kanker. In Nederland is de incidentie van maagkanker de afgelopen twee decennia gelukkig gedaald. Deze afname is vooral toe te schrijven aan de verkleinde kans op besmetting met de Helicobacter pylori-bacterie, een bacterie die in het zure milieu van de maag kan overleven en in verband wordt gebracht met het ontstaan van een maagslijmvliesontsteking en maagkanker. Slokdarmkanker is de achtste meest voorkomende kanker wereldwijd. In tegenstelling tot de incidentie van maagkanker is de incidentie van slokdarmkanker de laatste jaren toegenomen. Dit lijkt met name toe te schrijven aan de toename van het adenocarcinoom, een vorm van slokdarmkanker die ontstaat als een gevolg van overgewicht en reflux, oftewel het terugvloeien van maagzuur in de slokdarm. Kanker van de alvleesklier is de tiende meest voorkomende vorm van kanker in Nederland. Ondanks dat het niet een van de meest voorkomende kankersoorten is, is het wel de vierde meest voorkomende oorzaak van kankergerelateerde sterfte in de Westerse wereld. De meerderheid van de patiënten met een alvleeskliertumor heeft dan ook al uitzaaiingen op het moment van diagnose, maar liefst 55%. Deze percentages zijn lager voor patiënten met darm- (23%), slokdarm- en maagkanker (37%).

Patiënten met uitgezaaide vormen van kanker zijn veelal niet meer te genezen, om het leven te verlengen kunnen patiënten palliatief behandeld worden. Veelal bestaat deze behandeling uit chemotherapie al dan niet in combinatie met doelgerichte therapie. De medicatie gebruikt bij chemotherapie noemt men ook wel cytostatica, dit zijn medicamenten die cellen doden of de celdeling remmen. Sinds de introductie van de eerste cytostatica kort na de Tweede Wereldoorlog is er veel veranderd. Er zijn tal van nieuwe middelen bijgekomen.

Bovendien zijn we vaker combinaties van cytostatica gaan gebruiken. Aan het begin van de 21ste eeuw stagneerde de ontwikkeling van deze vorm van medicatie. Echter, met de komst van doelgerichte therapieën (targeted therapy) lijkt er een heel nieuw tijdperk aangebroken. Deze therapieën grijpen aan op specifieke eigenschappen van kankercellen of hun omgeving en brengen daardoor meestal minder schade toe aan de gezonde cellen dan chemotherapie. Deze ontwikkelingen tezamen hebben geleid tot een verviervoudiging van het aantal voorgeschreven systemische therapieën. Voor patiënten met niet uitgezaaide tumoren uitgaande van het bovenste maag-darmkanaal hebben de toegenomen voorschriften van chemotherapie in combinatie met centralisatie van de zorg in gespecialiseerde centra geleid tot een verbetering van de overleving.

In dit proefschrift hebben we ons gericht op de subgroep van patiënten met uitzaaiingen van tumoren die hun oorsprong vinden in het bovenste maag-darmkanaal. Tot het bovenste maag-darmkanaal rekenen wij de slokdarm, de maag, de alvleesklier en de dunne darm. We bestudeerden trends in de behandeling en overleving van patiënten die lijden aan een van deze vormen van kanker. We hebben gekeken of de voorschriften van chemotherapie toegenomen zijn over de tijd, en of dit van invloed is geweest op de overleving.

Daarnaast hebben we aandacht besteed aan twee veelbesproken onderwerpen binnen de gezondheidszorg. In het kader van de gewenste transparantie in de gezondheidszorg, hebben wij onderzocht of er een verschil was in het voorschrijven van chemotherapie tussen tien perifere ziekenhuizen in Noord-Brabant en Noord-Limburg. Verder hebben wij ons in het kader van de huidige normeringsdiscussie, afgevraagd of er ook in het geval van uitgezaaide kanker van de alvleesklier een relatie bestaat tussen het aantal met chemotherapie behandelde patiënten en de overleving van deze patiënten. Om de bovengenoemde onderzoeksvragen te kunnen beantwoorden hebben wij gebruik gemaakt van de data van de kankerregistratie van het Integraal Kankercentrum Nederland (IKNL).

De studie beschreven in **hoofdstuk 2.1** geeft inzicht in de behandeling en overleving van patiënten met een uitgezaaide vorm van slokdarmkanker (oesophagus carcinoom). Uit deze studie blijkt dat 30% van de patiënten met slokdarmkanker uitzaaiingen heeft op het moment dat de diagnose gesteld wordt. Dit percentage is sterk toegenomen van 22% in 1994-1998 tot 32% in 2009-2010. De meest waarschijnlijke verklaring voor deze toename

is stadiummigratie. Door verbetering van onder andere de kwaliteit van de CT-scan en door de introductie van nieuwe beeldvormende technieken zoals de PET-scan en de endo-echografie worden uitzaaiingen veelal in een eerder stadium opgespoord. Voor patiënten met uitzaaiingen van slokdarmkanker zijn er tal van palliatieve behandelingsmogelijkheden. Uitwendige bestraling, brachytherapie (inwendige bestraling van de slokdarm) en chemoradiotherapie (chemotherapie gecombineerd met uitwendige bestraling van de slokdarm) zijn met name gericht zijn op het verlichten van klachten veroorzaakt door de tumor in de slokdarm zelf. Chemotherapie, daarentegen, heeft als doel de uitzaaiingen aan te pakken en tijdelijk te verkleinen. In onze studie werden 1,020 patiënten met een uitgezaaide vorm van slokdarmkanker geïncludeerd. Hiervan ontving 62% tenminste één van de eerder genoemde behandelingen. Het percentage behandelde patiënten nam toe over de tijd van 56% in 1994-1998 tot 70% in 2009-2013, waarbij opvallende veranderingen in het gebruik van de verschillende modaliteiten hebben plaatsgevonden. Zo is het gebruik van uitwendige bestraling en brachytherapie (inwendige bestraling) sterk verminderd. De voorschriften van chemoradiotherapie en chemotherapie daarentegen toonden juist een sterke toename van respectievelijk 3% in 1994 tot 19% in 2013 en van 14% in 1994 tot 31% in 2013. Deze veranderde voorschriften over de tijd lijken tezamen met stadiummigratie en een adequate patiëntselectie een gunstig effect te hebben gehad op de overleving. De mediane overleving van patiënten met een uitgezaaide vorm van slokdarmkanker nam namelijk toe van 18 weken in 1994-1998 naar 25 weken in 2009-2013.

Ook patiënten met maagkanker presenteerde zich veelal met uitzaaiingen, in 2011 was dit percentage 44% **(hoofdstuk 3.1)**. Deze uitzaaiingen bevonden zich met name ter hoogte van het buikvlies, 44% van de patiënten had zogeheten peritoneale metastasering, ook een aanzienlijk percentage had uitzaaiingen ter hoogte van de lever (40%). Voor deze patiënten is genezing niet meer mogelijk, wel kan gepoogd worden met chemotherapie het leven te verlengen. In 1990 ontving slechts 5% van de patiënten met uitgezaaide maagkanker palliatieve chemotherapie. Gedurende de studieperiode is dit percentage echter gestegen tot 36% in 2011. Oudere patiënten lijken minder vaak behandeld te worden met chemotherapie. Hetzelfde geldt voor patiënten met comorbiditeiten en patiënten met uitzaaiingen in meerdere organen. Jongere patiënten evenals patiënten met een hoge sociaaleconomische status ontvangen juist vaker

chemotherapie. Rekening houdend met deze factoren is de meest opvallende bevinding de sterke variatie in het voorschrijven van chemotherapie tussen 10 verschillende ziekenhuizen in Noord-Brabant en Noord-Limburg. Zo werd in het ene ziekenhuis 9% van de patiënten behandeld terwijl dit percentage in een ander ziekenhuis ruim 27% was. Helaas heeft het toegenomen voorschrijven van chemotherapie niet kunnen leiden tot een betere overleving op populatieniveau, deze bleef voor patiënten met uitgezaaide maagkanker tussen de 15 en 17 weken. Wel was het zo dat patiënten die behandeld werden met chemotherapie een betere overleving hadden dan niet behandelde patiënten, 32-37 weken versus 9-16 weken. Hierbij moet de kanttekening worden gemaakt dat er in onze studie waarschijnlijk sprake was van selectiebias. Patiënten in een betere algemene toestand ontvingen vaker chemotherapie, terwijl de oudste en meest fragiele patiënten zeer waarschijnlijk niet behandeld werden. Door ontbrekende variabelen in onze dataset, zoals algemene fysieke conditie, voedingstoestand, en symptomatologie gerelateerd aan de ziekte was het onmogelijk om hier op een juiste manier onderzoek naar te doen.

In **hoofdstuk 3.2** hebben we aandacht besteed aan de grote groep maagkankerpatiënten met uitzaaiingen ter hoogte van het buikvlies (peritonitis carcinomatosa). Ondanks dat er gedacht wordt dat chemotherapie minder effectief is in deze subgroep van patiënten nam ook hier het percentage met chemotherapie behandelde patiënten sterk toe. Zo werd in de periode 1995-1998 slechts 11% van de patiënten met peritonitis carcinomatosa behandeld, in vergelijking met ruim 42% in 2007-2011. Helaas werd er ook in deze subgroep van patiënten geen verbetering van de mediane overleving gezien, deze bleef 4 maanden. Er wordt gedacht dat patiënten met peritonitis carcinomatosa uitgaande van de maag, evenals patiënten met peritonitis carcinomatosa van colorectale origine baat zouden kunnen hebben bij chemotherapie die direct wordt toegediend in de buikholte (intraperitoneale chemotherapie).

Een van de zeldzaamste tumoren van het maag-darmkanaal is het adenocarcinoom van de dunne darm. In **hoofdstuk 4.1** bespreken we de resultaten van één van de grootste tot nu toe gepubliceerde studies op populatieniveau naar de incidentie, behandeling en overleving van deze tumor.

De incidentie van het adenocarcinoom van de dunne darm neemt langzaam toe van 0.5 tot 0.7 nieuwe gevallen per 100.000 personen per jaar, in respectievelijk 1999 en 2013. Het grootste deel van deze tumoren lijkt voor te komen

in de twaalfvingerige darm oftewel het duodenum. In totaal had 30% van de door ons geïncludeerde populatie (N=3,930) uitzaaiingen op het moment van diagnose. Net als bij slokdarm- en maagkanker nam dit percentage toe over de tijd. Opvallend was dat de locatie van de primaire tumor bepalend leek voor het metastaseringspatroon, zo zaaiden tumoren gelokaliseerd in het duodenum veelal uit naar de lever, terwijl tumoren gelokaliseerd elders in de dunne darm meestal uitzaaiden naar het peritoneum.

De enige curatieve behandeling voor patiënten zonder uitzaaiingen was een curatieve resectie van de primaire tumor. In onze studie vonden we dat de locatie van de tumor van invloed was op het al dan niet ondergaan van een resectie. Zo werden tumoren gelokaliseerd in het duodenum beduidend minder vaak geopereerd (58%) dan tumoren elders in de dunne darm (95%). Dit kan worden toegeschreven aan de complexiteit van de betreffende chirurgische ingrepen. Hoewel er geen studies waren over de effectiviteit van chemotherapie rondom de operatie, werd het in toenemende mate voorgeschreven. Het percentage steeg van 7% in 1999-2003 tot 15% in 2009-2013. Ook voor patiënten met een gemetastaseerde tumor van de dunne darm was het bewijs voor palliatieve chemotherapie gering. Er waren slechts enkele retrospectieve op populaties gebaseerde studies die een gunstig effect van palliatieve chemotherapie op de overleving aan konden tonen. Toch nam ook hier het voorschrijven van palliatieve chemotherapie sterk toe van 19 % in 1999-2003 tot 37% in 2009-2013.

In onze studie was de mediane overleving van patiënten met een adenocarcinoom van de dunne darm 13 tot 14 maanden. Patiënten zonder uitzaaiingen hadden een mediane overleving van 25 maanden, deze nam significant toe in de loop der jarenvan 19 maanden in 1999-2003 tot 34 maanden in 2009-2013. Er zijn verschillende mogelijke verklaringen voor deze verbetering zoals het centraliseren van patiënten of de toename in het gebruik van chemotherapie. Patiënten met uitzaaiingen van dunne darmkanker hadden een gemiddelde overleving van 4 tot 5 maanden. Deze bleef onveranderd tijdens de studieperiode.

Alvleesklierkanker (pancreas carcinoom) is een van de meest agressieve vormen van kanker. Het merendeel van de patiënten heeft helaas al uitzaaiingen op het moment van diagnose **(hoofdstuk 5.1)**. Opnieuw zien we in onze studie dat verbeterde diagnostische technieken hebben geleid tot een toename van het aantal patiënten dat zich presenteerde met uitzaaiingen, van 35% in 1993-1996 tot maar liefst 59% in 2009-2010. Achttien procent van de totale studiepopulatie

werd behandeld met palliatieve chemotherapie, in de onderzochte periode verdrievoudigden de voorschriften van 10% naar 27%. Opvallend was dat het voorschrijfgedrag niet alleen beïnvloed werd door de leeftijd van de patiënt, maar dat ook zijn sociaal economische status en eventuele pathologische bevestiging van de tumor de kans op het ontvangen van chemotherapie beïnvloedden. Rekening houdend met de kenmerken van de patiënt die zich presenteerde in het ziekenhuis werd wederom een sterke variatie in voorschrijfgedrag tussen de verschillende ziekenhuizen waargenomen. Waar in het ene ziekenhuis slechts 5% van de patiënten chemotherapie ontving, bleek dit in een ander ziekenhuis wel 34%. Helaas heeft ook hier het toegenomen gebruik van chemotherapie niet geleid tot een verbetering van de zeer korte overleving, deze bleef mediaan 10 weken. Hopelijk zullen recent geïntroduceerde behandelingen hier in de nabije toekomst verandering in brengen.

Tijdens het bestuderen van alvleesklierkanker is ons opgevallen dat een aanzienlijk deel van de patiënten geen pathologische bevestiging had van de diagnose. Daarom hebben we in **hoofdstuk 5.2** onderzoek gedaan naar de relevantie van deze pathologische bevestiging in patiënten met een voor alvleesklierkanker verdachte afwijking. In de studie werden 3,321 patiënten geïncludeerd die tussen 1993 en 2010 werden gediagnosticeerd met een pathologisch bevestigde tumor van de alvleesklier of een voor alvleesklierkanker verdachte afwijking. We zagen dat in 59% van de patiënten de tumor pathologisch bevestigd was, dit percentage nam toe over de tijd van 56% in 1993-1996 tot 69% in 2009-2010. Jongere patiënten en patiënten met een hoge sociaaleconomische status hadden vaker een pathologisch bevestigde tumor. Verder lijkt het er op dat het verkrijgen van materiaal voor het stellen van een diagnose makkelijker is wanneer patiënten uitzaaiingen hebben. De positie van de alvleesklier in het lichaam en de reactie van het alvleesklierweefsel op de tumor bemoeilijken namelijk het verkrijgen van geschikt materiaal voor pathologisch onderzoek. Een biopsie van een uitzaaiing, waarmee men de diagnose ook kan bevestigen, is in sommige gevallen dan gemakkelijker.

Volgens de huidige richtlijnen heeft de meerderheid (85%) van de patiënten voorafgaand aan een behandeling met chemotherapie of chemoradiotherapie een pathologisch bevestigde diagnose. Wij vroegen ons af of deze bevestiging eigenlijk wel noodzakelijk was of dat een sterke verdenking op CT-scan in combinatie met een verhoging van tumormarkers niet voldoende zou kunnen zijn. Uit onze dataset blijkt dat de patiënten waarbij de diagnose is gesteld op basis

van beeldvormend onderzoek net zo'n slechte overleving hebben als patiënten waarbij de diagnose is gesteld op basis van pathologisch onderzoek. Derhalve stellen wij dat het verkrijgen van materiaal voor pathologisch onderzoek nog steeds zeer wenselijk is. Echter, indien dit onmogelijk blijkt, dient patiënten niet ten koste van alles behandeling te worden onthouden.

Uit de voorgaande studies is gebleken dat zowel patiënten met een uitgezaaide vorm van alvleesklierkanker als patiënten met een niet uitgezaaide vorm van alvleesklierkanker een slechte prognose hebben. We hebben ons in **hoofdstuk 5.3** afgevraagd of langetermijns overleving wel bestaat bij patiënten met alvleesklierkanker. We vonden dat 40 van de 2,564 patiënten (1.6%) geïncludeerd in deze studie vijf jaar na het stellen van de diagnose nog in leven waren. Eenentwintig van deze overlevenden waren geopereerd aan een niet uitgezaaide vorm van alvleesklierkanker. Van het totaal aantal geopereerde patiënten (N=207) blijkt dus slechts 10% vijf jaar na het stellen van de diagnose nog in leven te zijn. Na gedetailleerd onderzoek van de betreffende patiëntendossiers zagen we dat er zich bij 3 patiënten alsnog een lokaal recidief had voorgedaan. 7 anderen hadden uitzaaiingen ontwikkeld in andere organen. Dit houdt in dat de ziektevrije overleving na 5 jaar slechts 5% bedroeg. Wel dienen we er rekening mee te houden dat deze resultaten dateren uit een periode voor de centralisatie van alvleesklierchirurgie.

Zeventien overlevenden hadden een niet uitgezaaide en niet geopereerde vorm van alvleesklierkanker. Slechts bij 2 patiënten bleek de tumor ook bevestigd door pathologisch onderzoek. Beiden hadden een opvallend mild beloop van de ziekte. Opvallend was echter dat 15 van de 17 patiënten geen pathologische bevestiging hadden gekregen van de diagnose. Aanvullend onderzoek van de dossiers toonde aan dat bij 14 van de 15 patiënten de diagnose herzien was, meestal naar een goedaardige aandoening van de alvleesklier, zoals een ontsteking.

Er waren slechts twee patiënten met een uitgezaaide vorm van alvleesklierkanker die langer dan vijf jaar leefden. Een van deze twee patiënten had een bevestigde tumor en ontving verschillende lijnen chemotherapie. De andere patiënt had een niet pathologisch bevestigde tumor en bleek uiteindelijk ook geen alvleesklierkanker te hebben maar een ANCA-geassocieerde vasculitis, oftewel een ontsteking van de bloedvaten die meerdere organen treft.

In de laatste studie van dit proefschrift hebben we onderzocht of centralisatie van de niet-chirurgische zorg ook de overleving van patiënten met een uitgezaaide tumor van de alvleesklier zou kunnen verbeteren **(hoofdstuk 5.4)**.

Om deze vraag te kunnen beantwoorden hebben we een drietal hoog-volume centra gedefinieerd. Allereerst de hoog-volume incidentiecentra (N=13), gebaseerd op het aantal nieuw gediagnosticeerde patiënten met alvleesklierkanker in een bepaald ziekenhuis. Ten tweede de hoog-volume behandelcentra, gebaseerd op het aantal patiënten met gemetastaseerde alvleesklierkanker die behandeling ontvingen met palliatieve chemotherapie (N=7). Ten derde de hoog-volume chirurgische centra, gebaseerd op het aantal resecties met een curatieve intentie verricht in een bepaald centrum (N=4). In onze studiepopulatie bestaande uit 5,385 patiënten met een uitgezaaide tumor van de alvleesklier bleek dat 24% behandeling met chemotherapie ontving. Dit percentage was niet hoger in hoog-volume incidentie centra, wat suggereert dat het zien van meer patiënten niet automatisch leidt tot het voorschrijven van meer chemotherapie. Vanzelfsprekend was het percentage met chemotherapie behandelde patiënten hoger in de hoog-volume behandelcentra wanneer we deze vergeleken met laag-volume behandelcentra.

De mediane overleving van de gediagnosticeerde patiënten was 9.6 weken en daarmee vergelijkbaar met de overleving gevonden in onze eerdere studie. De met chemotherapie behandelde patiënten hadden mediaan genomen een overleving van 24 weken. We vonden een significant verschil in overleving tussen patiënten behandeld met chemotherapie in hoog-volume behandelcentra ten opzichte van patiënten behandeld in niet hoog-volume behandelcentra, 28 tegenover 23 weken. Aangezien deze analyse enkel werd verricht op behandelde patiënten lijkt selectiebias een minder belangrijke rol te spelen. Het zou kunnen dat de ervaring met de systemische behandelingen in grote behandelingscentra leidt tot vroegtijdige signalering en anticipatie op bijwerkingen.

Ook patiënten die gediagnosticeerd werden in een van de hoog-volume chirurgische centra hadden een betere overleving vergeleken met patiënten gediagnosticeerd in een van de andere centra, 9 versus 15 weken. Deze cijfers dienen wel met enige nuance te worden geïnterpreteerd, het populatie-gebaseerde karakter van onze studie kan geleid hebben tot selectiebias. Het zou kunnen dat de patiënten die gediagnosticeerd werden in hoog-volume chirurgische centra minder of kleinere metastasen hadden. Het zou ook kunnen dat de zorg voor deze specifieke subgroep van patiënten in hoog-volume chirurgische centra beter georganiseerd is. Naar alle waarschijnlijkheid beschikken deze centra bijvoorbeeld over interventieradiologen en maag-darm-leverartsen die meer ervaring hebben in de behandeling van deze complexe aandoening. Wat

ons betreft dient de gevonden relatie tussen grote centra en de verbeterde overleving van patiënten met uitgezaaide alvleesklierkanker in de toekomst verder bestudeerd te worden.
Uiteindelijk concluderen we in dit proefschrift, waarin we trends in de behandeling en overleving van patiënten met uitgezaaide tumoren van het bovenste maag-darmkanaal hebben bestudeerd, dat het toegenomen gebruik van chemotherapie alleen bij patiënten met uitgezaaide slokdarmkanker heeft geleid tot een verbetering van de overleving. Dit betekent overigens niet dat we nooit meer chemotherapie zouden moeten voorschrijven. Het blijft zo dat de individuele patiënt nog steeds baat kan hebben bij dergelijke behandeling. Dit benadrukt het belang van een adequate patiëntenselectie en een behandeling op maat.

About the author

Nienke Bernards was Born on November 27th of 1986 in Eindhoven, the Netherlands. She graduated from secondary education in 2005. In the same year she started to study Medicine at Maastricht University. In 2011 Nienke received her Medical Degree and began working as a resident for the department of Internal Medicine at the Catharina Hospital in Eindhoven.

In May 2012 she started her PhD at the Dutch Comprehensive Cancer Organization, located in Eindhoven. Under Supervision of prof. dr. V.E.P.P. Lemmens she performed several population-based studies on the treatment and survival of patients diagnosed with metastatic upper gastrointestinal malignancies.

During her PhD Nienke continued to combine her work as a researcher with the bed-side experience as a physician. Under supervision of her co-promotor G.J.M. Creemers, medical oncologist, she delivered care to patients with a variety of malignancies, at the department of medical oncology of the Catharina Hospital in Eindhoven.

In January 2015 she started her specialization to become a medical oncologist in the future.

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PhD training and teaching

	Year	Workload (Hours)
Courses		
Cursus wetenschappelijke integriteit, Erasmus MC, Rotterdam	2016	10 hours
Cursus statistiek en SPSS, wetenschapsbureau Maxima Medisch Centrum, Saskia Houterman	2013	30 hours
Scientific writing in English for publication in Biomedical Journals, Lisette van Hulst	2013	30 hours
Good Clinical practice Tapas group experts in clinical research	2013	20 hours
Seminars		
Nederlandse internistendagen, Maastricht, Netherlands	2016	20 hours
Nederlandse Oncologie dagen voor Nederlands, NVMO, Arnhem	2015	16 hours
9e gastrointestinale symposium, Vught, Netherlands	2015	4 hours
Nederlandse Oncologie dagen voor Nederlands, NVMO, Arnhem	2014	16 hours
8e gastrointestinale symposium, Vught, Netherlands	2014	4 hours
Presentations		
Oral presentation, 10e gastrointestinale symposium, Vught, Netherlands	2016	15 hours
Oral presentation, refeeravond “palliatieve sedatie en euthanasie” Eindhoven, Netherlands	2016	20 hours
Oral presentation, refereeravond “gemetastaseerd pancreascarcinoom”, Eindhoven Netherlands	2015	20 hours
Poster presentation European Society for Medical Oncology (ESMO), Madrid, Spain,	2014	15 hours
Poster presentation European Society for Medical Oncology (ESMO), Madrid, Spain	2014	15 hours
Poster presentation European Cancer Congress, Amsterdam, Netherlands	2013	10 hours
Poster presentation European Cancer Congress (ECCO), Amsterdam, Netherlands	2013	15 hours

	Year	Workload (Hours)
Presentations (continued)		
Oral presentation, Kamerlid Michiel van Veen (VVD) Eindhoven, Netherlands	2013	10 hours
Poster presentation World Congress on Gastrointestinal Cancer WCGC, Barcelona, Spain	2013	15 hours
Oral presentation, Werkgroep Urologie Eindhoven, Netherlands	2013	10 hours
Conferences		
Werkgroepen Medische oncologie, Eindhoven, Netherlands	2012-2014	60 hours
Projectgroepen Cytomanagement System, Eindhoven, Netherlands	2014-2015	120 hours
Other		
Medical residency, Internal medicine	2015-2016	
Total		**430 hours**