Improvement of the multimodality treatment of oesophageal cancer
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General introduction and outline of the thesis
Oesophageal cancer

As of today, oesophageal cancer is a difficult tumour to treat. Incidence and mortality rates are almost equivalent not only because many patients present with advanced disease but also because current day therapy often fails. A variety of combined modality approaches has been introduced to complement surgical treatment. Between 2003 and 2007, the incidence in the Netherlands has risen from around 1480 to 1650 new patients per year with an overall 5-year survival rate of 14% (Figure 1).

Despite technical surgical advancements and improvements in perioperative care, surgery alone in the management of oesophageal cancer often appears ineffective in achieving a long-term disease-free state. Five year-survival data in published trials using surgery as the sole therapeutic modality have ranged from 8% to 30%. In addition, local recurrence contributes to significant morbidity and mortality. Therefore, there are many challenges in improving the treatment of oesophageal cancer.

Figure 1: Survival data for patients diagnosed with oesophageal cancer in the Netherlands between 1998 and 2007.
Chemoradiation and surgery for oesophageal cancer

Over the past three decades, numerous clinical trials of combined modality therapy have been performed in an attempt to improve cure rates achieved by surgery alone. These combined modality strategies include postoperative radiotherapy alone, adjuvant chemotherapy with or without radiation, and various preoperative treatments. Neoadjuvant strategies have included radiation alone, chemotherapy alone, or both radiotherapy and chemotherapy prior to oesophagectomy. In addition, definitive chemoradiation without resection has been explored. While studies of adjuvant chemotherapy and/or radiotherapy have failed to demonstrate a significant survival benefit\textsuperscript{11-14}, neoadjuvant strategies have been employed with some success and are currently accepted by many clinicians as a standard of care in the treatment of this cancer.\textsuperscript{15} The potential benefits of neoadjuvant therapy include: (1) eradication of occult micrometastatic disease present at the time of presentation that results in distant failure and death despite "curative" resection, (2) the ability to determine chemosensitivity while the tumour is in situ, and (3) improved patient tolerance of toxic regimens prior to a surgical procedure as opposed to attempting to deliver that same therapeutic regimen in a relatively debilitated post-resection state.

Promising results have led to several randomised controlled trials\textsuperscript{16-20} and subsequent meta-analyses.\textsuperscript{21-27} However, most of these studies have focused on pathological response and survival rates. Outcome measures such as toxicity, resection rates and quality of life have been studied less frequently. Patients with a significant response to neoadjuvant therapy have an improved survival as compared to those that did not respond.\textsuperscript{28} The substantial response rates observed with preoperative chemoradiation in combination with the morbidity and mortality risk associated with oesophageal resection have led some investigators to challenge the role of surgery in the treatment of oesophageal cancer.\textsuperscript{29,30}

Use of pathological markers in oesophageal cancer treatment

For different types of tumours, extensive research has been performed to distinguish patients with low-risk and high-risk profiles on the basis of molecular techniques.\textsuperscript{31} Methods aimed at genomic expression analysis using array technology have not yet led to a clear set of gene expression profiles that can be used for individual patient management.\textsuperscript{32} Efforts continue to identify markers that can differentiate patients with a high risk for tumour recurrence after treatment of the primary tumour from those with a low risk for recurrent disease. Knowledge of such markers could potentially improve the efficacy of non-surgical therapy.
The tumour micro-environment plays a crucial role in the progression, growth and spread of cancers. Data suggest that stroma in the vicinity of tumours undergoes, or may be affected by, changes during tumour progression (Figure 2). In these studies, tumours with distinct patterns of intra-tumour stromal percentage were identified in a population of colon cancer patients. Two groups, “stroma-low” and “stroma-high” patients, were defined and showed statistically significant differences in overall and disease-free survival in favour of those with a low stroma production. In oesophageal cancer, this relationship between tumour-stroma ratio and survival has never been explored.

Figure 2: The tumour stroma interaction.

Abbreviations: ECM: extracellular matrix.
Source: reference 37

It is widely accepted that self-sufficiency in growth signals and insensitivity to growth-inhibitory signals play an important role in the development of cancer. There is increasing evidence that carcinogenesis must be understood in terms of accumulation of mutations in regulatory genes, including activation of oncogenes and inactivation or loss of tumour-suppressor genes. With the recent advances in drug development, there are emerging studies using antagonists of growth factor signal transduction- and activated kinases-pathways in targeted therapy. In lung cancer, the epidermal growth factor receptor (EGFR) inhibitor gefitinib has been proven safe and feasible in the preoperative setting. In oesophageal cancer, EGFR is commonly overexpressed, and has been connected to poor prognosis. However, mutations in EGFR are not frequently found in oesophageal cancer.
The Ras-Raf-MEK-ERK kinase-pathway is an important mediator in cellular responses to growth signals, proliferation and survival. KRAS genes are localized on the human chromosome 12. KRAS mutations have been detected in pancreatic, colon, small intestinal, and stomach cancer. In oesophageal cancer, previous reports of ras-mutations have resulted in widely varying results. BRAF is part of the RAF family genes. This gene plays an important role in proliferation, differentiation and programmed cell death. Recent data have shown that BRAF is mutated in about 7% of cancers, identifying it as another oncogene. The frequency of BRAF mutations in oesophageal cancer is unknown.

In recent years, numerous studies have been initiated to explore the role of targeted therapy in the treatment of oesophageal cancer. Mutational status, which could predict patient’s response to this type of treatment, deserves further investigation.

Quality assessment in oesophageal cancer treatment

Quality assurance in the treatment of cancer is of utmost importance since many studies have shown large variation in outcome between different providers. Not only differences in hospital volume and infrastructure have proven to be significantly related to outcome, also physicians' treatment choices, diagnostic and technical skills are important. Despite the success of a surgical audit in colorectal cancer treatment, few attempts have been made to spread the merits of quality assurance programs to other tumour types. At the end of 2005, a national guideline for the treatment of oesophageal cancer was published in the Netherlands. It has been recommended to concentrate the surgical treatment of oesophageal cancer in hospitals with a minimum of 10 resections annually. Whether this measure will be effective in raising the whole level of quality of care has been challenged. Preferably, the concentration of oesophageal cancer treatment is accompanied by a national quality assurance program, evaluating the different dimensions of quality of care in all hospitals performing oesophageal cancer treatments. Donabedian has conceptualized the evaluation of patient care in terms of structure, process, and outcome measures (Figure 3). Evidence-based indicators associated with outcome for the different dimensions of quality of care in oesophageal cancer surgery need to be defined.

Oesophageal resection can have serious negative effects on health-related quality of life, although after an initial postoperative decline, health-related quality of life often returns to baseline levels within one year after surgery. As stated before, many patients nowadays are treated with chemoradiotherapy in an effort to improve the poor 5-year survival rate after surgery only. However, potential gains in clinical outcomes resulting from combined modality treatment may be offset by negative effects on patients’ health-related quality
of life. Studies on long-term quality of life after potentially curative oesophageal cancer treatment may provide valuable information for pretreatment patient counseling.

Figure 3: The Donabedian quality of care framework

**Structural** measures of care are characteristics of the provider, reflecting the setting in which care is delivered (e.g., staff expertise).

**Process** measures of care refer to the interactions between the provider (i.e., physician) and the patient (e.g., multidisciplinary team management).

**Outcome** measures of care are measurable short-term outcomes affecting the final outcome of treatment (e.g., radicality of resection).

Source: reference 57
Outline of the thesis

The studies in this thesis aim to improve the multimodality treatment of oesophageal cancer. The thesis is divided into three parts. **PART I** focuses on chemoradiation and surgery, **PART II** investigates the use of pathological markers in oesophageal cancer treatment, and in **PART III**, quality assessment issues are addressed.

**PART I: Chemoradiation and surgery for oesophageal cancer**

In *chapter 1*, a systematic review of the recent English-language literature (January 2000 through December 2008) on neoadjuvant chemoradiation for oesophageal cancer was performed. The aim of this review was to describe the potential benefits (e.g., pathological complete response) and risks (e.g., toxicity) of neoadjuvant chemoradiation for patients with oesophageal cancer. *Chapter 2* describes the results of three different chemoradiation regimens for oesophageal cancer. Toxicity and efficacy of these regimens that are applied in the neoadjuvant or definitive setting were evaluated in a retrospective patient series.

There is a known inverse relationship between the number of oesophagectomies and in-hospital mortality. The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (NKI-AVL) is a tertiary referral centre with a high case-load of patients with oesophageal cancer, but with a low yearly volume of oesophagectomies. In *chapter 3*, the results of oesophageal cancer surgery in the NKI-AVL were analysed. And, these results were compared with published data from high surgical volume institutions.

**PART II: Use of pathological markers in oesophageal cancer treatment**

The amount of stroma in direct relation to a tumour could be of influence on patients' overall and disease-free survival chances. In *chapter 4*, we evaluated the prognostic value of the tumour-stroma ratio in patients who had undergone oesophageal resection for adenocarcinoma without neoadjuvant therapy. A similar study on biopsy material could possibly provide prognostic information before the start of treatment. Therefore, in *chapter 5*, the inter- and intraobserver agreement for measuring the tumour-stroma ratio in oesophageal adenocarcinoma biopsies was assessed. Subsequently, the tumour-stroma ratio biopsy scores were correlated to other pathological and clinical parameters.

*Chapter 6* describes the incidence of EGFR, KRAS and BRAF mutations in oesophageal cancer in a group of patients who were treated with neoadjuvant chemoradiotherapy. For these investigations, archival biopsies sampled before the start of treatment were used.
PART III: Quality assessment in oesophageal cancer treatment

In chapter 7, we performed a review of the literature to identify evidence-based standards for high-level quality of care in oesophageal cancer surgery. With the use of the Donabedian quality-of-care model, we aimed to describe structural, process, and outcome parameters that adequately measure quality of care for surgical oesophageal cancer patients. In the end, a minimum dataset of evidence-based quality-of-care indicators was constructed for future registration and benchmarking.

In chapter 8, the quality of care for oesophageal cancer patients referred to the NKI-AVL was evaluated. For this, indicators for quality of care were defined and investigated in two time periods (2003 through 2005 and 2006 through 2008).

Clinical outcomes have been investigated extensively in studies on oesophageal cancer treatment. Less is known about long-term health-related quality of life. In chapter 9, a range of health-related quality of life outcomes was studied in a group of oesophageal cancer patients who were treated with potentially curative intent at least one year earlier.

In PART IV, the results of the studies described in chapters 1 to 9 are summarized. Following this, several answers are given to the question 'How to improve the multimodality treatment of oesophageal cancer further?' in Future perspectives.
Reference List


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114(3):205-209.


45. Lyronis ID, Baritaki S, Bizakis I, Krambovitis E, Spandidos DA. K-ras mutation, HPV infection and smoking or alcohol abuse positively correlate with esophageal squamous carcinoma.
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61. Brooks JA, Kesler KA, Johnson CS, Ciaccia