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Modern view on multimodality treatment of esophageal cancer

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Modern view on multimodality treatment of esophageal cancer

Thoughts on Patient Selection and Outcome

proefschrift

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Preface

While writing my thesis I was inspired by the spirit animal dragonfly and the color turquoise.

The dragonfly is an elegant and powerful insect. She achieves her purpose simply and effectively with her two pairs of wings, a long slim abdomen, and large eyes. The flight of the dragonfly stands for progress and flexibility, but also the endlessness of possibilities in life. In various cultures the dragonfly is seen as the bringer of new insights and she represents playfulness, change, and harmony. The dragonfly stands for spiritual growth and positive thoughts. As a totem animal, the dragonfly demands strength in the balance between emotions, thoughts, and change. Coherent, turquoise is a color of creativity and vision with the ancient symbol reformer and key phrase future-oriented innovation. This capacity is achieved by searching for new forms of living together through humanization and technocratic society reform.

Through collaboration with different departments, agencies, and people both nationally and internationally, we have tried to bring together the power of various insights into innovative approaches. As a result, the studies described in this thesis aim to provide novel insights into the management and treatment outcome in patients with esophageal cancer.

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General introduction

and outline of the thesis

Curative treatment strategies in esophageal cancer

While the incidence of esophageal cancer (EC) in Europe is rising, survival remains poor despite improved and more sophisticated treatments in recent years. EC is a heterogeneous disease, therefore it is necessary to identify clinicopathological factors in order to stratify patients better for adequate treatment aiming to prevent unnecessary side effects, to limit postoperative morbidity and to improve outcome.

Due to the aging of the population in the Western world with a shift in the peak incidence from 65–70 to 70–79 years, the absolute incidence of EC has grown over the past decades. At the time of diagnosis, 30% of the patients with EC are currently ≥ 75 years [1]. Approximately 50% of patients with EC have incurable disease due to invasion of surrounding organs (T4b-stage) or systemic metastases (M-stage). Of patients with a potentially curable esophageal tumor, more than 40% has locally advanced disease with regional nodal involvement [2].

During the last two decades, both staging and curative treatment regimens have evolved. Although curative treatment options commonly depend on the extension of the primary tumor and presence of locoregional lymph node metastases, patient- and other tumor-related factors including co-morbidity, age, histologic type, and tumor location play a role in the treatment decision. For early EC, (Tis-T1a), endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are well-established techniques with a relatively low morbidity. For years, esophagectomy performed via an open transthoracic approach with regional lymph node dissection

was the treatment of choice. During the late 1990 and early 2000, tri-modality treatment, including neoadjuvant chemoradiotherapy (nCRT) plus surgery was introduced and this has led to improved outcomes. Nowadays, nCRT or (perioperative) chemotherapy (CT) followed by esophagectomy is the treatment of choice for locally advanced EC (T3-T4a) or documented lymph node (LN) involvement according to the 8th edition of the AJCC (Table 1). Definitive chemo-radiotherapy (dCRT) has shown to be an alternative in patients who are medically unfit for surgery or deny curative intended resection and for locally irresectable (cT4b) tumors.

Neoadjuvant CRT may induce down staging/sizing of the primary tumor and sterilization of nodal metastases in up to 60% of patients. Moreover, by targeting locoregional and distant micro-metastases, nCRT seems to decrease the potential risk of developing distant metastases. Two commonly used preoperative CRT regimes, cisplatin and 5-fluorouracil in combination with 50.4 Gy, and carboplatin with paclitaxel and 41.4 to 50.4 Gy, are now considered as standard care in the Western world [5–7]. Following nCRT and surgery, the resection specimen may show different pathologic tumor response grades including a pathologic complete, partial or no response. Pathologic complete response to chemoradiotherapy is associated with improved long term survival. This may be explained by an increased rate of a resection with microscopic tumor-negative resection margins (so-called radical or R0-resection) and, as a consequence, decreased rate of locoregional recurrences [5].

About 15-36% of the resection specimens after nCRT show a pathologic complete response (pCR), including absence of microscopic vital tumor cells both at the primary tumor site and nodal regions (ypT0N0) [8]. Theoretically, esophagectomy is not of additional value in these patients [5]. However, identification of patients with a complete response, even with state of art imaging modalities prior to surgery is difficult, whereas esophagectomy may cure patients with partial response (PR) and persistent disease after nCRT. Moreover, patients with little or no response (NR) to nCRT are also advised to undergo an esophagectomy although it is known that these patients generally have a poor outcome [9]. At present, all patients are exposed to the risks of morbidity and mortality of neoadjuvant treatment and surgery given the fact that it is still impossible to accurately predict response to treatment and prognosis in individual patients.

A German study showed equal overall survival (OS) in patients with squamous cell carcinoma (SCC) following nCRT (41.4 Gy) with surgery compared to patients after dCRT (65 Gy or more) [10]. Likewise, a French trial reported no survival benefit of surgical resection after nCRT compared to dCRT [11]. These studies underline the use of dCRT as an alternative in patients with a potentially curative EC. Definitive CRT in patients with locally advanced EC can be applied for several reasons. Patients may be medically unfit to undergo high risk surgery or have a technically difficult localisation of the tumor and/or locoregional disease, while some patients do not opt for surgery [12-16]. To improve the outcome for dCRT, Minsky et al. investigated the benefit of high radiation dose (64.8 Gy) compared to a standard dose, but found no benefit and even a trend towards reduced survival in the experimental arm [17]. In response to these results and the observed side effects, the standard radiation dose for dCRT is 50–50.4 Gy in the United States and Europe.

Although the clinical CR (cCR) rates are high and short-term survival is favorable following dCRT, persistent or recurrent locoregional (LR) cancer is common [9]. In some Japanese studies the observed cCR rate is between 63-89% among patients with stage I to stage II/III SCC disease [18,19]. However, in patients with T4 tumors and/or extraregional lymph node metastases (previously called M1a), the reported cCR after dCRT is around 33% [20]. Depending on the histological type about 40-60% of the patients who achieved cCR eventually will develop local recurrences (LR)[21, 22]. Usually additional CRT will not control the LR potential because most patients already have received the maximal radiation doses, whereas the chance for distant metastasis is relatively high precluding the possibility to perform curative surgery. On the other hand, a selected group of patients with an isolated LR may be suitable for curative intended “salvage surgery” after adequate staging [9].

The increased experience with dCRT and a more intensive follow up of patients afterwards may increase the number of patients who benefit from salvage surgery in case of isolated recurrent or persistent EC. The reported rate of salvage surgery ranges between 4% and 29% and most procedures are performed 4 to 18 months after completion of dCRT, reflecting the lack of criteria in the management of LR in EC [9]. However, salvage esophagectomy is associated with high rates of morbidity and in-hospital mortality of around 50-79% and 6-22%, respectively. The reported 5 year survival rates vary between 0 and 33 % [13, 23, 24]. Postoperative complications, including pneumonia and sepsis, occur frequently and impact on patient's pulmonary, cardiac, and renal functioning, diminishing the long-term health-related quality of life and survival. Another problem is that patients' immune system seems to be suppressed after dCRT, and that the irradiation of the proximal stomach, particularly in distal EC, may affect the viability of the gastric conduit and anastomosis [11].

Given the high rate of complications after salvage esophagectomy, this procedure should be limited to a carefully selected group of patients and in hospitals with ample experience in upper GI surgery. Crucial in the selection of patients with isolated recurrent or persistent disease is the adequacy of follow-up of potential candidates [9].

However, there are still no guidelines to select patients properly for follow up and eventually surgery. According to recent publications it is relevant to take into account the accuracy of restaging methods following dCRT, patient's performance status / fitness, the potential to obtain a complete R0 resection, and the detection of suspected systemic metastases [25-27].

A better understanding of biological behavior in combination with improved technology like molecular targeted therapy, new radiotherapy techniques such as proton therapy will provide us the opportunity to improve individual therapies, diagnosis and prevention strategies in EC.

Outline of the thesis

This thesis is divided in three parts. PART I includes the impact of co-morbidity on treatment offered to patients in two population based studies. PART II focuses on clinico-pathological factors and outcome after treatment. PART III addresses the different treatment options with respect to persistent and recurrent disease.

PART I - Impact of co-morbidity: population-based studies

Chapter 1

In the Netherlands, the incidence of esophageal cancer (EC) has increased over the last three decades, particularly in patients over the age of 50 years. Nowadays 30% of the patients are 75 years or older at the time of diagnosis. In this chapter we evaluated trends in management and survival of patients aged 75 years or older with EC.

Chapter 2-3

Surgery still is the cornerstone in the treatment of EC patients. However, some patients with locally advanced EC (T1/N1-3 and T2-4a/any N/M0) are not fit for surgery due to severe co-morbidity or have denied surgery for other reasons. Definitive chemoradiotherapy (dCRT) is a good alternative for these patients. In this chapter, we assessed the impact of co-morbidity and age >75 years on the choices of treatment made by the multidisciplinary board.

PART II - Impact of different clinico-pathological factors on prognosis

Chapter 4

Besides the presence and number of nodal metastases, lymph vascular involvement, intramural metastases and circumferential resection margin (CRM) predict poor prognosis. Earlier studies showed that involvement of the CRM is an independent prognostic factor for recurrent disease and survival after surgery alone. In this chapter, we evaluated the usefulness and impact on prognosis of both definitions of CRM as tumor-free (R0) based on a surgery-alone approach as described by the College of American Pathologists (CAP; >0 mm) or the Royal College of Pathologists (RCP; >1 mm), in current practice with nCRT.

Chapter 5 and 6

Extramural venous invasion (EMVI) is a known potent adverse prognostic factor in patients with colorectal carcinoma. In contrast to colorectal cancer, the incidence and prognostic significance of EMVI in EC have not been studied. As nCRT is a common standard treatment for EC, nCRT may have a potential effect on the degree of EMVI and survival as seen in colorectal cancer patients. In this chapter, we described the prevalence, prognostic and diagnostic value of EMVI in patients with locally advanced stage T3/T4 EC and the potential impact for patients treated with nCRT.

PART III – Frequent treatment failures and intended curative treatment on locoregional recurrent and persistent disease

Chapter 7

In the curative treatment of patients with esophageal cancer (EC), external beam radiotherapy is commonly used either in a neo-adjuvant or definitive approach. Breathing motion of surrounding vital organs are of influence on planned dose distributions in thoracic radiotherapy. In this prospective study we have evaluated the magnitude of the breathing motion on repeat 4D computed tomography scans, by using the diaphragm as an anatomical landmark for EC.

Chapter 8

Improvements in the treatment of patients with esophageal cancer with neoadjuvant chemoradiotherapy (nCRT) have significantly increased the rates of pathologic complete response. Recently, a watchful waiting strategy and surgery only as needed has been proposed for patients with a clinical complete response in a study context. In this study, we investigated the site of residual tumor after nCRT in relation to target volumes and its impact on prognosis.

Chapter 9

Definitive CRT is a curative treatment option for a selected group of patients with locally advanced EC. The presence of isolated persistent or recurrent local/regional disease after dCRT could be an indication for salvage surgery. In this chapter, we reported a systematic review that investigated the safety and efficacy of salvage surgery in persistent or recurrent EC after dCRT and in patients after nCRT who underwent delayed surgery.

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PART I

Impact of co-morbidity: population-based studies

*‘The specialist must know everything of something,
something of everything.’*

- C.V. Wedgwood