Improving patient selection towards personalized treatment decisions in esophageal cancer
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CHAPTER 1

General introduction

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INTRODUCTION

Esophageal cancer is the 8th most commonly diagnosed malignancy worldwide [1]. The incidence, especially that of esophageal adenocarcinoma, has increased markedly in most Western countries during the last three decades [2-4]. In the Netherlands the number of newly diagnosed patients has increased from around 800 to 2500 yearly, during the period 1990 to 2015 [5]. At the time of diagnosis approximately 50% of the patients already have distant metastases or irresectable disease and are not amenable for cure, resulting in a low overall 5-year survival rate between 15% and 25% [6,7].

In patients with potentially curable esophageal cancer, surgery is the main therapeutic option. However, at the time of diagnosis most patients already have locally advanced disease with lymph node metastases. In these patients, tumor recurrence is common even after a curative intended surgical resection and lymphadenectomy. The overall survival is therefore low between 25% and 35% [8-11]. In order to improve the outcome in patients with locally advanced esophageal cancer, the CROSS (ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study) trial was initiated, in which patients were treated with neoadjuvant chemoradiotherapy prior to surgery [12]. The CROSS treatment schedule, which consists of carboplatin and paclitaxel with concurrent radiotherapy (41.4 Gy, given in 23 fractions of 1.8 Gy) followed by esophagectomy, increased the 5-year overall survival with 13%, to 47% [12]. In many European countries, including the Netherlands neoadjuvant chemoradiotherapy (nCRT) according to the original CROSS regimen became standard treatment for locally advanced esophageal cancer. However, approximately 20-25% of these patients do not benefit from the administered nCRT, and may suffer from harmful side-effects. It should be mentioned that the side-effects are relatively mild in the CROSS approach, compared to those in the less frequently applied Cisplatin-5-Fluorouracil (Cis-5FU) combination [12-14].

On the other hand, between 25% and 42% of the patients treated with nCRT have a pathologic complete response [12,15,16]. In the future, patients who are highly suspected for a pathologic complete response to nCRT might benefit from a personalized treatment approach with refraining from surgery followed by extensive follow-up and salvage surgery in case of isolated loco-regional recurrence or local residual disease. For this approach to be worthwhile, prediction of complete response with medical imaging techniques should match pathologic outcome. However, even in patients with a pathologic complete response early tumor recurrences may occur within 6 months, which might be explained by inadequate pre-treatment staging and biological aggressive behaviour [17].
STAGING IN ESOPHAGEAL CANCER

The standard staging work-up in patients with esophageal cancer consists of endoscopy with biopsies of suspect lesions, a diagnostic computed tomography (CT) scan, a $^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) or integrated $^{18}$F-FDG PET/CT scan, and an endoscopic ultrasound (EUS) [18-20]. Anatomic staging methods, such as CT and EUS, enable detection of disrupted anatomical structures, whereas the $^{18}$F-FDG PET is a metabolic imaging technique that depicts abnormal uptake of radioactive $^{18}$F-labeled fluorodeoxyglucose ($^{18}$F-FDG).

After staging, the outcome of these sophisticated staging techniques are scored according to the TNM classification of the American Joint Committee on Cancer, in which the T-stage stands for the local tumor depth of growth, the N-stage for the lymph node status, and the M-stage for distant metastases [21]. Thereafter, patients are discussed in a multidisciplinary tumor board meeting to determine the optimal treatment based on the TNM stage, presence of comorbidities, patients physical and mental condition, and patient preferences. In order to optimize treatment decision making and to advance towards a more personalized treatment approach, adequate pre-treatment staging and restaging after nCRT is of great importance.

Of all staging techniques, EUS is the best method to determine the growth depth of the primary tumor (T-stage) and to detect lymph node metastases (N-stage) with a sensitivity between 71-92.4% and 80-84.7% and a specificity of 84.6-99.4% and 70-84.6% [22,23]. The advantage of EUS is the possibility to obtain fine-needle aspiration cytology from suspect lymph nodes, which increases the sensitivity and specificity in detecting metastatic lymph nodes [23,24]. Downsides of EUS are the relative high patient burden and the risks of bleeding, aspiration, and perforation [25]. Other downsides of the EUS include that the accuracy of EUS is highly dependent on the performers skill and that passage of the primary tumor is not possible in 20-36% of the patients, because of tumor stenosis [26-29]. Preventing an unnecessary EUS should therefore be pursued.

The best staging technique to detect distant metastases (M-stage) is the $^{18}$F-FDG PET, with a sensitivity and specificity of 71% and 93%, respectively [22]. Because of the high sensitivity of $^{18}$F-FDG PET/CT in detecting distant metastases, an upfront $^{18}$F-FDG PET/CT is the best predictor for curative resectability in potentially curable esophageal cancer and is the most cost-effective staging approach [30, 31]. With the current availability of integrated $^{18}$F-FDG PET/CT scans, the detection of lymph node metastases is also a feasible goal. The additional value of a standard EUS after $^{18}$F-FDG PET/CT might therefore be limited. So far, no study has been performed to determine the value of EUS after integrated $^{18}$F-FDG PET/CT scanning, but several studies reported contradictory
results about the additional value of EUS after CT-alone [32-34]. One of the additional advantages of the $^{18}$F-FDG PET/CT upfront staging sequence is that fine-needle aspiration can be performed with the EUS to determine if $^{18}$F-FDG PET/CT suspect lymph nodes contain tumor cells. Even with the combined information of all current optimal staging methods, the accuracy of detecting lymph node metastases remains low. In patients treated with surgery-alone, the lymph node stage is incorrect in approximately 25% [35]. Inaccurate nodal staging might lead to either (1) over-treatment with neoadjuvant chemoradiotherapy while surgery-alone was more suitable or (2) under-staging causing treatment with surgery-alone while neoadjuvant chemoradiotherapy followed by surgery would be more appropriate [35-37]. Moreover, determining the exact localization of suspect lymph nodes is also important in current treatment paradigm, especially for accurate radiotherapy target volume delineation. In patients with a pathologic complete response of the primary tumor, metastatic lymph nodes may still be left behind, which might have been a consequence of inadequate lymph node staging [38-42]. Therefore, the definition of a complete response to nCRT, both clinical and pathological, should be based on response of the primary tumor and regional lymph nodes as well [43,44].

Furthermore, after extensive staging with the current optimal staging techniques, between 8 and 17% of all patients have interval metastases in the period between neoadjuvant treatment and surgery [45-48]. For a personalized treatment approach, progressive disease and interval metastases should be detected to prevent futile surgery and to change the treatment to a suitable palliative treatment. Even with the high number of patients with progressive disease after neoadjuvant chemoradiotherapy, restaging was not considered standard of care in many medical centers [20]. The use of $^{18}$F-FDG PET/CT scans is preferable, as it detected about 3 out of 4 patients with progressive disease compared to 2 of 4 patients with CT [45-47].

**TREATMENT OUTCOME AFTER NEOADJUVANT CHEMORADIOThERAPY**

To improve treatment selection and the treatment outcome of patients with esophageal cancer, it is important to determine which patients benefit less from neoadjuvant chemoradiotherapy. One of the major advantages of neoadjuvant chemoradiotherapy is tumor downsizing, which results in a significantly higher number of microscopic tumor free resection margins (R0 resection) compared to surgery-alone approach [12]. Although the circumferential resection margin is a well-established prognostic factor in patients treated with surgery-alone, its value after neoadjuvant chemoradiotherapy remains unclear [49-55].
Moreover, even in patients with tumor-free resection margins, the number of patients with tumor recurrence is high, emphasizing the importance of adequate pre-treatment staging and treatment selection. Based on the good results and the relative high pathologic complete response rate of 29% in the CROSS trial, patients with potentially curable esophageal cancer who did not meet the initial CROSS eligibility criteria, were also treated accordingly. This raises the question whether these patients benefit equally from this regimen.

**RESPONSE PREDICTION IN ESOPHAGEAL CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMORADIOThERAPY**

Pathologic complete response, which is achieved in 25-42% of the patients, leads to a significantly better outcome [12,15,16]. In the future patients with a pathologic complete response might even benefit from refrainment of surgery. The most commonly applied method to predict response to neoadjuvant chemoradiotherapy is to measure the decrease in the maximal value of the standardized uptake value (SUV$_{\text{max}}$) on $^{18}$F-FDG PET scans. However, this yields an insufficient sensitivity and specificity of 67% and 68%, respectively [56]. A major shortcoming of the SUV$_{\text{max}}$ is the susceptibility to noise artifacts as it is based on a single voxel. Currently, radiomics (tumor imaging features) are becoming increasingly important in the prediction of response to neoadjuvant therapies [57]. Textural features, derived from $^{18}$F-FDG PET scans, depict the spatial correlation of $^{18}$F-FDG uptake between voxels, and therefore display heterogeneity in uptake [58-63]. So far, several studies found textural features to be better predictors of response to neoadjuvant chemoradiotherapy than the SUV$_{\text{max}}$, although this benefit is still insufficient for clinical decision making [58]. Moreover, predicting response by comparing pre- and post-neoadjuvant chemoradiotherapy $^{18}$F-FDG uptake histograms showed promising results as well: longitudinal patterns in $^{18}$F-FDG uptake provided useful information in detecting response [64].

Recently, diffusion-weighted magnetic resonance imaging (DW-MRI) has been introduced to assess response to neoadjuvant chemoradiotherapy [65-69]. DW-MRI is sensitive to water mobility (diffusion) and can be used to measure the apparent diffusion coefficient (ADC). ADC changes might represent alterations in tissue (micro)structures. So far, several studies showed ADC changes to be predictive for tumor response in EC [67, 68]. However, further studies are necessary for clinical application of DW-MRI in response prediction.

**In conclusion,** neoadjuvant chemoradiotherapy has increased the survival of locally advanced esophageal cancer, but not all patients will benefit from the trimodality treatment. In order to increase the outcome in general, the patient selection needs to be improved towards a more personalized treatment in locally advanced esophageal cancer.
OUTLINE OF THIS THESIS

The aim of this thesis is to improve the patient selection, with the focus on improving staging strategies and treatment outcome, and on the predicting response to neoadjuvant chemoradiotherapy followed by surgery. The different chapters address circumstances towards a more personalized treatment by increasing staging accuracy and improving treatment related outcome (part I), and increasing prediction of pathologic complete response to nCRT (part II).

PART I: IMPROVING STAGING AND NEOADJUVANT CHEMORADIOThERAPY OUTCOME IN ESOPHAGEAL CANCER

The additional value of endoscopic ultrasound (EUS) after an upfront $^{18}$F-FDG PET/CT remains unknown, especially in regard to its impact on the given treatment. In Chapter 2, the staging approach was optimized by determining the impact of EUS and fine needle aspiration on the given treatment in a $^{18}$F-FDG PET/CT upfront model in a multicenter study.

Improving the detection of lymph node metastases is of vital importance in the era of neoadjuvant chemoradiotherapy for accurate radiotherapy delineation. In Chapter 3, we examined the effectiveness of combined CT, $^{18}$F-FDG PET/CT, and EUS in the detection of lymph node metastases.

The relatively high rate of progressive disease after neoadjuvant chemoradiotherapy, dissembled the benefit of surgery, indicating the importance in detecting interval metastases before esophageal resection. In Chapter 4 we therefore determined the value of CT restaging in detecting tumor progression after neoadjuvant chemoradiotherapy.

To improve treatment outcome of patients with esophageal cancer, we should determine which patients will benefit from neoadjuvant chemoradiotherapy. In Chapter 5 we assessed the prognostic value of circumferential resection margins after neoadjuvant chemoradiotherapy.

To optimize selection of patients that may benefit from neoadjuvant chemoradiotherapy, we determined the effect of extending the CROSS eligibility criteria for neoadjuvant chemoradiotherapy on the toxicity rate and survival in Chapter 6.

PART II: IMPROVING PREDICTION OF RESPONSE TO NEOADJUVANT CHEMORADIOThERAPY

Prediction of response to neoadjuvant chemoradiotherapy is a basic step towards a personalized treatment approach in patients with esophageal cancer. In part II the focus is on non-invasive methods to predict response to neoadjuvant chemoradiotherapy.
In Chapter 7 we assessed the impact of textural features derived from pre-treatment $^{18}$F-FDG PET/CT imaging in predicting response to neoadjuvant chemoradiotherapy.

In Chapter 8 we determined the value of changes in textural features and histogram distances after neoadjuvant chemoradiotherapy in detecting response. Finally, in Chapter 9 we report the outcome of a pilot study about the additional role of diffusion-weighted magnetic resonance imaging (DW-MRI) to $^{18}$F-FDG PET/CT scans, in identifying tumor response to neoadjuvant chemoradiotherapy.
REFERENCES


PART I

Improving staging and neoadjuvant chemoradiotherapy outcome in esophageal cancer patients