The use of PET/CT in the radiotherapy treatment planning for esophageal cancer.

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Contents

Chapter 1

General introduction and outline of the thesis

General introduction

The incidence of esophageal cancer is substantially rising and is becoming an increasing health problem worldwide. This rising incidence is mainly determined by an increased incidence of adenocarcinoma, especially among Caucasian males. In the Netherlands, the incidence of adenocarcinoma (AC) has doubled in the last twenty years[1] and the current incidence (2010) is approximately 10.8 per 100.000 inhabitants[2], while the incidence of squamous cell carcinoma (SCC) remained more or less stable.
Although esophageal cancer is considered relatively uncommon, it is the seventh most common cause of cancer-related death worldwide [2,3,4]. The poor prognosis of patients with esophageal cancer can partly be explained by the insidious onset and usually late presentation of symptoms. Therefore, esophageal cancer is generally diagnosed at an advanced stage when many patients are already beyond cure.

Treatment

For a long period, surgery has been the primary treatment modality for patients with non-metastatic esophageal cancer in the mid or lower esophagus. Despite improvements obtained in diagnostic procedures, overall survival (OS) after surgery alone remained rather poor, with 5-year OS rates of approximately 35% [5,6]. Only moderate gain has been reached by the transthoracic surgical approach with en-bloc nodal dissection as standard procedure [7,8].
More recently, major efforts have been made to improve locoregional tumour control and survival by exploring new and emerging treatment strategies [9]. At present, curative intended chemoradiotherapy has gained general acceptance and plays an important role in the neo-adjuvant setting and as definitive treatment.

The role of neo-adjuvant chemoradiotherapy (neo-CRT) has been debated for several decades, because of conflicting results. However, meta-analyses suggested a survival benefit after neo-CRT when followed by surgery [10-13]. Gebski et al [12] found a hazard ratio (HR) for all-cause mortality of 0.81 (95% CI 0.70-0.93; p=0.002) in favour of neo-CRT, corresponding to a 13% absolute difference in OS at 2 years. The results were similar for the different histological tumour types; the HR for SCC was 0.84 (95% CI 0.71-0.99; p=0.04) and 0.75 (95% CI 0.59-0.95; p=0.02) for AC. Kaklamanos et al [13] found a 6.4% (95% CI -1.2%–14.0%) gain in 2-year OS which was not statistically significant. This could be explained by the 3.4% (95% CI 0.1%-7.3%) increase in treatment-related mortality found after neo-CRT followed by surgery as compared to surgery alone.
Recently, the CROSS trial, a multicenter randomised trial performed in the Netherlands showed a significant improvement in OS (HR 0.66, 95% CI 0.50-0.87) and disease free survival (DFS) (HR 0.50, 95% CI 0.36-0.69) among patients who received neo-CRT followed by surgery, as compared to those treated with surgery alone. The median OS was 49.4 months in the neo-CRT group versus 24.0 months in the surgery-alone group. Postoperative complications were similar as well as in-hospital mortality rates which was 4% in both arms.
At present, based on these results, neo-CRT has become the standard of care for operable patients with non-metastatic esophageal cancer in the mid or lower esophagus.

For patients who are not eligible for surgery, curative chemoradiotherapy (CRT) is a good alternative and is considered to be superior to radiotherapy alone (RT). This has been demonstrated in RTOG 85-01 trial [14], in which patients were randomly assigned to receive CRT (50 Gy in 25 fractions with concurrent cisplatin/ 5FU) or RT (64 Gy in 32 fractions). The authors found fewer patients with persistent residual tumours (23% vs. 37%) and showed significant improvement of the OS in favour of CRT. The 5-year OS rate among patients treated with CRT was 26% (95% CI 15%-37%) compared to 0% after RT, with a median survival of 14.1 vs. 9.3 months.
These results were confirmed by a Cochrane meta-analysis, which analysed 11 randomised controlled trials that compared concurrent CRT to RT alone [15]. Concurrent CRT resulted in less local recurrences (OR 0.60, 95% CI 0.39-0.92), and better OS (HR 0.73, 95% CI 0.64-0.84) and DFS (HR 0.56, 95% CI 0.40-0.78). However, CRT lead to a significant increase in acute grade 3 and 4 toxicities, mainly hematologic, and should therefore only be applied to patients who are in good general condition.
Recently, a retrospective study was performed in the North East of the Netherlands, analysing the treatment outcome after CRT or RT which showed similar results [16]. The DFS was significantly higher in de CRT (n=110) group as compared to the RT (n=177) group (26 vs. 17% at 2 year), which was mainly explained by an improvement of locoregional control (LRC) (46% vs. 24% at 2 year). Interestingly, the authors also demonstrated more favourable LRC rates (17% vs. 7% at 5 year) for patients with SCC as compared to AC, which translated into better DFS and OS; 24% vs. 10% and 29 vs. 17% at 2 year for patients with SCC vs. AC.

For patients with irresectable tumours, concurrent CRT is also considered a curative option [17,18]. However, studies concerning CRT for T4b-tumours are limited. In a randomised trial, Kumar et al [19] showed a significant survival benefit in favour of CRT compared to RT in patients with irresectable tumours (HR 0.65, 95% CI 0.44-0.98, p=0.04). The 1, 2 and 5 year OS rates were 32.3%, 22.8% and 13.7% for the RT group vs. 57.6%, 38.9% and 24.8% for CRT groups. Both RT and CRT were associated with manageable acute and late morbidity, such as ulcers (5% vs. 15%) and strictures (13% vs. 28%).

For some patients, CRT is contra-indicated due to co-morbid diseases and/or poor general condition. In these cases, RT can still be applied with curative intent. In stage I tumours, a numbers of authors reported excellent results after RT, with OS rates varying from 36 to 84% at 5 year [20,21,22,23,24,25]. However, for the more advanced tumours (stage II - IV], results are generally worse with OS rates varying from 0 to 20% at 5 years after RT [26,27,28].
In a retrospective study at our institute, we investigated treatment outcome among patients with inoperable or irresectable esophageal carcinoma treated with curatively intended external radiotherapy combined with intraluminal brachytherapy, between 1998 and 2008 [29]. The OS rates at 1, 2 and 5 years were 57, 34 and 11%, respectively, with a median OS of 15 months. However, severe toxicity, including ulceration, stricture, radiation pneumonitis, perforation, esophageal-pleural-tracheal fistula and acute esophageal bleeding, was observed in a substantial part of the patients (16%). Therefore, we recommended that the addition of brachytherapy (n=62), with consequently high surface doses, should be limited to well-selected patients.

Tumour recurrences

Despite the current improvements in the treatment of esophageal cancer, locoregional recurrence remains the predominant pattern of failure. Button et al [30] evaluated the patterns of recurrence after CRT and demonstrated that most recurrences were locoregional recurrences (65%), located within the PTV. Seventy-one percent of these patients experienced relapse within the PTV margin after evidence of initial response to CRT. These results were similar to the RTOG 85-01 trial [14], in which most failures were also locoregional recurrences. However, recurrences were more common in the group receiving RT (53%), as compared to the group receiving CRT (36%).
After neo-CRT followed by surgical resection, distant metastases were the most occurring sites of failure. However, in 22% of the patients with recurrent disease, the first site of recurrence was still locoregional. Furthermore, local tumour response to neo-CRT at pathologic evaluation was significantly associated with disease recurrence [31]. Patients with a complete tumour response had a lower incidence of locoregional recurrences and distant metastases manifested later, as compared to metastases among partial or non-responders.
Locoregional recurrences reflect incomplete response to cytotoxic treatment, which can be caused by an insufficient radiation dose or by resistance of the tumour to radiotherapy and/or cytotoxic agents. So far, in esophageal cancer, no dose-effect relationship could be demonstrated in the only randomised study that investigated the possibility of dose escalation [14].
Differences in the biological behaviour and/or sensitivity of the tumour to (chemo)radiation are demonstrated by the difference in tumour response to neo-CRT. After a radiation dose of 41.4 Gy, tumour response varied from the absence of viable tumour cells to a complete lack of tumour regression with local tumour progression.
Insufficient response of the tumour to the chemoradiotherapy, and/or consequently locoregional tumour residue or recurrence, can also be caused by inadequate irradiation of the esophageal tumour. Accurate identification and delineation of the gross tumour volume (GTV) is the basis of adequate irradiation. However, tumour delineation is one of the difficulties in the radiotherapy of esophageal cancer, which is shown by the rather large intra- and interobserver variability [32,33] among radiation oncologists regarding the delineation of the GTV. Consequently, it might be important to improve the identification and delineation of the actual GTV in order to increase treatment outcome.

Target volume delineation

Currently, computer tomography (CT) is the reference imaging modality for delineation of the GTV for radiotherapy of esophageal cancer, integrated with information derived from other diagnostic modalities, such as endoscopic ultrasound (EUS). However, the discriminative value of CT is generally poor, which may hamper the identification of the GTV. Furthermore, it remains difficult to relate the endoscopic (ultrasound) information to the CT images.
Recent studies speculate about the incorporation of metabolic data from 18F- Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scans to improve the accuracy of tumour delineation by identifying a metabolic tumour volume. FDG-PET already showed to be very useful in the staging process of esophageal tumours [34], in particular with regard to the detection of distant metastases and nodal staging, especially for non adjacent lymph nodes. Furthermore, integrated FDG-PET/CT has a higher sensitivity, specificity and accuracy for the detection of pathologic lymph nodes as compared to CT or FDG-PET alone [35,36].

So far, it remains difficult to determine the exact value of FDG-PET in the delineation of the primary GTV in addition to the current standard, i.e. planning-CT scan in which other diagnostic information is taken into account.

Therefore, the main and general objective of this thesis was to determine the value of the (PET/) CT-scan for radiotherapy of esophageal cancer and its potential to improve the treatment outcome, in terms of efficacy and toxicity.

Outline of the thesis

In **Chapter 2**, a review of literature is provided regarding the use of FDG-PET/CT in the tumour delineation process for radiotherapy in comparison with CT alone among patients with esophageal cancer. More specifically, this review focuses on: 1) changes in target volume delineation; 2) the pathologic validation with regard to GTV delineation; 3) consequences for the inter- and intra-observer variability in target volume delineation; 4) consequences for radiotherapy treatment planning with regard to either target volumes or organs at risk, and finally; 5) the validation of FDG-PET/CT based tumour delineation regarding treatment outcome. Most of the subjects of this review will also be discussed in the following chapters of the thesis.

The use of FDG-PET(/CT) for radiotherapy might reveal new findings, which will influence the treatment (intent). In **chapter 3** we report on the consequences of FDG-PET/CT specifically made for radiotherapy treatment planning as compared to the diagnostic FDG-PET(/CT). Furthermore, we tested the hypothesis that the time interval between the diagnostic and therapeutic FDG-PET/CT-scan performed for radiotherapy treatment planning was associated with tumour progression in terms of increased SUV-values, tumour length, newly diagnosed pathologic lymph nodes and distant metastases.

The aim of the study described in **chapter 4** was to determine the actual changes in tumour delineation and subsequent target volumes due to the additional use of PET/CT information, compared to the use of CT alone. Secondly, we investigated the possible consequences of target volume modifications with regard to co-irradiation of the normal tissues and the subsequent changes in NTCP-values based on NTCP-models.
The adjustments to the target volume based on the additional use of FDG-PET/CT may result in a reduction as well as an increase of the GTV, CTV and PTV. Subsequently, these changes may result in inadequate dose coverage of the PTV, and in some cases even the CTV and GTV. Furthermore, it also resulted in clinically relevant changes in dose distributions to normal tissues [9,12,15]. However, the question that remains to be answered is if these changes are justified. More specifically, the question is as to whether the FDG-PET/CT-based changes correspond better with the actual pathological tumour extension.

Chapter 5 describes a new method, which was developed to reconstruct radiotherapy target volumes intraoperatively on the esophageal resection specimen to provide information regarding the

exact location of pathologic tumour in relation to the GTV and CTV with the aim to improve the pathologic examination. Currently, the reference imaging modality for delineation of the GTV for radiotherapy of esophageal cancer is CT, integrated with information derived from other diagnostic modalities. Therefore, we used the demarcation method to analyse the accuracy of the current GTV and CTV delineation for radiotherapy, based on CT, at pathologic examination after neo-adjuvant chemoradiotherapy.

Finally, the results of the so-called RESPECT study are described in **chapter 6.** In the RESPECT-trial, the value of PET/CT for the radiotherapy planning with regard to outcome was evaluated. The aim of this prospective multicenter study was to determine the proportion of patients with a locoregional recurrence after CT-based (chemo)radiotherapy that could have been prevented if PET/CT-based treatment planning was used instead of CT-based treatment planning alone.

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Chapter 2

A systematic review on the role of FDG-PET/CT in tumour delineation and radiotherapy planning in patients with esophageal cancer

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Abstract

Purpose

FDG-PET/CT has proven to be useful in the staging process of esophageal tumours. This review analysed the role of FDG-PET/CT in tumour delineation and radiotherapy planning in comparison with CT alone among patients with esophageal cancer. Thereby we focused on the detection of the primary tumour and lymph nodes by FDG-PET/CT, changes in target volume (TV) delineation based on FDG-PET/CT and its validity, changes in inter- and intra-observer variability in TV delineation, consequences for radiotherapy treatment planning with regard to either target volumes or organs at risk and finally on the validation of FDG-PET/CT-based TV's in terms of treatment outcome.

Methods

A literature search was performed in MEDLINE and Cochrane library databases for studies concerning the current value of FDG-PET/CT in tumour detection and delineation and radiotherapy-planning procedures among patients with esophageal cancer. Both prospective and retrospective studies were included.

Results

Fifty publications met the eligibility criteria, of which 19 were review papers and one was a case report. The remaining 30 publications reported on the results of original studies.
FDG-PET was able to identify most primary tumours, with a sensitivity and specificity for the detection of metastatic lymph nodes of 30-93% and 79-100%. The use of FDG-PET/CT resulted in changes of target volumes, and consequently in changes in treatment planning. However, evidence supporting the validity of the use of FDG-PET/CT in the tumour delineation process is very limited. Only three studies reported a significant positive correlation between FDG-PET-based tumour lengths and pathological findings. There were two studies that tested the influence of FDG-PET/CT to the inter- and intra-observer variability. One of them found a significant decrease in inter- and intra-observer variability, while the others did not. Furthermore, there are no studies demonstrating the use of PET/CT in terms of improved locoregional control or survival.

Conclusion

Since the literature is very limited standard implementation of FDG-PET/CT into the tumour delineation process for radiation treatment seems unjustified and needs further clinical validation first.

Introduction

Esophageal cancer is the seventh leading cause of cancer-related death worldwide. In the last two decades, major efforts have been made to improve locoregional tumour control and survival by exploring new and emerging treatment strategies [34]. Treatment of first choice remains surgical resection. However, combined chemo-radiotherapy is increasingly applied, either as definitive therapy or in the neo-adjuvant setting prior to a curatively intended surgical resection [35].
Accurate delineation and subsequent irradiation of the gross tumour volume (GTV) is a prerequisite for a successful treatment of esophageal cancer with radiotherapy. This is particularly true for the use of modern radiation (delivery) techniques, such as intensity-modulated radiotherapy (IMRT) or proton irradiation, enabling a high level of radiation dose conformity and thus a higher risk of a lower dose than desired to the GTV in case of inadequate delineation.
Adequate tumour delineation for esophageal carcinoma is often hampered by the poor discriminative value of currently used imaging modalities, in particular computed tomography (CT), and the inability to relate endoscopic (ultrasound) information to CT images.
Addition of positron emission tomography (PET) information may improve the accuracy in the delineation process. 18F-Fluoro-2-deoxy-D-glucose (FDG) PET provides additional information on the metabolic activity, i.e., glucose utilization of the tumour. Tumour visualisation and thus tumour delineation may improve by adding the functional information of FDG-PET to the anatomical information of CT. Incorporation of FDG-PET, referred to as FDG-PET/CT, in the delineation process seems to improve tumour coverage and seems to spare normal tissues in various tumour types, in particular in non-small cell lung cancer (NSCLC) [8,38].
Several studies showed that FDG-PET has been very useful in the staging process of esophageal tumours [37]. FDG-PET is superior in detecting distant metastases and seems to improve nodal staging as well, especially for non-adjacent lymph nodes. Furthermore, FDG-PET can be an effective tool for restaging esophageal malignancies after (neo-adjuvant) treatment [41,42].

This review focuses on the additional value of FDG-PET/CT in the tumour delineation process in comparison with CT alone among patients with esophageal cancer. More specifically, the purposes of this review were: 1) to analyse the ability of FDG-PET(/CT) to detect the primary tumour and/or pathologic lymph nodes; 2) to determine if, and to what extent, the addition of FDG-PET changes target volume delineation; 3) to assess the validity of FDG-PET/CT with regard to GTV delineation; 4) to assess if the addition of FDG-PET improves inter-observer and intra-observer variability in target volume delineation; 5) to determine the consequences for radiotherapy treatment planning with regard to either target volumes or organs at risk, and finally; 6) to assess the validation of FDG-PET/CT-based tumour delineation on treatment outcome.

Methods

Search strategy and selection criteria

A literature search was performed to retrieve articles concerning the detection of esophageal tumours and pathologic lymph nodes using the following keywords:
- synonyms for esophageal cancer
- synonyms for PET/CT
- synonyms for detection or synonyms for visualisation

These keywords were combined using 'AND'. The search was carried out in MEDLINE and Cochrane Library. In addition, references lists of papers were screened in order to retrieve additional relevant papers.
A similar search was performed for studies concerning the current value of FDG-PET/CT in tumour delineation and radiotherapy-planning procedures among patients with esophageal cancer. The following keywords were used:
- synonyms for esophageal cancer
- synonyms for PET/CT
- synonyms for tumour delineation or synonyms for radiotherapy.

To be selected for this review, studies had to fulfil the following eligibility criteria: 1) squamous cell or adeno-carcinoma of the esophagus or the gastro-esophageal junction; 2) eligible for curative treatment; 3) use FDG-PET in conjunction with CT; 4) FDG used as a tracer in PET.
Both prospective and retrospective studies were included. Studies only available in abstract form were excluded from this review. Articles in languages other than English were excluded as well.
The selection process of both search strategies together is summarized in Figure 1.

Results

Literature search

Using the search strategies described, we were able to identify 114 publications. However, only 50 publications met the eligibility criteria, of which 19 were review papers. In these papers, the use of FDG-PET/CT in tumour staging process or in radiotherapy in general was reviewed. One publication reported on a single case.
In the 30 studies, a total number of 1222 patients were included. Table 1 summarizes the original studies concerning the detection of esophageal cancer. Table 2 summarizes the original studies concerning the tumour delineation process.

There were no studies available that provided level I or II evidence for the benefit of FDG-PET/CT vs. FDG-PET in the tumour delineation process.

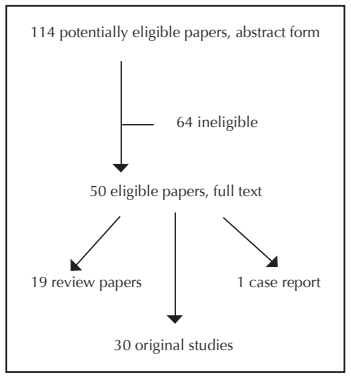

Figure 1.
The study selection process, both search trategies combined

For reasons of clarity, the abbreviation FDG-PET/CT refers to both software fusion-based PET added to CT and PET/CT images acquired with an integrated PET/CT scanner.

FDG-avidity of the primary tumour

Several studies have investigated the detection of the primary tumour by FDG-PET. Increased uptake of FDG was seen in 68-100% of the esophageal tumours *(Table 1)*. Undetected tumours are mostly stages T1 and T2 tumours. Especially T1a tumours, remaining within the submucosa, are difficult to detect by FDG-PET [3,17].

Kato et al. [16] found a significant relationship between the intensity of the primary tumour FDG-uptake, expressed as SUV, and the depth of the tumour invasion. However, Flamen et al. [10] found no correlation between SUV and pT-stage.

Detection of locoregional metastatic lymph nodes

The ability of different imaging modalities to identify metastatic lymph nodes has been widely investigated. However, the literature is not very consistent when it comes to the ability of CT, FDG-PET or FDG-PET/CT to identify pathologic locoregional lymph nodes. The sensitivity of CT and FDG-PET varied widely; 11-93% vs. 30-93%. There was less variation regarding the specificity of CT and FDG-PET; 71-100% vs. 79-100%, respectively *(Table 1)*.

Recently, van Vliet et al. [36] published a meta-analysis on staging investigations for esophageal cancer. In this analysis, they found a pooled sensitivity for the detection of regional lymph node metastases by CT and FDG-PET of 0.50 (95% CI 0.41-0.60) and 0.57 (95% CI 0.43-0.70), respectively. The pooled specificity of CT was 0.83 (95% CI 0.77-0.89) vs. 0.85 (95% CI 0.76-0.95) for FDG-PET. The pooled sensitivity of EUS was significantly higher than both CT and FDG-PET, but showed a similar diagnostic performance.

Four other studies evaluated the use of FDG-PET/CT for the detection of locoregional lymph node metastases. Yuan et al [46] found a significant improvement of the sensitivity (93%), accuracy (92%) and negative predictive value (98%) in the assessment of locoregional lymph nodes for esophageal cancer by the use of integrated FDG-PET/CT, compared to the use of FDG-PET alone. Sihvo et al [33] also compared the ability of CT and FDG-PET to identify metastatic lymph nodes to integrated FDG-PET/CT. In this study, the sensitivity was 42%, 35% and 50% for CT, FDG-PET and integrated FDG-PET/CT, respectively. Although FDG-PET/CT improved the sensitivity, it remained significantly lower than that for EUS (p=0.001). Both FDG-PET and FDG-PET/CT had a specificity of 100%, while CT showed a specificity of 82%. Schreurs et al. [32] compared the detection of locoregional lymph node metastases on fused FDG-PET/CT to the detection of CT and FDG-PET side by side in 18 patients. They found that the use of fused FDG-PET/CT images improved the sensitivity (87% vs. 80%) and the specificity (87% vs. 83%). Kato et al. [15] also evaluated the additional value of PET/CT over PET for the detection of a metastatic lymph node group. This study demonstrated that PET/CT had a higher sensitivity in lower thoracic regions than both PET and CT (p<0.05).

Table 1
Overview eligible original studies concerning the use of PET/CT for the detection of esophageal cancer

Author	*Primary tumour*				*Lymph node metastases*					*Remarks*
	N	*Detection rate on CT (%)*	*Detection rate on PET (%)*	*Sensitivity of PET for LN (%)*	*Specivicity of PET for LN (%)*	*Sensitivity of CT for LN (%)*	*Specivicity of CT for LN (%)*	*Sensitivity of PET/CT for LN (%)*	*Specivicity of PET/CT for LN (%)*	
Pfau et al [28]	44	80	92	-	-	-	-	-	-	4 of 5 undetected were T1-T2
Rankin et al [29]	19	95	100	-	-	-	-	-	-	
Salahudeen et al [30]	25	-	100	-	-	-	-	-	-	
Wren et al [43]	21	-	-	71	86	57	71	-	-	
Kato et al [17]	149		80	32	99	23	97	-	-	Most undetected were T1
Kato et al [16]	32	-	78	78	93	61	71	-	-	The not visible tumours were T1
Flamen et al [10]	39		95	33	89	0	100	-	-	All false negative on PET were T1
Himeno et al [13]	22	-	68	42	100	38	96	-	-	All undetected tumours were T1
Block et al [3]	58	-	94	52	79	29	79	-	-	2 undetected lesions were T1a
Kato et al [15]	167	-	74	33	99	27	98	-	-	Most undetected were T1-2
Kim et al [18]	52	98	94	52	94	42	97	-	-	False negative on PET was T1 tumour
Meltzer et al [23]	47	97	87	35-41	90	63-87	14-43	-	-	
Yoon et al [44]	79	82	92	30	90	11	95	-	-	All undetected tumours were T1
Kole et al [19]	26	81	96	92	88	38	100	-	-	
Sihvo et al [33]	55	69	82	35	100	42	82	50	100	Of the false-negative 7 T1 tumours and 3 T2 tumours
Yuan et al [46]	45	-	-	82	87	-	-	94	92	
Schreurs et al [32]	85	-	-	-	-	-	-	87	87	

Target volume modifications

In nine studies, the use of FDG-PET/CT, based on either software fusion [25,26,31,40] or integrated FDG-PET/CT [9,11,14,21,39], resulted in changes of target volumes.
Gondi et al. [11] found that the addition of FDG-PET resulted in GTV reduction with more than 5% in 10 out of 16 patients (62.5%). The mean overlap between FDG-PET/CT- and CT-based GTV's was low, only 46%. The observers delineated the GTV's independently.
Moureau-Zabotto et al. [25] evaluated the impact of the addition of FDG-PET to CT on GTV and PTV delineation among 34 patients treated with 3D-conformal radiotherapy. In this study, the target volume was initially based on CT images. The corresponding FDG-PET data were used as an overlay to the CT data to define the GTV. This resulted in tumour length reduction in 12 patients (35%) and an increase in 12 patients (35%). Modifications in GTV delineation resulted in a mean reduction of the GTV of 21.3% and a mean increase of 20.0%. These changes in GTV affected the planning target volume (PTV) in 18 patients (53%).
Leong et al. [21] also evaluated the impact of FDG-PET on CT-based target volume delineation. They found an exclusion of FDG-PET-avid disease in 11 out of 16 patients (69%) when the GTV was based on CT alone, with a median exclusion of FDG-PET/CT-based GTV of 38%. In five patients (31%), the FDG-PET/CT-based GTV was located outside the CT-based PTV, with a median exclusion of 5%. Modifications based on FDG-PET/CT were mainly seen in longitudinal direction.
Vrieze et al. [40] focused on the detection of pathologic lymph node regions, instead of primary tumour extension and suggested that the GTV should not be reduced based on negative FDG-PET findings given the low sensitivity of FDG-PET in esophageal cancer. Therefore, they stated that the GTV could only be enlarged based on positive FDG-PET findings. In this study, the irradiated volume was based on conventional imaging modalities, including CT and endoscopic ultrasound (EUS). In 6 patients (20%), 8 pathologic lymph node regions were detected on FDG-PET which were not visible on conventional imaging. In three of these patients (10%) this would have led to an increase of the CTV.
In most studies visual interpretation of FDG-PET images was used for target volume delineation. Only a few studies used automatic contouring, based on certain intensity levels, such as the standard uptake value (SUV) level, a percentage of the maximal SUV or the source-to-background ratio (SBR) [20,22,47].

Pathological validation of FDG-PET findings

As described above, the addition of FDG-PET/CT resulted in changes in the delineation of target volumes in a considerable proportion of patients (20-94%). However, the question that remains to be answered is whether these changes are justified. More specifically, the question arises as to whether the FDG-PET/CT-based changes correspond better with the actual pathological tumour extension. The most ideal method to validate the additional value of FDG-PET/CT would be to compare GTV delineations based on different imaging modalities with the pathological specimens. However, accurate validation is hampered by the difficulties in obtaining pathological material and in comparing resected specimens with pre-surgical imaging. Therefore, reports on pathologic validation are limited.
Mamede et al. [22] evaluated the correlation between tumour length of esophageal carcinoma based on FDG-PET and pathological data (n=17). These tumour length measurements were taken

Table 2.
Overview eligible original studies concerning PET/CT in tumour delineation process

Author	*N*	*Fusion/ integrated*	*Contour method*	*Conclusions*
Tumour delineation and radiotherapy				
Gondi et al [11]	*16*	*Integrated*	*SBR (liver activity)/ Visual*	*Incorporation of PET led to GTV changes. is Conformality index (CI) comcommeded for more comprehensive comparison.*
Konski et al [20]	*25*	*Separately*	*≥2.5 SUV*	*The PET-tumour length was significantly longer as measured by CT scans. PET-length correlated better with endoscopy than with CT.*
Vrieze et al [40]	*30*	*Separately*	*-*	*The irradiated volume should not be reduced based on negative PET findings, because of low sensitivity. However, thanks to the high specificity it is possible to adapt the treatment volume.*
Hong et al [14]	*25*	*Integrated*	*Visual/ ≥mean activity of the liver + 2 SD*	*PET/CT appears to provide clinically meaningful data with a significant impact on target definition compared with CT alone.*
Moureau et al [25]	*34*	*Fusion*	*Visual*	*PET/CT had impact on tratment planning. Impact on treatment outcome remains to be demonstrated.*
Leong et al [21]	*16*	*Integrated*	*SBR (liver activity)/ Visual*	*PET/CT influences tumour delineation, with the potential to avoid geographic miss of tumour.*
Vesprini et al [39]	*10*	*Integrated*	*Visual*	*PET/CT decreased the inter- and intra-observer variabiliteit identification of the GTV.*
Schreurs et al [31]	*28*	*Fusion*	*SBR (liver activity)/ Visual*	*Combining FDG-PET and CT may improve target volume definition with less geographic misses, but without significant effects on inter-observer variability in esophageal cancer.*
Muijs et al [26]	*21*	*Fusion*	*SBR (liver activity)/ Visual*	*TV's based on CT might exclude PET-avid disease. Consequences are under dosing. The addition of PET in radiation planning might result in clinical important changes in NTCP.*
Comparison tumour length PET-based vs. pathology				
Mamede et al [22]	*17*	*Integrated*	*SBR (liver activity),*	*FDG-PET tumour length of untreated esophageal carcinomas different SUV-thresholds correlates well with surgical pathology results.*
Zhong et al [47]	*36*	*Integrated*	*≥2.5 SUV/ 40% SUVmax/ Visual*	*The optimal PET method to estimate the length of gross tumour varies with tumour length and SUVmax, an SUV cutoff of 2.5 seems best.*
Han et al [12]	*22*	*Integrated*	*Visual /SUV-values for autocontouring*	*A standardized uptake value cutoff of 2.5 on FDG PET/CT provided the closest estimation of GTV length*
Yu et al [45]	*16*	*Integrated*	*SBR (liver activity)/ SUV-values for autocontouring*	*The SUVbgd + 20% (SUVmax(slice) - SUVbgd) method optimally estimated gross tumor length, but only reached an unsatisfactory CI for GTV*

Abbreviations
GTV = gross target volume
SBR = Source to background ratio
SUV = standard uptake value

from fresh tissues obtained by surgical resections, without neo-adjuvant treatment. They reported a significant positive correlation between FDG-PET-based tumour lengths, estimated for different SUV-thresholds, and pathological findings. The best correlation was estimated for a SUV-threshold of 2 - standard deviations ($r = 0.74$; $p < 0.001$).
Similar results were found by Zhong et al. [47], comparing FDG-PET-based tumour lengths with pathological specimens (n=36). In this study, three different methods were used to delineate the GTV: 1) visual interpretation (LengthVis); 2) threshold at SUV 2.5 (Length2.5), and; 3) threshold at SUV at 40% of the maximum SUV (Length40). To correct for shrinkage of the surgical specimens, the pathological tumour length was obtained by measuring the tumour in situ before surgical removal. In addition, after surgical resection, the specimen was longitudinally opened and stretched to the same length as measured in vivo and pinned on a flat board. The FDG-PET-based tumour length correlated well with the pathological tumour length, for all three thresholds (Lvis: $r = 0.828$; L2.5: $r = 0.887$; L40: $r = 0.857$; $p < 0.001$). However, the tumour length at a cutoff of SUV 2.5 seemed most approximate to the pathological tumour length.
Recently, Han et al. [12] compared FLT-PET- and FDG-PET-based tumour lengths with the tumour length in the pathologic specimen of 22 patients. They found that for FDG-PET a SUV cutoff of 2.5 provided the closest estimation of GTV length.
Yu et al. [45] performed a similar study and compared FDG-PET-based tumour lengths with the length of the gross tumour region in vivo in 16 patients. They found no significant difference in absolute value between the CT-, PET- (SUVcutoff: SUVbackground + 20%) and pathology-based tumour lengths. However, regarding the spatial conformity index, the conformity index (CI) of pathology and (PETSUV+20%) was significantly superior to the CI obtained with pathology and CT. FDG-PET-based tumour lengths were also found to correlate well with EUS based tumour lengths [22] , the gold standard for clinical T-staging. Konski et al. [20] demonstrated that EUS-based measurements of tumour length closely approximated FDG-PET-based tumour measurements (n=25), using a SUV-threshold for malignancy of 2.5. The tumour length as determined by PET correlated better with endoscopy than with CT and was significantly shorter as compared to those measured by CT, regardless of the SUV. In this study, the CT-based tumour length was determined on the CT part of the integrated FDG-PET/CT scan. The CT- and FDG-PET-based tumour lengths were determined independently by two different observers.

Inter- and intra-observer variability

Another way to investigate the validity of new imaging techniques in target volume delineation is to test inter- and intra-observer variability, based on the assumption that lower inter- and intra-observer variability represents more accurate delineation.
The effect of the addition of FDG-PET/CT on intra- and inter-observer variability in target volume delineation in patients with gastro-esophageal cancer was investigated in two studies. In the study of Vesprini et al. [39], target volumes (n=10) were delineated based on CT and FDG-PET/CT in ten patients by six radiation oncologists. Combined use of FDG-PET/CT for delineation of the GTV significantly decreased both intra- and inter-observer variability. In 57% of the cases, observers felt more confident with the results of GTV contouring.
Schreurs et al. [31] also evaluated the effect of the additional use of FDG-PET on the inter-observer variability in tumour volume definition. For 28 patients the TVs were delineated by 3 observers. In this study, they found no significant effect on the inter-observer variability.
For further reduction of the inter-observer variability, various automatic or semi-automatic contouring methods were proposed. However, usable SUV-thresholds, in order to distinguish pathologic tissue from normal tissue, could not be determined [14,47].

Consequences for radiotherapy planning and normal tissues

In only three studies, the consequences of FDG-PET-based target volume modifications on radiation dose distributions to target volumes and organs at risk were analysed.
Leong et al. [21] reported 6 out of 16 patients (38%) with inadequate dose coverage (<95% receiving at least 95% of the prescribed dose) of the FDG-PET/CT-based PTVs, if the treatment plans were based on CT information alone. In these patients the percentage of the FDG-PET/CT-based PTV, receiving at least 95% of the prescribed dose, ranged from 63% to 92%. They found on average no clinically significant differences in radiation doses to the lungs, spinal cord and liver between the CT and FDG-PET/CT-based treatment plans.
In contrast, Moureau-Zabotto et al. [25] found that FDG-PET/CT-based changes in treatment plans resulted in changes in dose distribution to normal tissues in virtually all cases. The percentage of total lung volume receiving >20 Gy (V20) was reduced after co-registration with FDG-PET-CT fusion in 12 patients with a mean reduction of 29.1% ± 5% (range 5-69.8%). The V20 was increased in 13 patients, with a mean increase of 25.3% ± 4% (range 3.4-47%). As a result of the FDG-PET/CT-fusion, the percentage of total heart volume receiving >36 Gy increased in 11 patients (median 15.4%; range 0.3-103.3%), and decreased in 12 patients (median 21.8%; range 3.5-100%).
Recently, Muijs et al. [26] evaluated the consequences of the additional use of FDG-PET for radiotherapy dose distribution for esophageal cancer. They demonstrated that the use of CT-based treatment plans may result in geographic mismatches and under dosing of PET-avid disease. Furthermore, they showed that the addition of PET led to significant changes in dose distributions to heart and lungs.

Validation of the addition of PET by evaluating treatment outcome parameters

The main clinical advantage of improved target volume delineation would be that the percentage of locoregional recurrences outside the delineated CTV reduces, eventually resulting in improved locoregional control and subsequent overall survival. Therefore, analysis of the localisation of locoregional recurrences reference to the delineated target volumes and ultimate radiation dose distributions, is of major importance. So far, there are no data available on the evaluation of the use of FDG-PET/CT in the delineation process for esophageal cancer by evaluating treatment outcome parameters, as locoregional tumour control and survival.

Discussion

The results of this review showed that FDG-PET is able to detect most esophageal tumours. Furthermore, FDG-PET/CT seems useful for the detection of locoregional lymph nodes. The sensitivity and specificity of FDG-PET/CT was better than of CT or PET alone.

We also showed that the use of FDG-PET/CT in target volume delineation results in both reductions and increases of the GTV, CTV and PTV in a considerable proportion of patients *(Table 2)*. Subsequently, these changes may result in both inadequate dose coverage of the PTV and, in some cases, even of the CTV and GTV, and in clinically relevant changes in dose distributions to normal tissues [11,21,25].

There is no doubt that GTV delineation is affected by the diagnostic information used. In clinical practice, all available information, such as physical examination, endoscopy reports, EUS and diagnostic contrast-enhanced CT scans, is applied for delineation of the target volume. In most of the reviewed studies, this information was available for both CT- and FDG-PET/CT-based GTV delineation [11,14,21,39]. However, in other studies, this information, which we consider essential, was disregarded and the delineation of the GTVs was exclusively based on CT- or FDG-PET/CT-information [20,25,40]. This implies that the results of these latter studies may be less representative for use in clinical practice.

The clinical use of FDG-PET/CT may also be hampered by some technical issues. For FDG-PET/CT-based GTVs, two types of contouring methods were used, including visual interpretation (with or without source-to-background correction), or semi-automatic contouring based on different SUV-thresholds. However, these methods are neither objective nor uniform. For visual interpretation, which is the main tool used in clinical practice and used in most of the reviewed studies, image representation can be controlled by changing window-widths and window-levels, which is highly observer dependent, and may result in significant differences in visible tumour volumes. The SUV is, on the other hand, a semi-quantitative parameter for evaluation of the FDG-uptake in tumours. However, many factors, such as patient preparation procedures, scan acquisition, image reconstruction and data analysis settings, affect the outcome of the SUV [5,6]. Even though these factors have small effects individually, accumulation of many of these factors can result in considerable differences in SUV outcome [4]. For this reason, recommendations for standardisation and quantification of FDG-PET studies have been made by Boellaard et al. [4,6]. In the currently available literature, SUV-thresholds to distinguish pathological tissues from normal tissues could not be determined for esophageal cancer. For other tumours, for example NSCLC, estimation of a reliable automatic contouring method remains difficult as well [27].

The way in which additional FDG-PET information is incorporated in the tumour delineation process, will also influence the changes in target volume. In the reviewed studies, two main methods were used: 1) *(Table3)* delineation of the CT-based GTV and modification of this target volume based on the additional PET information; 2) independent delineation of CT- and PET/CT-GTVs. Using the latter method, target volume modifications could partially be explained by intra-observer variability. On the other hand, observers using the first method are more prejudiced by their CT findings. The lack of uniformity in the methods, by which FDG-PET information has been used to contour the GTV, illustrates the difficulty to incorporate FDG-PET information properly into the tumour delineation process.

Another shortcoming is the use of co-registered FDG-PET/CT images for tumour delineation. Software-based co-registration seems less accurate, considering the errors associated with this type of image co-registration. To minimize these errors, all FDG-PET- and CT-scans, used in the reviewed studies, were made in treatment position.

Despite the non-standardised way of the use of FDG-PET for tumour delineation, which might result in an over or under estimation of the GTV modifications, these changes may have an effect

Table 3.
Changes in target volume by addition of PET(/CT) in tumour delineation process

Authors	TV changes					TV of interest	PET interpretation	Contour method	Fusion/ intergrated PET/CT
	overall proportion	increase proportion	increase size	decrease proportion	decrease size				
Vrieze, et al [40]	20 (6/30)	10 (3/30)	not defined	10 (3/30)	not defined	CTV	not described	I	Fusion
Gondi, et al [11]	94 (15/16)	31 (5/16)	not defined	62.5 (10/16)	> 5%	GTV	SBR (liver activity)/ Visual	II	Integrated
Hong, et al [14]	84 (21/25)	-	Δ sup/ inf extent > 1cm	-	Δ sup/ inf extent > 1cm	GTV	Visual/ ≥mean liver activity +2SD	II	Integrated
Moureau,	56 (19/34)	21 (7/34)	20% ±8.7	35 (12/34)	21.3% ±4.7	GTV	Visual	I	Fusion
et al [25]	53 (18/34)	21 (7/34)	22% ±11	33 (11/34)	9.8% ±7.4	PTV2			
Leong, et al [21]	>69 (11/16)	-	not defined	-	not defined	GTV	SBR (liver activity)/ Visual	II	Integrated
Muijs, et al [26]	76 (16/21)	24 (5/21)	> 3 mm	52 (11/21)	> 3 mm	GTV	SBR (liver activity)/ Visual	II	Integrated

Abbreviations
TV = target volume
GTV = gross tumour volume
CTV = clinical target volume
PTV = planning target volume
SBR = source to background ratio

Contour method:
I; CT-delineations were modified based on PET/CT images
II; CT- and PET/CT-GTV's were delineated

on treatment outcome in terms of both the locoregional tumour control and the incidence of radiation-induced side effects.
It is clear that the main advantage of FDG-PET/CT in the management of esophageal cancer is the higher validity with regard to lymph node status and the detection of occult metastases. Integrated FDG-PET/CT has overall a higher sensitivity, specificity and accuracy compared to CT or FDG-PET alone [1,2]. In this respect, the addition of FDG-PET/CT will certainly have an impact on treatment strategies, e.g., in deciding about the intent of treatment (e.g., in case of detection of distant metastases) and in assessing radiotherapy target volume definition (e.g., in case of detection of pathological lymph nodes). However, one of the questions that still remains to be answered is whether the FDG-PET/CT-based GTV corresponds better with the pathological tumour than CT-based GTV.
FDG-PET-based tumour lengths correlate well with tumour lengths as assessed by pathologic examination or EUS. However, tumour length correlation does not automatically mean correct tumour imaging in terms of tumour localisation. It is not unlikely that low FDG-uptake in pathologic areas on one side is compensated on the other side by, for example, false-positive uptake in areas of inflammation. It is well known that areas surrounding the tumour can become inflammatory, and FDG-PET frequently shows false-positive uptake in areas of inflammation [24]. Therefore, the available data published so far do not provide sufficient evidence that the FDG-PET/CT-based changes in the GTV represent better pathological tumour coverage than CT-based GTV delineation.
Ultimately, the use of FDG-PET/CT for GTV delineation for radiotherapy treatment-planning purposes should be validated based on treatment outcome parameters, such as locoregional control and survival. However, as to our knowledge, no such studies, evaluating the use of FDG-PET/CT in the radiotherapy process for esophageal cancer, have been carried out.
We were able to retrieve only one study in which recurrence analysis was performed after irradiation with the use of CT and EUS-based 3D-conformal radiation treatment plans [7]. In this study, 55 out of 85 relapses (65%) were local recurrences that were located within the PTV. Only 3 patients (4%) developed regional recurrences outside the PTV, which theoretically could have been prevented by improved GTV delineation, e.g., by the additional use of PET. These results suggest that the target volumes were adequately defined based on CT/EUS in the fast majority of cases. In this study, localisations of the relapses were considered in relation to the PTV (within or outside the PTV). However, margins to the PTV are defined to compensate for set up uncertainties to assure adequate dose coverage of the clinical target volume (CTV). Variations in daily positioning of the patient are unavoidable, despite measures to ensure a high reproducibility and accuracy. Furthermore, intrafractional tumour motion within the patient occurs due to cardiac action and respiration. Therefore, the actual dose delivered to the PTV itself will be less than the prescribed dose, depending on the size and type (random or systematic) of the set up deviations. Based on the results of this study we cannot conclude that CT-based treatment plans were adequate or not.
The increasing use of more advanced and emerging radiation delivery techniques, generally resulting in higher conformality of the required radiation dose to the target volume, requires more accurate imaging tools for accurate delineation of the GTV in order to prevent geographical misses. In this respect, additional tools to identify pathological tumour are of great importance. However, the current review shows that the available data do not provide sufficient evidence that the integration of FDG-PET/CT will necessarily improve the accuracy of GTV delineation and, eventually, subsequent locoregional tumour control.
Currently, a prospective multicenter study (RESPECT-study) is running in the Netherlands aiming to

determine the proportion of patients with a locoregional recurrence after CT-based radiotherapy or chemoradiation that can be considered preventable when PET/CT-based treatment planning was used instead of CT-based treatment planning alone. In this study, pre-treatment FDG-PET/CTs are made for planning as well as CTs during follow up. In case of tumour recurrence, FDG-PET/CT is made to localise the recurrence in relation to the CT- and PET/CT-based CTVs.

Conclusion

FDG-PET is able to detect most esophageal tumours and seems useful for the detection of locoregional lymph nodes. However, evidence supporting the use of FDG-PET/CT in the tumour delineation process and radiotherapy planning is very limited. Tumour length comparison as pathological validation has important shortcomings and seems therefore unreliable. Furthermore, there are no studies demonstrating the use of PET/CT in terms of improved locoregional control or survival. Standard implementation of FDG-PET/CT into the tumour delineation process for radiation treatment seems therefore unjustified at this moment and needs further clinical validation first. This is now subject of a prospective multicenter study in the Netherlands.

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Chapter 3

Esophageal tumour progression between the diagnostic ^{18}F-FDG-PET and the ^{18}F-FDG-PET for radiotherapy treatment planning

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Abstract

Background and purpose

To test whether the interval between diagnostic and therapeutic FDG-PET-scanning is associated with early tumour progression.

Material and methods

All patients (n=45) underwent two PET scans, one for staging ('baseline PET') using an HR+ positron camera or PET/CT-scanner and one for radiotherapy planning ('therapeutic PET') using a PET/CT-scanner. All images were reviewed in random order by an experienced nuclear physician. If there were any discrepancies, the images were also compared directly. SUVmax, tumour length, lymph node metastases and distant metastases were assessed.

Results

The median time between the PET scans was 22 days (range: 8-49). The SUVmax increased (>10%) (19 patients, 42%) or decreased (11 patients, 24%). Fourteen patients (31%) showed tumour length progression (>1 cm). TNM progression was found in 12 patients (27%), with newly detected mediastinal nodes (N) in 8 patients (18%) and newly detected distant metastases (M) in 6 patients (13%). No significant prognostic factors were found. However, a trend was noted towards TNM progression for the type of PET-camera (p=0.05, 95% CI 0.01-0.66) and for the interval between the PET scans (p=0.09, 95% CI -0.9-12.5).

Conclusion

This study suggests rapid esophageal tumour progression. Therefore, the interval between relevant imaging and start of the radiotherapy should be minimized. Furthermore, 'state of the art' PET scanners should be used.

Introduction

In the last two decades, major efforts have been made to improve survival by exploring new and emerging treatment strategies in esophageal carcinoma [1,2]. Neo-adjuvant chemoradiotherapy (CRT) followed by surgery has been shown to significantly improve the survival rates as compared to surgery alone [3]. However, despite the introduction of these multimodality treatment strategies into routine clinical practice, treatment failure, including both loco-regional recurrences and distant metastases are frequently observed, even after complete local tumour response.
In esophageal cancer, TNM-stage, standardized uptake value (SUV) and tumour length are important prognostic factors for overall survival. More specifically, small sized tumours with low SUV values without lymph node metastases are associated with better overall survival. Although tumour length is not included in the current TNM staging system, the association between tumour length and outcome in terms of loco-regional tumour control and overall survival has been well recognized [4,5].
Tumour progression can be identified by an increased SUV on FDG-PET. A high SUV is commonly associated with tumour aggressiveness as expressed by an increased tumour length and nodal involvement [6]. As tumour progression growth continues during both the diagnostic and the preparation phase for irradiation, it is worthwhile to examine the clinical impact of tumour progression in this time interval. The routine introduction of an increased number of sophisticated diagnostic procedures to improve staging and accuracy of target definition and delineation for radiotherapy has certainly led to an improvement of quality, but often at the expense of increased time required to perform all these procedures. Moureau-Zabotto et al. [7] found new distant metastases on FDG-PET/CT-scans made for radiotherapy treatment planning in 6% of the patients which consequently lead to a change of treatment strategy from curative to palliative intent.
Therefore, in the current study, we tested the hypothesis that the time interval between the diagnostic and therapeutic FDG-PET-scan performed for radiotherapy treatment planning is associated with tumour progression in terms of increased SUV-values and tumour lengths, newly diagnosed pathologic lymph nodes and distant metastases.

Methods and materials

Patients

The study population was composed of patients who met the following eligibility criteria: histologically confirmed esophageal cancer (adeno- or squamous cell carcinoma); stage T2-T4a/N0 or T1-T4a/N1-N3, M0; selected for curative (neo-adjuvant) CRT, and no previous treatment or active infection.
All patients were staged according to the 7th edition of the TNM-system of the Union International Contre le Cancer (UICC) [8], based on the following procedures: physical examination, endoscopic ultrasonography (EUS), cervical/ thoracic/ abdominal CT, and whole body FDG-PET. Fine needle aspiration biopsy (FNAB) or other additional investigations were carried out only when indicated. After collection of all diagnostic information, the patients were discussed in a multidisciplinary tumour board.

All patients were included in a prospective trial to assess the impact of a planning-PET/CT compared to the standard planning-CT on the delineation of target volumes for curative (CH-)RT of esophageal cancer. For this purpose, all patients underwent a second, i.e a research, FDG-PET(/CT)-scan for future radiotherapy treatment planning. This study was approved by the local ethics committee and all patients provided written informed consent.

Imaging

Staging FDG-PET(/CT)- scans were performed after the initial diagnosis of the primary esophageal tumour. These FDG-PET-scans will be referred to as 'baseline PET'. For radiotherapy treatment planning, a second PET/CT scan was performed in treatment position over a limited field of view within 2 weeks after referral to the department of Radiation Oncology, and will be referred to as 'therapeutic PET'.
The baseline PET scans were performed using an ECAT HR+ PET camera (Siemens/CTI, Knoxville, TN, USA) or an integrated PET/CT scanner (Biograph mCT 4-64 PET/CT, Siemens, Knoxville, TN, USA). The therapeutic PET images were all acquired using the integrated PET/CT scanner. All PET-scans were reconstructed according to a validated and standardised protocol to minimize the variability of SUV measures due to the use of different PET-cameras [9,10].
Serum glucose levels were measured after the patients had fastened for at least 4 hours. Depending on body weight (5MBq/kg for HR+ and 3MBq/kg for integrated PET/CT), a median dose of 378 MBq FDG (range 170-618) was administered intravenously. Emission scans were obtained 60 minutes after injection of FDG and were performed for 5 minutes per bed position on the HR+ and 2-3 minutes per bed position on the integrated PET/CT. The baseline PET included the skull to mid femur. For the therapeutic PET the neck, thorax and the upper abdomen, including the liver, were included.
All images were reviewed in random order and without knowledge of the patient's details by an experienced nuclear physician (JP). For quantitative analysis of the FDG uptake, the maximum standardized uptake value (SUVmax) based on body weight and corrected for serum glucose was used [10,11]. Serum glucose levels were measured before each PET examination, using a calibrated glucose meter.
For further analyses, the following features were used: visual tumour length, tumour length using 70% of the SUVmax (SUV70%), and visual interpretation of lymph nodes involvement and/or the presence of distant metastases.
If there were any discrepancies after the independent scoring between the two FDG-PET scans of one individual patient, the images were also compared directly in order to verify the origin of the discrepancies.

Follow up

Histo(cyto)pathological confirmation of the tumour progression as detected by the therapeutic FDG-PET(/CT) was not performed, since both PET-scans were reviewed and compared during or after the neo-adjuvant chemoradiation. Therefore, we compared the overall survival for the patients with and without TNM- progression. Routine follow up was performed every 3 months in the first year and 6 months in the second years, followed by a yearly control. In the first 2 years, a CT-scan of the thorax and abdomen was part of this follow up for non-metastasized patients.

Statistical analysis

Univariate analysis was carried out to assess the association between the interval between prognostic determinants and TNM progression, tumour length progression or an increased SUV. An independent t-test was performed for dichotomised variables, while a chi-square test was used for continues variables.
Overall survival time was calculated from the last day of external radiotherapy, according to the Kaplan-Meier method. Survival curves were compared using the log rank test. To perform these calculations, SPSS version 18.0 was used.

Results

Between March 2009 and June 2011, a total of 45 patients were included, with a median age of 64 years (range: 41-85 years). Most tumours were adenocarcinoma (76%) and located at the distal esophagus (91%). Patients and tumour characteristics are listed in Table 1. All patients underwent a second FDG-PET/CT scan, which was performed after a median interval of 22 days (range: 8-49 days) after baseline PET.

The therapeutic FDG-PET/CT-scan revealed 18 new pathologic lymph nodes, which resulted in a changed N-stage in 8 patients (18%). Histology, SUVmax, tumour length, sex, type of PET camera or interval between the 2 PET-scans were no significant prognostic factors for finding of new pathologic lymph nodes.
Two lymph nodes, that were suspicious at baseline PET, were no longer visible at the therapeutic FDG-PET/CT, suggesting a non-malignant origin. In one of these patients, the N-status changed from N1 to N0. In this patient, FDG-uptake in a lymph node at the minor curvature with an initial SUV of 2.9 was no longer observed at the therapeutic FDG-PET/CT.
All patients were initially staged as M0 on their baseline FDG-PET(/CT). However, new distant metastases became manifest in 6 patients (13%), making them ineligible for curative treatment.
Overall, a total of 12 patients (27%) showed tumour progression in terms of a worse TNM-stage *(Figure 1)*. There characteristics are listed in Table 2. We found no significant prognostic factors for TNM progression. However, a trend was noted towards TNM progression for the type of PET-camera used (p=0.05, 95% CI 0.01-0.66) and for the interval between the two PET scans (p=0.09, 95% CI -0.9-12.5).

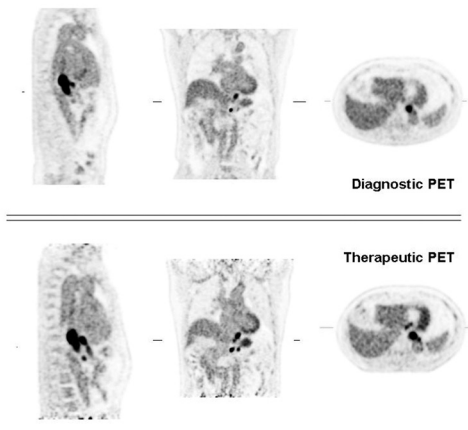

Figure 1.
Lymph node progression was found within an interval of 31 days between the diagnostic and therapeutic PET scan, which were both performed on the integrated PET/CT scanner.

At visual interpretation 14 patients (31%) showed progression in tumour length with >1 cm. A tumour length reduction was found in 2 patients (4%). For the other 29 patients (65%), the tumour length at the baseline FDG-PET was similar to the tumour length at the therapeutic FDG–PET/CT. Univariate analyses showed no significant prognostic factors for tumour length progression.

The corrected SUVmax of the primary tumour increased with more than 10% in 19 patients (42%), while a decrease of the corrected SUVmax with more than 10% was seen 11 patients (24%). The mean and median corrected SUVmax of the primary tumour of the baseline PET and the second PET were comparable.
The SUVmax and length of the primary tumour at the baseline PET images were significant prognostic factors for an increase of the SUV at the second PET. Patients with an increased SUV had smaller tumours (38 vs 50 mm) with a lower SUV (11 vs 16) at the baseline PET.
The newly diagnosed pathologic lymph nodes at the second PET-scan had a median SUV of 4.5 (rang 2.6-9.9). Nine patients showed an increased SUV (mean increase 2.9) of previously diagnosed lymph nodes. Six of them also had an increased SUVmax of the primary tumour. However, two patients showed a decrease of the SUVmax of the primary tumour.
Three patients showed a decreased SUV of pathologic lymph nodes diagnosed at the baseline PET. In all these patients we found more than 10% increase of the SUV of the primary tumour and/or an increased number of pathologic lymph nodes. In one patient the SUV max remained the same.

Table 1.
Patient and tumour characteristics

Characteristics	***n=45 (%)***
Gender	
Male	*33 (73)*
Female	*12 (27)*
Age (years)	
Median (range)	*63 (41-85)*
Histology	
AC	*34 (76)*
SC	*11 (24)*
Tumour localization	
High	*1 (2)*
Mid	*3 (7)*
Distal/GEJ	*41 (91)*
Clinical stage	
T2N0M0	*4 (9)*
T2N1M0	*4 (9)*
T3N0M0	*4 (9)*
T3N1M0	*12 (27)*
T3N2M0	*11 (24)*
T3N3M0	*4 (9)*
T4aN0M0	*2 (4)*
T4aN1M0	*2 (4)*
T4aN2M0	*2 (4)*

At the time of analysis, 15 patients (33.3%) had died within 2 to 22 months after start of treatment. The other 30 patients were still alive (66.7%) at a median follow up time of 14 months. The 1-, 2- and 3-year overall survival (OS) rates were 84%, 72%, and 59%, respectively. The mean survival was 18 months (95% CI; 15-21 months).
TNM progression between the two PET-scans and an increased number of pathologic lymph nodes were significant prognostic factors for OS *(Table 1)*. For the TNM-progression group the mean survival was 12 months (95% CI; 6-17 months) as compared to 20 months for the group without TNM-progression (95% CI; 17-23 months).
The causes of death were not significantly different between the group with or without TNM progression (p=0.35). In the group with TNM-progression 2 patients (17%) died post-operative.

The other 5 patients (42%) died of progressive disease. For patients without TNM-progression the causes of death were in hospital in 2 patients (6%), intercurrent disease in 1 patient (3%) and progressive disease in 5 patients (15%). Another patient (3%) died because of pulmonary complications and decompensatio cordis within 90 days after surgical resection, which might have been treatment related as well.

Discussion

In the present study, tumour progression between baseline FDG-PET and a research/therapeutic FDG-PET/CT, in terms of increased tumour length and/or more advanced TNM-stage, was found in a substantial portion of the patients (31% and 27%, respectively), despite the relatively short interval between the two PET scans (median 22 days).
Studies on repeated PET-CT imaging prior to the neo-adjuvant treatment are scarce. However, several studies reported on post-neoadjuvant distant metastases, with incidences varying from 8 to 17% [12-16]. Interval distant metastases may be explained by tumour progression during and/or after neo-adjuvant treatment. In the two largest studies by Bruzzi et al. and Blom et al., interval distant metastases were described in 8% of the patients. All of these patients were diagnosed with distal adenocarcinomas with positive nodal stages, suggesting lymph node involvement to be a risk factor for the development of interval metastases. Progression of the metastatic tumour burden prior to the treatment might also explain the post-neoadjuvantly detected metastases, since the expected systemic effect of the chemotherapy regimen used for the neoadjuvant chemoradiation seems limited [3].
In the present study, newly detected pathologic lymph nodes or distant metastases were found pre-treatment in 27% of the patients, after comparison of the 2 PET-scans. However, progression over time seemed not the only factor for the detection of pre-treatment tumour progression. There was also a trend noted for TNM progression and the type of PET camera used. Despite the use of a validated and standardized protocol [10] to minimize the variability for both cameras, the spatial resolution of the integrated PET/CT scanner is higher at the visual interpretation settings. This could explain some of the differences in the detectability of small tumour lesions. Furthermore, additional information of the CT-images will also increase the visualization of both regional lymph nodes and distant metastases [17,18]. However, in the current study, the CT images were available for both the diagnostic en the therapeutic scan, at the direct comparison of PET images in case of possible TNM progression. These findings underline the importance of the use of 'state of the art' techniques and PET scanners to prevent the miss of relevant tumour lesions.
The current study revealed newly detected distant metastases in 6 patients (13%), which developed within 49 days. Consequently, the treatment intent changed from curative to palliative intent since metastatic disease implies that curative treatment was no longer possible [19]. A curatively intended treatment, consisting of neo-adjuvant chemoradiation followed by a surgical resection, is very intense with the subsequent risk of (post-)operative morbidity and/or mortality, and should therefore be prevented in patients that cannot be cured. Therefore, for the detection of interval metastases, it remains important to reevaluate the M-stage before surgical resection.
Newly diagnosed pathologic lymph nodes were found in 8 patients in the current study. Accurate identification of regional pathologic lymph nodes, and thus adequate inclusion in the gross

tumour volume (GTV) in order to ensure optimal dose coverage, is essential for the successful radiotherapy. A treatment plan based on the diagnostic PET information would have missed these newly involved lymph nodes as detected on the therapeutic PET, which might result in a geographic miss [19-22] and might lead to recurrence or residual tumour [23]. Given the rapid progression found in the study, it's important to minimize the time between the relevant imaging and start of the radiotherapy.
FDG-PET has some limitations regarding its use for the detection of regional lymph node metastases. Nonspecific inflammation in the mediastinum may result in a false-positive uptake of FDG on the PET images. This seemed the case in two patients in which suspected lymph nodes at the baseline PET were no longer visible at the second PET, suggesting temporarily inflammatory involvement. Potentially, this flaw can be avoided by including late time imaging in the protocol, as it has been shown that in time the uptake in inflammatory lesions tends to decline, whereas in most tumours the uptake is still rising after one hour after injection [24,25]. Furthermore, the spatial resolution of FDG-PET is limited. Luketisch et al. [26] stated that small regional lymph node metastases with mean greatest dimensions range from 2 to 10 mm could not be detected by FDG-PET, while Kato et al. [27] found a threshold size of 6-8 mm for lymph node metastases. The detection of metastatic disease FDG-PET faces the same limitations. Regional or metastatic disease could already be present for quite some time before it becomes visible. However, the results of the current study suggest rather fast visualization and thus progression of esophageal cancer.
This was confirmed by the survival rates of the group with TNM progression which were significantly worse as compared to the group without TNM progression. In the current study, a total of 4 patients died in hospital after surgery, and one patient died because of pulmonary complications and decompensatio cordis within 90 days after surgical resection, which had its effect on the survival rates. Although the causes of death between the group with or without TNM progression were not significantly different, the percentage of patients who died of post-operative complications was slightly higher in the group with TNM progression. It seems reasonable that metastatic tumour progression might influence the risk of post-operative complications.

The results of the current study suggest rapid esophageal tumour progression, in terms of an increased tumour length and/or an advanced TNM-stage. Therefore, the interval between relevant imaging and start of the radiotherapy should be minimized, including re-evaluation if the start of the treatment is delayed. Furthermore, to prevent the miss of tumour lesions, 'state of the art' PET scanners should be used with high spatial resolution.

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Chapter 4

Consequences of additional use of PET information for target volume delineation and radiotherapy dose distribution for esophageal cancer

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Abstract

Background and purpose

To determine the consequences of target volume (TV) modifications, based on the additional use of PET information, on radiation planning, assuming PET/CT-imaging represents the true extent of the tumour.

Materials and methods

For 21 patients with esophageal cancer, two separate TV's were retrospectively defined based on CT (CT-TV) and co-registered PET/CT-images (PET/CT-TV). Two 3D-CRT plans (prescribed dose 50.4 Gy) were constructed to cover the corresponding TV's. Subsequently, these plans were compared for target coverage, normal tissue dose volume histograms and corresponding normal tissue complication probability (NTCP) values.

Results

Addition of PET led to modification of CT-TV with at least 10% in 12 out of 21 patients (57%) (reduction in 9, enlargement in 3). PET/CT-TV was inadequately covered by the CT-based treatment plan in 8 patients (36%). Treatment plan modifications resulted in significant changes ($p < 0.04$) in dose distributions to heart and lungs. Corresponding changes in NTCP values ranged from -3% to +2% for radiation pneumonitis and from -0.2% to +1.2% for cardiac mortality.

Conclusions

This study demonstrated that TV's based on CT might exclude PET-avid disease. Consequences are under dosing and thereby possibly ineffective treatment. Moreover, addition of PET in radiation planning might result in clinical important changes in NTCP.

Introduction

Esophageal cancer is an increasing health problem in the Western world. In the Netherlands, the incidence has doubled in the last twenty years [1,2]. In the last decades, surgery has been the primary treatment modality for esophageal cancer. However, combined chemo-radiotherapy is increasingly applied, either as definitive therapy or in the neoadjuvant setting prior to a curatively intended surgical resection [3].

With modern radiation delivery techniques, accurate delineation and subsequent adequate irradiation of the tumour volume is a prerequisite for successful treatment. However, tumour definition is often hampered by the poor discriminative value of currently used imaging modalities, in particular computed tomography (CT) and the inability to relate endoscopic (ultrasound) information to CT-images. Addition of positron emission tomography (PET) information may improve accuracy in the delineation process. 18F-Fluoro-2-deoxy-D-glucose (FDG) PET provides additional information on the metabolic activity i.c. glucose utilization of the tumour. Because FDG-PET adds functional information to the anatomical information of CT, tumour visualisation and thus tumour delineation may improve.

Another problem in radiotherapy (RT) is the co-irradiation of normal tissues, while irradiating the tumour. Thoracic irradiation may result in heart, lung and esophageal injury and subsequent late radiation-induced side effects [4,5,6]. The clinical relevance of these side effects is increasing when survival rates improve. In the last decade, the overall survival of patients with esophageal cancer, who received radiotherapy with curative intent, has improved, especially when radiotherapy is combined with concurrent chemotherapy [7,3,8]. However, the probability of treatment-related side effects has increased as well [9,10]. Therefore, reduction of normal tissue co-irradiation and subsequent normal tissue complication probabilities (NTCP) has become increasingly important.

Numerous investigators have shown that the addition of PET, or integrated PET/CT, into the radiotherapy planning process results in target volume modifications [11,12,13,14,15,16]. These modifications will result in adjustments of radiation treatment plans, which also might effect co-irradiation of normal tissues [13].

The purpose of the present study was to determine the changes in tumour delineation and subsequent target volumes due to the additional use of PET information, compared to the use of CT alone. Secondly, we investigated the possible consequences of target volume modifications with regard to co-irradiation of the normal tissues and the subsequent changes in NTCP-values based on validated NTCP-models.

Methods and materials

Patients

The study population was composed of 21 consecutive patients who met the following eligibility criteria: histological confirmed esophageal cancer (adeno- or squamous cell carcinoma); stage T2-4, N0-1, M0-1a; without recent thoracic surgery and/or stenting.

All patients were staged according to the TNM-system of the Union International Contre le Cancer (UICC) [17], based on the following examinations: physical examination, endoscopic ultrasonography (EUS), cervical/ thoracic/ abdominal CT, whole body FDG-PET. Fine needle aspiration biopsy or other additional investigations were carried out when indicated.

All patients provided informed consent. The 21 patients had a mean age of 63 years (range: 48-76 years). Patients and tumour characteristics are listed in Table 1.

Table 1.
Patient characteristics

Characteristics	***n=21 (%)***
Sex	
Male	*16 (76)*
Female	*5 (24)*
Age (years)	
Median	*63*
Range	*48-76*
Histology	
AC	*17 (81)*
SC	*4 (19)*
Localization	
High	*3 (14)*
Low	*16 (76)*
GEJ	*2 (10)*
Clinical stage	
T2N0M0	*3 (14)*
T3N0M0	*7 (33)*
T3N1M0	*8(38)*
T3N1M1a	*2 (10)*
T4N1M0	*1 (5)*

Abbreviations:
AC= adenocarcinoma; SC= squamous cell carcinoma; GEJ= Gastro-esophageal junction. Clinical stage = staging based on clinical examination, endoscopic ultrasound, computed tomography, positron emission tomography, additional investigations when necessary, but without FDG-PET/CT co-registration.

Imaging

Radiotherapy treatment planning was determined using CT and FDG-PET images, made within 2 weeks after the initial diagnosis. A 16 or 64 multidetector row spiral CT scanner was used (Somatom Sensation, Siemens Medical Systems, Erlangen, Germany). After administration of intravenous contrast agents, 3 mm CT-images were obtained in cranial-caudal direction, including tumour, lymph node areas, lungs and liver. Lymph nodes with a diameter of 10 mm or more were considered to be pathological, as well as round, hypo dense lymph nodes measuring >5 mm. The FDG-PET-scans were performed with an ECAT 951/31 or an ECAT HR+ positron camera (Siemens/ CTI, Knoxville, TN, USA). The 951/31 acquires 31 planes over 10.9 cm, while the HR+ acquires 63 planes over a 15.8 cm axial field of view. Patients had to fasten for at least 4 hours before 130-750 MBq FDG (mean 362 MBq, depending on body weight) was administered intravenously. Ninety minutes after intravenous contrast injection, emission scans were performed for 5 minutes per bed position from the crown to mid-femur. To distinguish tumour from normal tissue we used the method described by Nestle et al [18]. According to this method, FDG-PET images are normalized reference to the physiological FDG uptake in the liver. FDG-uptake was scored on a four-point scale of intensity: 'normal' (physiological), 'slightly increased', 'moderate increased' and 'intensely increased'. All 'moderate increased' and 'intensely increased' lesions were defined as hotspot. Suspect lesions were verified if possible by fine needle aspiration biopsy (FNAB).

FDG-PET images were co-registered with the CT images on a Siemens Workstation using the Oncentra MasterPlan 1.5 software program (Nucletron, Veenendaal, The Netherlands). An experienced physician carried out the co-registration process.

Tumour delineation

All CT images were reviewed by two experienced radiologists, while the FDG-PET images were reviewed independently by two experienced nuclear physicians. The tumour volume was defined by an experienced radiation oncologist, using additional information of EUS, FNAB outcome, physical examination and reports of CT and PET (only for PET/CT delineation). The gross tumour volume (GTV) was first delineated on CT images, and second, independent and blinded, to the co-registered PET/CT images. The GTV contained the primary tumour and pathologic lymph nodes. The clinical target volume (CTV) was obtained by adding a 1 cm margin in transversal plane and a 3 cm margin in cranial-caudal direction (2 cm margin if the tumour expanded into the stomach) to the primary tumour and 1 cm margin around pathological lymph nodes. In addition, the CTV was adjusted to anatomical structures such as bones. The planning target volume (PTV) was generated by expanding the CTV with 1 cm margins to account for setup uncertainties. The primary tumour length was measured in cranial-caudal direction, based on CT and PET/CT-co-registration. Volumetric analysis of the GTV's and CTV's was performed to determine the proportion of PET-positive disease that was excluded if CT information alone was used for tumour definition. The CT-based and PET/CT-based volumes were quantitatively compared by means of an index of conformality, as described by Gondi et al. [12]. This index represents the ratio of the intersection of two volumes of interest to their union, i.e., the percentage of the total volume that overlaps. A value of 1 implies that the volumes are equal, while a value of 0 indicates that there is no overlap between the two volumes.

We used the same principle to calculate the percentage of PET/CT-GTV located outside the CT-GTV. The Geographic-Miss-Index (GMI) was estimated by dividing PET/CT-GTV minus the intersection, by the PET/CT-GTV in total. In this case, a value of 0 indicates that the PET/CT-based GTV is covered totally by the CT-based GTV, while a value near 1 implies that the PET/CT-GTV is completely different from the CT-GTV. Similarly, we quantified the proportion of PET/CT-GTV excluded by the CT-CTV. This type of geographic mismatch might result in inadequate dose coverage of the primary tumour, assumed that PET/CT represents disease extension best. PET-avid disease incorporated by the CT-based CTV seemed more relevant than inclusion by the CT-PTV; in this study, set up uncertainties are irrelevant, since they are identical (same patient).

Organs at risk, such as lungs, heart, liver and spinal cord, were outlined on CT images. The heart was contoured to the level of the pulmonary trunk superiorly, including the pericardium, excluding the major vessels. Lungs were considered as one organ.

Radiotherapy planning

3D-conformal RT (3D-CRT) plans were made, using 1.8 Gy per fraction to a total dose of 50.4 Gy. A commercial treatment planning system (Pinnacle TPS version 8.0d, Philips Radiation Oncology Systems, Milpitas, CA) was used to design a RT plan that would cover 98% of the PTV with at least 95% of the prescribed dose. A 3-field technique (anterior, posterior and left lateral) was applied in all patients using two small additional manually-shaped beams, if necessary.

The iso-centre and dose-specification point were placed centrally in the PTV. Wedges and MLC shielding were applied to fit the 95%-isodose closely around the PTV in three dimensions, and to obtain a uniform dose distribution according to the recommendations of the International Commission on Radiation Units and Measurements (ICRU) [19].

If possible without reducing the target coverage, the following dose constraints were maintained; spinal cord <50 Gy; mean lung dose (MLD) < 20 Gy, lung V20 <30%, heart V40 <30% and liver V30 <60%.

First, RT planning was based on CT-based target volume definition (CT-PTV). Second, the plans were modified to cover PET/CT-PTV *(Figure 1)*. In case planning optimisation was not compromised, factors as wedge fractions, beam weighting and the dose- normalisation point were kept constant.

Treatment planning evaluation

To assess the implications of normal tissue irradiation, treatment planning software (Pinnacle TPS version 8.0d, Philips Radiation Oncology Systems, Milpitas, CA) was used to obtain several dosimetric values from the dose-volume histograms (DVH), including the mean heart dose, proportion of heart receiving ≥40 Gy (V40), mean lung dose, spared lung volume (receiving ≤5Gy) and relative volume of lung receiving ≥20 Gy (V20). Target coverage was determined by evaluating proportions of CT- and PET/CT-based PTV receiving at least 95% of the prescribed dose. Coverage was considered inadequate if less than 96% of the target volume received 95% of the prescribed dose. This threshold was set at 96% instead of 98% to discard small neglectable differences between the treatment plans.

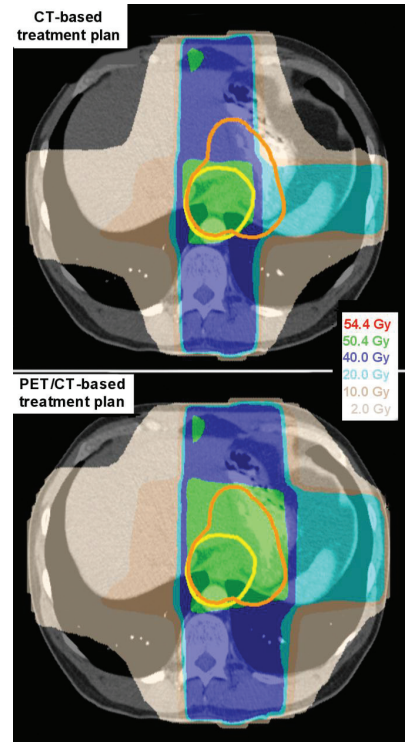

Figure 1.
Dose coverage in CT- and PET/CT-based treatment plans. The CT-based plan covers the CT-PTV contour, but shows under dosing of the PET/CT-PTV. The PET/CT-based plan covers the PET/CT-PTV, while the CT-PTV is incorporated by the PET/CT-radiation field as well.

Validated NTCP models were used to evaluate the potential clinical relevance of changes of NTCP values for the comparison of CT- and PET/CT-based treatment plans. The NTCP for symptomatic radiation pneumonitis, lungs considered as one organ, was calculated with model parameters (TD_{50}= 29.9 Gy, m=0.41, n=1, α/β=3 Gy) derived from the meta-analysis published by Semenenko et al.[20]. This model was based on cumulative experience at various institutions. The NTCP for cardiac mortality after 10-15 years was calculated based on a seriality model derived by Gagliardi et al [6]. Therefore the following parameter values were used; D50= 52.3 Gy, γ=1.28, s=1, α/β=3 Gy.

Both models consider 3 parameters; the dose giving 50% complication probability (TD_{50}), volume dependence (n/s) and the steepness value of the dose-response curve ($m/\gamma\alpha$). Influence of altered fractionation dose was taken into account, with a reference dose of 2 Gy.

Statistical analysis

For comparison of the CT and PET/CT-based plans, various dosimetric parameters were analyzed using SPSS 16.0 software. The Wilcoxon signed rank test was used to determine the statistical significance of the differences between these parameters. Tumour lengths were compared the same way. P-values <0.05 were considered statistically significant.
To give insight in the real differences between the two treatment plans, we divided the ones showing an increase from the ones showing a reduction in order to avoid mediation of the differences.

Results

Tumour delineation

The addition of PET resulted in a change in average tumour length of 73 mm (range: 32-140 mm) on CT to 65 mm (range: 23-135 mm) on co-registered PET/CT (p=0.02).
The addition of PET reduced the tumour length in 11 out of 21 patients (52%) with a mean reduction of 17 mm (SD: ±13 mm), while increased tumour length was seen in 5 patients (24%) with a mean increase of 6 mm (SD: ±4 mm). To avoid a partial volume effect, differences smaller than 3 mm (slide thickness) were considered equal. This was the case in 5 other patients (24%).
Adjustment of the GTV with more than 10% was seen in 62% of the cases; 9 patients (43%) showed a GTV reduction, while in 4 patients (19%) the addition of PET resulted in an enlargement of the GTV.
Adjustments regarding GTV were mainly seen at the caudal/cranial extent of the tumour. Therefore, we did not analyse the volumes separately. Volume modifications correlated with length modifications and were considered in the volume indexes.
The mean GTV Conformality Index (CI) was 0.68 (range: 0.01-0.94; SD ± 0.22); 68% of the PET/CT- and CT-GTV's overlapped. The CTV- and PTV-CI's were 0.78 (range: 0.22-0.97; SD ±0.16) and 0.81 (range: 0.31-0.96; SD ±0.14), respectively.
Assuming that PET/CT represents the true extent of the tumour, exclusion of PET/CT-based disease by CT-based target volumes would be more interesting than the conformality of CT- and PET/CT-based volumes. Therefore the GTV Geographic Miss Index (GMI) was calculated. The average GTV-GMI was 0.16; 16% (range: 0-99%; SD ±0.24) of the PET-avid disease was located outside the CT-GTV. In 13 patients (61%) more than 5% of the PET/CT-GTV was excluded by the CT-based GTV. The mean CTV and PTV GMI were 0.10 (range: 0.01-0.76; SD ±0.14) and 0.08 (range: 0.01-0.65; SD ±0.17).
To determine possible inadequate dose coverage of the PET-based tumour volume, PET/CT-GTV and CT-CTV (counting for microscopic tumour spread) were compared, showing in one patient a PET-tumour volume exclusion of 60%.

Treatment planning evaluation: dose coverage by CT-based plans

For all patients, 98.0-98.5% of the CT-PTV received 95% of the prescribed dose. The PTV's based on PET/CT were, however, inadequately covered by the CT based treatment plan in 8 out of 21 patients (38%). The median coverage, receiving 95% of the prescribed dose, was 92%. In three

Table 2.
Dose delivered to normal tissues; differences between CT- and PET/CT-based treatment plans

		Normal tissue radiation exposure			
Normal tissue	***N***	***CT-based plan (Gy ± SD)***	***PET/CT-based plan (Gy ± SD)***	***difference (absolute) (Gy ± SD)***	***P-value****
Lung					
V20-all(%)	*21*	*19,4 (±5,7)*	*18,2 (±4,7)*	*-1.2*	*0.065*
V20-increase (%)	*6*	*15,3 (±5,6)*	*17,1 (±6,0)*	*1.8*	*0.028*
V20-decrease (%)	*11*	*21,9 (±5,0)*	*18,7 (±4,4)*	*-3.2*	*0.003*
MLD-all (Gy)	*21*	*10,8 (±2,7)*	*10,3 (±2,3)*	*-0.3*	*0.076*
MLD-increase (Gy)	*6*	*9,0 (±2,9)*	*9,7 (±3,1)*	*0.7*	*0.028*
MLD-decrease (Gy)	*11*	*11,9 (±2,2)*	*10,5 (±2,0)*	*-1.4*	*0.003*
Heart					
V40-all	*21*	*28,4 (±11,1)*	*26,3 (±10,8)*	*-2.1*	*0.073*
V40-increase (%)	*5*	*24,5 (±11,1)*	*27,3 (±11,9)*	*2.8*	*0.04*
V40-decrease (%)	*13*	*32,3 (±10,5)*	*27,9 (±11,1)*	*-4.4*	*0.001*
Liver					
V30 (%)	*21*	*9,3 (±5,6)*	*8,3 (±5,9)*	*-1*	*0.102*
Spinal cord					
Dmax (Gy)	*21*	*44,6 (±4,0)*	*44,1 (±3,6)*	*-0.5*	*0.779*

** Wilcoxon signed rank test*

Abbreviations:
V20= percentage of total lung volume receiving > 20Gy, MLD= mean lung dose, V40= percentage of total heart volume receiving > 40 Gy, V30= percentage of total liver volume receiving >30 Gy.
Dmax: maximum dose delivered to spinal cord

cases (14%) the coverage was below 90%, of which one even below 42%, demonstrating the importance of accurate tumour delineation. Geographic mismatches can result in inadequate coverage's, resulting in under dosing *(Figure 1)* of the tumour and thereby possibly ineffective treatment. The PET/CT based GTV was inadequately covered by the CT-based plan in one patient, with 80% coverage.

Treatment planning evaluation; normal tissue radiation exposure

Dose coverage of corresponding PTV's maintained between 98.0 and 98.5%, for both CT- en PET/CT-based treatment plans. The radiation dose didn't exceed the normal tissue tolerance doses, except for the heart V40 in 6 patients, where PTV overlapped with the heart.
DVH analysis was performed to determine the consequences of tumour volume modifications for normal tissues. An overview of the normal tissues radiation exposure, comparing CT-and PET/CT-

based plans, is shown in Table 2. On average, incorporation of PET information in the radiation planning did not result in statistically significant differences in any of the dosimetric factors analysed. However, significant differences in heart and lung radiation exposure between the CT- and PET/CT-based treatment plans were revealed when we separated the cases with increased values from the ones with decreased values. Differences were largest for V40 heart, showing a mean decrease of 4.4% and a mean increase of 1.7%. Modifications in normal tissue dose distribution resulted in corresponding NTCP changes *(Table 3.)*. The absolute difference in NTCP value for symptomatic radiation pneumonitis ranged from +2% to -2.7%. Eleven out of 21 cases (52%) showed a mean reduction of the NTCP value of 1.4% (SD: ±0.8). An increase in NTCP was seen in 6 patients (29%), with a mean value of 0.7% (SD: ±0.7). Individually, the differences can be of great

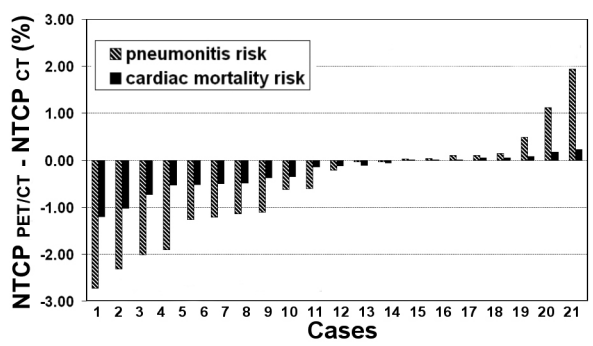

Figure 2.
Differences in normal tissue complication probability (NTCP) values derived from DHV's of the CT-based and PET/CT-based treatment plans. Black= risk of cardiac mortality. Striped = risk of radiation pneumonitis.

Table 3.
Estimated NTCP, comparing CT- and PET/CT-based treatment plans, for symptomatic pneumonitis and cardiac mortality after 10-15 years resulting from irradiation

Normal Tissue Complication Probability

Endpoint		*CT-based*	*PET/CT-based*	*P-value**
Symptomatic pneumonitis (%)	*Overall*	*6,4 (±2,6)*	*5,7 (±2,0)*	*0.033*
	Increased lung dose	*4,5 (±2,2)*	*5,1 (±2,4)*	*0.028*
	Decreased lung dose	*6,9 (±2,2)*	*5,5 (±1,6)*	*0.003*
Cardiac mortality (%)	*Overall*	*2,8 (±1,4)*	*2,5 (±1,3)*	*0.011*
	Increased heart dose	*1,9 (±1,0)*	*2,0 (±1,0)*	*0.225*
	Decreased heart dose	*3,4 (±1,3)*	*2,9 (±1,4)*	*0.002*

** Wilcoxon signed rank test*

Abbreviations:
NTCP = normal tissue complication probability; CT= computer tomography; PET= positron emission tomography. Data presented as mean values, with standard deviation in parenthesis.

importance as is demonstrated in Figure 2. Moreover, the relative differen-ces were large and ranged from +34.3% to 28.9%.
For the risk of cardiac mortality, modifications in normal tissue dose distributions resulted in a mean NTCP reduction of 0.5% in 13 patients (62%) (range: 0.11-1.20). The NTCP value increased in 6 patients (range: 0.05-0.23), with a mean value of 0.1%.

Discussion

In this study, addition of PET revealed possible geographic misses when the radiotherapy planning was based on CT alone. PET-avid disease (GTV) was excluded by the CT-based GTV with more than 5% in 13 patients (61%). Geographic mismatches can result in inadequate coverage's, resulting in under dosing of the tumour and thereby possibly ineffective treatment. In this study, PET/CT-based target volumes (PTV) were inadequately covered by CT-based radiation plans in 8 patients (38%).
In the current study, the term 'geographic misses' was based on the assumption that PET/CT represents the true extent of the tumour. However, the question arises whether this is justified as data from well designed studies on this subject are very limited. One study reported an incremental effect of PET on the accuracy of initial staging over CT of 14% [21]. Others reported a significant positive correlation between PET-based tumour length, estimated for different SUV thresholds, and pathologic findings [22,15]. Mamede et al. [22] also found a correlation between PET-based tumour length and the tumour length based on EUS, the gold standard for T staging. Konski et al. [14] also demonstrated that EUS measurements of tumour length closely approximated PET tumour measurements. In that study, they used a SUV threshold for malignancy of 2.5. These results indicate that PET-based GTV definition is more accurate than CT-based GTV definition.
Leong et al.[11] also evaluated the impact of FDG-PET on CT-based radiotherapy treatment planning. They found an exclusion of PET-avid disease in 11 patients (69%), with a median exclusion of PET/CT-GTV of 38%. Discordances between PET/CT- and CT-based GTV resulted in inadequate coverage of the PET/CT-PTV by the CT-plan in 38% (6/16) of the patients. Similar results were found in the current study.
Internal mobility of the tumour due to breathing movements can cause differences in tumour localisation if images are acquired at different times during the respiratory cycle. PET is performed over many respiratory cycles, while in the current study CT imaging was performed in several seconds, capturing part of the respiratory cycle. However, these differences are expected to be rather small and will be mainly seen in the distal esophagus[23]. To avoid these differences in tumour localisation, 4D-PET/CT imaging should be used to synchronise the respiratory cycle.
Addition of PET information may either result in a reduction of tumour volume or an enlargement. Several other studies described similar modifications [15,12,13,11,16,14,15]. Vrieze et al.[16] claimed however, that GTV should not be reduced based on negative PET findings, because of the low sensitivity of FDG-PET in esophageal cancer. Enlargement of the GTV was justified, based on the high specificity of PET. However, Vrieze et al. focused on detection of pathologic lymph nodes regions, instead of tumor extent.
PET had trouble to distinguish adjacent lymph nodes from primary tumours with high FDG-accumulation. CT can make characterization of the FDG-activity easier by providing an anatomical

context. Sensitivity for diagnosing lymph node metastases improved significantly by using PET/CT [24,25,21], compared to PET alone. CT, on the other hand, has limited ability detecting normal-sized pathologic lymph nodes. In these cases, addition of the functional information of PET can improve the sensitivity. However, tumour involved lymph nodes < 5mm are difficult to detect by PET [26]. Combined PET/CT resolves most of the individual shortcomings of PET and CT, and showed to be more sensitive in the diagnostic process than these images modalities individually. Therefore it is not right to claim that addition of PET should not lead to a reduction of the GTV's of lymph nodes, based on the limited sensitivity of PET alone compared to CT alone.

Usable SUV-thresholds, based on a certain SUV-level or a percentage of the maximal SUV, to distinguish pathologic from normal tissue, could not be determined for esophageal cancer [15,27]. SUV measurements are influenced by many factors, such as patient preparation procedures, scan acquisition, image reconstruction and data analysis settings, which make them less accurate and less reproducible. Therefore, visual interpretation was used for target volume delineation in the current study.

Assuming that PET/CT represents the true extent of the tumour, tumour definition based on CT can result in geographic misses, with consequently under dosing of the tumour and thereby possibly ineffective treatment. Button et al [28] described sites of first recurrences of esophageal cancer after irradiation with EUS and CT based treatment plans. The relapses were mainly seen within the radiation field (within PTV); 65% of the relapses were local recurrences. Only 3 patients (4%) developed regional recurrences outside the radiation field. These results suggest that the target volumes were adequately defined in the fast majority of cases. Only 3 cases could be considered possibly preventable by the additional use of PET. However, localisation of the relapses where considered in relation to the PTV (within or without the PTV), accounting for patient set up variations. Because of these variations, the real irradiation dose in the PTV is always lower. Therefore, in order to get a more accurate picture on the real percentage of possibly preventable recurrences, the number of recurrences outside the CTV rather than outside the PTV are most relevant.

Addition of FDG-PET will probably not improve the delineation of T1-tumors; PET has trouble detecting these tumours, especially of T1a (remaining within the muscularis mucosae) [21,26]. As no gain was expected for T1-tumours, they were excluded from this study.

GTV modifications by the use of PET/CT, resulted in adjusted CTV's and PTV's and subsequent radiation treatment plans, resulting in changes in dose distributions to heart and lungs. We found significant reductions of V20 lung, MLD and V40 heart when PET was added to CT. In individual cases, these reductions can be of clinical relevance, as illustrated by the NTCP-models of Semenenko et al. [20] and Gagliardi et al. [29] However, the impact in terms of changes in NTCP-values, resulting of dose volume modifications, depends on the range in which these changes occur and the corresponding steepness of the NTCP-curve. In this cohort, we found a MLD reduction in the 7-14 Gy dose range, resulting in a NTCP-reduction within a range of 1-3%. In case of dose escalation to 60 Gy (radiotherapy only) the impact on the estimated NTCP-values will be much larger, because the MLD changes are seen in a higher dose range, corresponding to the increased prescribed dose.

Chemotherapy seems also associated with the incidence of radiation pneumonitis. Studies comparing radiotherapy with concurrent chemoradiotherapy suggest that chemotherapy can be a risk factor for grade ≥2 pneumonitis [10,9]. This implies that minimization of radiation dose to the organs at risk, would be even more beneficial when concurrent chemotherapy is given.

NTCP models have their shortcomings, as well as the models used in the current study.

The NTCP model by Semenenko is based on lung cancer patients. Although these patient groups seem comparable, because of their intra thoracic tumours, other factors such as co-morbidity are probably different in these groups, which might affect the NTCP as well. For cardiac mortality, we used the model of Gagliardi, in absence of a NTCP model based on patients with esophageal cancer. Gagliardi based his NTCP model on data sets of breast cancer patients, who were irradiated. However, the irradiation technique for beast cancer differs from the one used for esophageal cancer. Subsequently, the dose distribution to the heart will be different, which might have consequences for the NTCP-values. Since it remains to be clarified which parts of the heart are involved in developing cardiac toxicity, the estimated NTCP-values in this paper should be interpreted with great caution. For more accurate estimation of the NTCP, more research regarding side-effects after irradiation of esophageal tumours is required.

Enlargement of the GTV (based on PET/CT) will increase co-irradiation of normal tissues and therefore the estimated complication risks. In our study, enlargement of the target volume and consequently the changes in NTCP were limited. However, if we enlarge the target volumes according to Vrieze et al, the changes in normal tissue dose distribution will be much larger. In clinical practice, this method is probably seen more often, based on the uncertainty of the radiation oncologist. However, PET/CT seems to improve the confidence of the oncologist regarding their contours [30].

In case of GTV enlargement, it would be relevant to determine whether possible benefits of more (accurate) irradiation outweigh to the increased complication risks. Effects of GTV enlargement on locoregional control and survival are however unknown. More research regarding treatment outcome and possible side-effects/complication risks needs to be done.

Conclusions

This study demonstrated that tumour volumes based on CT might exclude PET-disease, resulting in a geographic miss. Consequences for treatment plans are under dosing and thereby possibly ineffective treatment. Moreover, the results showed that the addition of PET led to changes in dose distributions to normal tissues, which might be of clinical importance in individual cases. To determine whether the changes based on the addition of PET to CT will result in higher probabilities on local control, prospective studies are needed in which recurrence analysis, i.e. relating local recurrence position to dose distributions, are investigated.

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Chapter 5

Residual tumor after neo-adjuvant chemoradiation outside the radiotherapy target volumes: A new prognostic factor for survival in esophageal cancer

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Abstract

Purpose/objective

The aim of this study was to analyze the accuracy of gross tumor volume (GTV) delineation and clinical target volume (CTV) margins for neo-adjuvant chemoradiotherapy (neo-CRT) in esophageal carcinoma at pathologic examination and to determine the impact on survival.

Methods and materials

The study population consisted of 63 esophageal cancer patients treated with neo-CRT. GTV and CTV borders were demarcated in situ during surgery on the esophagus, using anatomical reference points, to provide accurate information regarding tumor location at pathologic evaluation. To identify prognostic factors for disease-free survival (DFS) and overall survival (OS), a Cox regression analysis was performed.

Results

After resection, macroscopic residual tumor was found outside the GTV in 7 patients (11%). Microscopic residual tumor was located outside the CTV in 9 patients (14%). The median follow up was 15.6 months. With multivariate analysis, only microscopic tumor outside the CTV (HR 4.96, 95% CI 1.03-15.36) and perineural growth (HR 5.77, 95% CI 1.27-26.13) were identified as independent prognostic factors for OS. The one year OS was 20% for patients with tumor outside the CTV and 86% for those without ($p<0.01$). For DFS, microscopic tumor outside the CTV (HR 5.92, 95% CI 1.89-18.54) and ypN+ (HR 3.36, 95% CI 1.33-8.48) were identified as independent adverse prognostic factors. The one year DFS was 23% vs. 77% for patients with or without tumor outside the CTV ($p<0.01$).

Conclusion

Microscopic tumor outside the CTV is associated with markedly worse OS after neo-CRT. This may either stresses the importance of accurate tumor delineation or may reflect aggressive tumor behavior requiring new adjuvant treatment modalities.

Introduction

Neo-adjuvant chemoradiotherapy (neo-CRT) followed by surgical resection increases the rate of microscopic radical resections and significantly improves disease-free survival (DFS) and overall survival (OS) as compared to surgical resection alone [1,2]. Therefore, neo-CRT has become standard of care for operable patients with curatively resectable non-metastatic esophageal carcinoma. The histopathological tumor response to neo-CRT is an important predictor for both locoregional tumor control and survival [3,4]. To attain optimal tumor response, accurate radiotherapy, and therefore accurate identification and delineation of the target volumes, is essential. However, delineation of the gross tumor volume (GTV) in esophageal cancer remains difficult. Currently, computed tomography (CT) is the reference imaging modality for delineation of the GTV for radiotherapy of esophageal cancer, integrated with information derived from other diagnostic modalities. However, the discriminative value of CT is generally poor and not sufficient to detect all aspects of tumor extension, such as submucosal spread. Therefore, the current standard is to use relatively large margins, specifically in cranial-caudal directions, to account for possible microscopic tumor spread, resulting in a clinical target volume (CTV).
Pathologic examination is the gold standard to evaluate the tumor response, and the exact location of macroscopic and microscopic residual tumor. To bypass the shrinkage of the esophageal specimen after resection, anatomical reference points can be used to reconstruct and demarcate the radiotherapy target volumes borders in vivo on the esophageal specimen. By using this method, information regarding the exact localization of residual tumor can be obtained in relation to the GTV and CTV.

Therefore, the aim of this study was to analyze the accuracy of GTV delineation and CTV margins for neo-CRT in esophageal carcinoma by means of detailed pathologic analysis and to determine the impact on DFS and OS.

Materials and methods

Patients

The study population consisted of 63 patients with resectable non-metastatic esophageal carcinoma (adeno- or squamous cell carcinoma (AC or SCC)) who were eligible for curative treatment consisting of neo-CRT, followed by surgical resection. All patients were staged according to the 7thTNM system [5] based on physical examination, endoscopic ultrasonography (EUS), CT and FDG-PET. Additional investigations were carried out when indicated. All patients were discussed in a multidisciplinary tumor board.
The median age was 65 (range: 41-83) years. Patients and tumor characteristics are listed in Table 1. This prospective study was performed according to the rules approved by the local ethics committee.

Target volume delineation

The GTV was delineated by experienced radiation oncologists on a planning CT scan, using all available diagnostic information. The GTV contained the primary tumor and pathologic lymph nodes (LN). The CTV was obtained by adding a 1 cm margin in the transversal plane and a 3.5 cm margin in the cranial and caudal directions (2.5 cm margin if the tumor expanded into the stomach) to the primary tumor, adjusted to anatomical structures. For pathologic LN, a 1 cm margin was used. The planning target volume (PTV) was generated by expanding the CTV with 5 mm margins to account for setup uncertainties; this assured adequate dose coverage of the CTV.

Treatment

All patients were treated at the University Medical Center Groningen from August 2009 to June 2012. Radiotherapy consisted of 41.4 Gy in daily fractions of 1.8 Gy, five times per week. The treatment plan was designed according to the ICRU recommendations, meaning that >95% of the prescribed dose covers 98% of the PTV. Patients received 5 weekly cycles of concurrent chemotherapy, which consisted of paclitaxel (50 mg/m2) and carboplatin (AUC= 2). A transthoracic esophagectomy with 2-field lymphadenectomy was performed 4 to12 weeks after completion of neo-CRT. All surgical procedures were performed by two experienced surgical teams.

Table 1.
Patient characteristics

Characteristics	***n=63 (%)***
Sex	
Male	*48 (76)*
Female	*15 (24)*
Age (years)	
Median	*65*
Range	*41-83*
Histology	
Adenocarcinoma	*52 (83)*
Squamous cell carcinoma	*11 (17)*
Localization	
High	*0*
Mid	*1 (2)*
Distal/GEJ	*62 (98)*
Clinical stage	
T2N0M0	*6 (9)*
T2N1M0	*5 (8)*
T2N2M0	*1 (2)*
T3N0M0	*7 (11)*
T3N1M0	*15 (24)*
T3N2M0	*23 (36)*
T3N3M0	*4 (6)*
T4N1M0	*1 (2)*
TxN1	*1 (2)*

Abbreviations:
GEJ: Gastro-esophageal junction

Demarcation of the GTV and CTV borders

For the orientation of the GTV and CTV, we defined five anatomical reference points: the caudal border of the arcus aortae, the tracheal bifurcation, the vena azygos, the origo of the left gastric artery and the celiac trunk. These reference points could be easily identified on the CT images by the radiation oncologist as well as by the surgeon during the esophagectomy.
Distances for the GTV and CTV borders to the aforementioned reference points were measured in longitudinal direction on the CT images *(Figure I)*. During the surgical procedure, these distances were measured again and projected on the esophagus when still in situ. Marking stitches were placed on the esophagus to demarcate the GTV and CTV borders. To bypass shrinkage of the esophageal specimen, this was performed in situ, before the intersection. After resection the specimen was carefully stretched to its original length as measure in vivo and was pinned on a flat board, as described by Zhong et al [6].

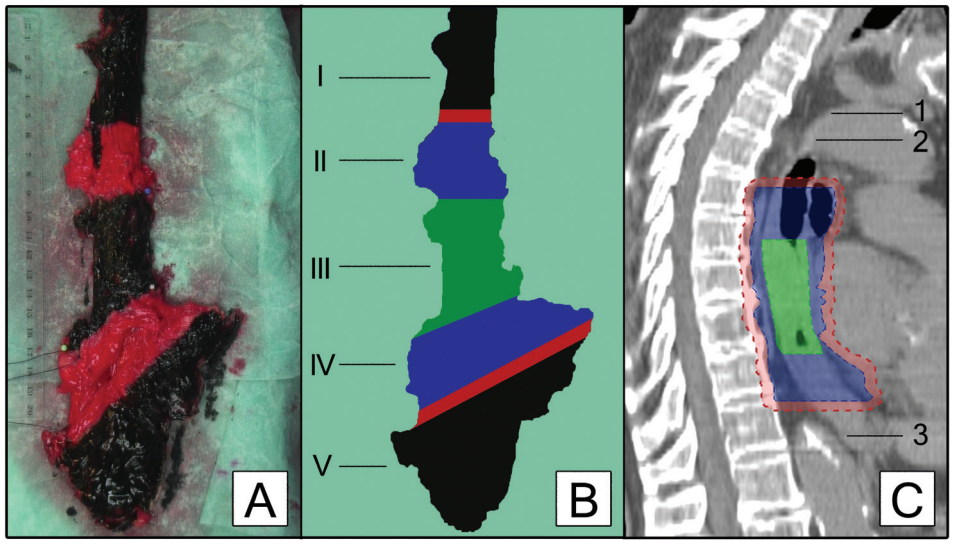

Figure 1.
A: Oesophageal specimen with 5 inked areas; I: above CTV; II: proximal CTV; III: GTV; IV: distal CTV; V: below CTV.
B: Systematic overview.
C: CT images with the GTV in green, CTV in blue and PTV in red. Distances from GTV and CTV borders to the anatomical reference points (1=arcus aortae, 2= tracheal bifurcation, 3= coeliac trunk) are measured in longitudinal direction on the CT images.

Pathologic evaluation

The specimen was fixed in 10% phosphate-buffered formalin for approximately 48 hours. The surgical specimens were divided in five areas *(Figure I)*: outside proximal CTV (I), proximal CTV (II), GTV (III), distal CTV (IV) and outside distal CTV (V). The outer surfaces of the areas were inked in different colours before the specimen was cut into transverse slices at a thickness of approximately 3 mm. All slices were ordered by area of origin and evaluated macroscopically for the presence of residual tumor. The slices were completely embedded in paraffin blocks and were microscopically evaluated by routine hematoxylin and eosin staining. The 7thTNM classification and 2010 World Health Organization criteria for tumor grading were used [7,8]. R0 resection was defined as histologically tumor-free resection margins with a distance of >1 mm between tumor and all resection margins, including the circumferential margin (CRM) according to the Royal College of Pathologists (RCP) [9,10]. In case of microscopic tumor at a distance of ≤ 1mm, the resection was considered as R1.
Tumor response to neo-CRT was evaluated using the five-tiered Mandard classification [11], which is based on the ratio of viable residual tumor cells in relation to the area of fibrosis. Furthermore, we evaluated the localization of the original tumor bulk based on the presence of residual tumor and/or regressive changes. The analysis and classification was performed by an experienced gastrointestinal pathologist.

Table 2.
Pathologic characteristics

Pathology characteristics	***n= 63 (%)***	***Tumor outside CTV n=9 (%)***	***Tumor within CTV n=54 (%)***
Histopathological T-classification			
ypT0	*15 (24)*	*1 (11)*	*14 (27)*
ypT1	*12 (19)*	*0 (0)*	*12 (22)*
ypT2	*9 (14)*	*2 (22)*	*7 (13)*
ypT3	*27 (43)*	*6 (67)*	*21 (38)*
ypT4	*0 (0)*	*0 (0)*	*0 (0)*
Histopathological N-classification			
ypN0	*38 (60)*	*1 (11)*	*37 (69)*
ypN1	*17 (27)*	*4 (45)*	*13 (24)*
ypN2	*3 (5)*	*2 (22)*	*1 (2)*
ypN3	*5 (8)*	*2 (22)*	*3 (5)*
Macroscopic tumor extension			
All within GTV	*12 (19)*	*6 (67)*	*6 (11)*
(Partly) outside GTV	*7 (11)*	*3 (33)*	*4 (7)*
Microscopic tumor extension			
within CTV	*54 (86)*		
outside CTV	*9 (14)*		
Completeness of resection			
R0	*54 (86)*	*6 (67)*	*48 (89)*
R1 (according to RCP)*	*9 (14)*	*3 (33)*	*6 (11)*
Lymphangio invasion			
Negative	*48 (76)*	*4 (44)*	*44 (81)*
Positive	*15 (24)*	*5 (56)*	*10 (19)*
Perineural growth			
Negative	*56 (89)*	*6 (67)*	*50 (93)*
Positive	*7 (11)*	*3 (33)*	*4 (7)*
Tumor regression grade – overall			
I	*12 (19)*	*0 (0)*	*12 (22)*
II	*29 (46)*	*6 (67)*	*23 (44)*
III	*13 (20)*	*0 (0)*	*13 (24)*
IV	*8 (13)*	*2 (22)*	*7 (13)*
V	*1 (1)*	*1 (11)*	*0 (0)*

Abbreviations:
R0: complete resection
R1: microscopic resection margin <1mm
RCP: Royale college of pathologists
**: Royal College of Pathologists*

Table 3.
Influence of missing demarcations

Patient	Missing demarcation	Influence of analysis
1	CTV demarcations	Complete microscopic response; no influence
2	lower GTV and CTV border	Reconstruction performed, seemed correct; no influence
3	upper CTV and GTV border	Tumor foci were only located proximal
4	upper GTV border	Reconstruction performed, no proximal residual tumor; no influence
5	GTV demarcations	No macroscopic residual tumor; no influence

Abbreviations:
CTV: clinical target volume
GTV: gross tumor volume

Follow up

After resection, routine follow up was performed every 3 months in the first year and every 4 months in the second year, followed by annual evaluations. For 43 patients, who participated in a trial, a CT-scan of the thorax and abdomen was part of this follow up every 6 months, for the first 2 years. The remaining 20 patients were given additional radiological examinations based on clinical suspicion of recurrent disease.

Statistics

DFS and OS time were calculated from the first day of neo-CRT, according to the Kaplan-Meier method and compared using the Log-rank test. To identify prognostic factors for DFS and OS, univariate Cox proportional hazards analyses were performed. Multivariate analyses were performed using the Cox proportional hazards model, entering the parameters of influence on outcome according to univariate analysis (defined as those with $p<0.1$) using backwards selection. A p-value <0.05 was considered significant. The statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, Chicago IL, USA) version 18.0 software.

Results

All patients underwent neo-CRT without severe (≥ grade 3) toxicities. However, 9 patients (14%) did not receive the final cycle of chemotherapy because of hematologic toxicities (7), hepatologic toxicity (1) and allergic reaction (1). Another patient received only 2 cycles because of hearing loss during chemotherapy.
The transthoracic esophagectomy with lymphadenectomy was performed after a median time of 48 days (range: 26-89) after neo-CRT. A complete resection was performed on 54 patients. Nine

Table 4.
Tumor characteristics of patients with microscopic tumor outside the CTV

Sex	Age	Clinical stage	Histo-logy	Resection margin	ypT-classification	ypN-classification	Positive lymph nodes	Lymph-angio invasion	Peri-neural growth	Tumor regression grade
male	70	T3N2	AC	R0	2	0	0	no	no	2
male	62	T3N1	AC	R1	3	2	6	yes	yes	4
male	63	T3N0	AC	R0	3	0	0	no	no	2
male	69	T3N3	AC	R0	3	1	2	yes	no	2
female	46	TxN1	AC	R0	0	1	2	yes	no	2
female	69	T2N0	AC	R0	2	0	0	yes	no	4
male	64	T3N1	AC	R1	3	3	8	no	yes	2
male	56	T3N3	AC	R1	3	3	7	yes	yes	5
male	66	T3N2	AC	R0	3	0	0	no	no	2

Abbreviations:
AC: adenocarcinoma
R0: complete resection
R1: microscopic resection margin <1mm

patients (14%) underwent a R1 resection. Pathologic characteristics are listed in Table 2.
Complete demarcations were performed in 58 patients. In 5 patients demarcations of the GTV and CTV borders were incomplete. However, in these patients the missing demarcations did not influence the analysis *(Table 3)*.

Accuracy of the gross tumor delineation (GTV)

Macroscopically evident residual tumor was found in 19 patients (30%) and was located in the original GTV in 12 patients. In 7 patients (11%), the macroscopic residual tumor, or part of it, was located outside the original GTV. However, all macroscopic residual tumor remained within the original CTV. Using the Mandard classification, 4 of these 7 patients were partial responders (Mandard 2-3) and 3 were minimal or no responders (Mandard 4-5).
In most patients (75%) the bulk of the original tumor, based on residual tumor and evident regressive changes, indicative for pre-existent carcinoma, was located in the GTV. In 7 patients (11%), the bulk of the original tumor was found in both GTV and CTV, while in 8 patients (13%) the original bulk was located in the CTV margin. In one patient, the tumor affected the GTV and CTV as well as the area located cranially to the CTV, and no clear tumor bulk could be identified.

Accuracy of the CTV margin for microscopic tumor spread

A complete microscopic response of the primary tumor (ypT0) was seen in 15 patients (24%). However, 4 of them had residual tumor cells in their LN (ypT0N1).
Overall, a complete (Mandard 1), partial (Mandard 2-3) and almost no (Mandard 4-5) response

was found in 12 (19%), 41 (65%) and 10 (16%) patients, respectively. The microscopic residual tumor remained restricted to the original CTV in 86% of the patients. However, in 9 patients (14%), microscopic tumor was also found outside the CTV. In a subgroup of 6 of these patients, the microscopic tumor extended beyond the distal CTV margin; in 4 of them, a CTV margin of 25 mm was used because of expansion into the stomach. In one out of the group of 9 patients, microscopic residual tumor was found beyond both CTV borders, while another patient showed only extension cranial to the proximal CTV margin. The final patient showed exclusively a positive lymph node cranial to the proximal CTV margin. Importantly, none of these patients had incomplete CTV demarcations. R1-resections were found in 3 out of the group of 9 patients, including 2 with circumferential invasion and only one with invasion of the cranial and caudal borders.
Tumor characteristics of these 9 patients are listed in Table 3. These patients showed different distributions of their original tumor bulk; it was located within the GTV in only 3 patients, in the caudal CTV in 3 patients and within the GTV/CTV area in 2 patients. In one patient, no clear tumor bulk could be identified. According to the Mandard classification, 6 of these 9 patients were partial responders, while 3 patients showed almost no response to neo-CRT.
The median number of resected LN was 17 (range 7-33). Positive LN were seen in 25 patients (40%). For LN-positive patients, the median positive-to-negative ratio was 0·17 (range 0.04-0.69). Most positive LN (72%) were located in the original GTV and CTV, except for 4 out of 25 patients (16%) with positive LN in area I or V (outside the CTV). In 3 patients, the location of the positive LN was not documented.

Influence of pathological findings after neo-CRT on DFS and OS

At the time of analysis, 19 out of 63 (30.2%) patients had died within 4 to 29 months after start of treatment. The median follow up time was 16.6 months (95% CI 14.0-20.0).
The most frequently reported first site of recurrence was distant. All patients with reported recurrences turned out to have distant metastases. Concurrent regional metastases were reported in only two of these patients (16%).
The one year OS was 79%, and the one year DFS was 71%. In univariate analysis, microscopic tumor extension outside the CTV, ypN+, lymphangio-invasion, perineural growth, LN ratio >0.10 and >5 positive LN were associated with worse DFS and OS *(Table 5)*. In multivariate analysis, only perineural growth (HR 5.77, 95% CI 1.27-26.13) and microscopic tumor extension outside the CTV (HR 4.96, 95% CI 1.03-15.36) were significantly associated with OS. The one year OS was 20% for patients with tumor outside the CTV vs. 86% for patients without such tumor (p<0.01). For patients with perineural growth the one year OS was 0% vs. 85% for those without (p<0.01). For DFS, microscopic tumor extension outside the CTV (HR 5.93, 95% CI 1.89-18.56) and ypN+ (HR 3.41, 95% CI 1.35-8.63) were identified as independent adverse prognostic factors. The one year DFS was 23% for patients with tumor outside the CTV vs. 77% for those without such tumor (p<0.01). For patients with ypN+, the one year DFS was 58% vs. 80% for patients with ypN0 (p<0.01).

Table 5. Univariate analysis for overall survival

			OS				DFS			
	Univariate	***N***	***HR***	***95% CI upper***	***95% CI lower***	***p-value***	***HR***	***95% CI upper***	***95% CI lower***	***p-value***
Sex	*man*	*48*	*1.00*			*0.85*	*1.00*			*0.98*
	female	*15*	*0.90*	*0.30*	*2.73*		*1.02*	*0.37*	*2.81*	
Age	*≥65*	*30*	*1.00*			*0.20*	*1.00*			*0.26*
	<65	*33*	*1.85*	*0.72*	*4.74*		*1.69*	*0.68*	*4.19*	
cT-classification	*cT2*	*12*	*1.00*			*0.22*	*1.00*			*0.27*
	cT3	*49*	*2.57*	*0.58*	*11.43*		*2.46*	*0.56*	*10.78*	
	cT4a	*1*	*8.49*	*0.73*	*98.60*		*7.03*	*0.62*	*79.69*	
cN-classification	*cN0*	*13*	*1.00*			*0.32*	*1.00*			*0.25*
	cN1	*22*	*1.43*	*0.36*	*5.73*		*1.44*	*0.36*	*5.76*	
	cN2	*24*	*2.97*	*0.80*	*10.99*		*3.14*	*0.86*	*11.46*	
	cN3	*4*	*0.00*				*0.00*			
cN positive	*no*	*13*	*1.00*			*0.28*	*1.00*			*0.25*
	yes	*50*	*2.00*	*0.58*	*6.89*		*2.05*	*.60*	*7.05*	
Tumor length >5cm	*no*	*37*	*1.00*			*0.97*	*1.00*			*0.70*
	yes	*26*	*1.02*	*0.41*	*2.53*		*1.19*	*0.49*	*2.88*	
PA type	*AC*	*52*	*1.00*			*0.63*	*1.00*			*0.76*
	PCC	*11*	*1.31*	*0.43*	*3.98*		*1.19*	*0.40*	*3.57*	
ypT-classification	*ypT0*	*15*	*1.00*			*0.27*	*1.00*			*0.15*
	ypT1	*12*	*0.28*	*0.03*	*2.49*		*0.26*	*0.03*	*2.29*	
	ypT2	*9*	*0.93*	*0.17*	*5.07*		*1.01*	*0.19*	*5.54*	
	ypT3	*27*	*1.75*	*0.56*	*5.45*		*2.04*	*0.67*	*6.28*	
ypN positive	*ypN0*	*38*	*1.00*			***0.03****	*1.00*			***0.01****
	ypN+	*25*	*2.86*	*1.13*	*7.29*		*3.44*	*1.37*	*8.567*	
>5 positive lymph nodes	*no*	*57*	*1.00*			***0.00****	*1.00*			***0.00****
	yes	*6*	*6.12*	*1.89*	*19.80*		*6.86*	*2.39*	*19.67*	
Lymph node ratio>0.1	*no*	*51*	*1.00*			***0.01****	*1.00*			***0.00****
	yes	*12*	*3.91*	*1.52*	*10.05*		*4.95*	*1.97*	*12.44*	
Resection margin	*R0*	*53*	*1.00*			*0.25*	*1.00*			*0.11*
	R1	*10*	*2.15*	*0.59*	*7.88*		*2.56*	*0.82*	*8.03*	
Tumor response	*Mandard 1***	*12*	*1.00*			*0.77*	*1.00*			*0.62*
	Mandard 2	*29*	*2.28*	*0.50*	*10.48*		*2.51*	*0.55*	*11.50*	
	Mandard 3	*13*	*1.71*	*0.31*	*9.39*		*2.05*	*0.37*	*11.23*	
	Mandard 4	*8*	*3.26*	*0.53*	*20.24*		*4.04*	*0.72*	*22.73*	
	Mandard 5	*1*	*0.00*				*0.00*			
Tumor response	*CR*	*11*	*1.00*			*0.50*	*1.00*			*0.34*
	PR	*43*	*1.93*	*0.44*	*8.55*		*2.13*	*0.48*	*9.45*	
	NR	*9*	*2.99*	*0.48*	*18.59*		*3.64*	*0.64*	*20.62*	
Perineural growth	*no*	*56*	*1.00*			***0.00** ***	*1.00*			***0.00** ***
	yes	*7*	*11.27*	*2.87*	*44.33*		*9.71*	*2.68*	*35.30*	
Lymphangio invasion	*no*	*48*	*1.00*			***0.01****	*1.00*			***0.01****
	yes	*15*	*3.47*	*1.31*	*9.23*		*3.36*	*1.34*	*8.39*	
Microscopic residual tumor outside CTV	*no*	*54*	*1.00*			***0.00****	*1.00*			***0.00****
	yes	*9*	*6.80*	*2.12*	*21.84*		*5.87*	*1.94*	*17.75*	
Macroscopic residual tumor outside GTV	*no*	*56*	*1.00*			*0.12*	*1.00*			*0.21*
	yes	*7*	*2.41*	*0.79*	*7.35*		*2.03*	*0.68*	*6.10*	
Upstaging T	*no*	*59*	*1.00*			*0.80*	*1.00*			*0.95*
	yes	*3*	*0.76*	*0.10*	*5.84*		*0.94*	*0.13*	*7.09*	
Downstaging T	*no*	*33*	*1.00*			*0.22*	*1.00*			***0.09****
	yes	*29*	*1.82*	*0.70*	*4.77*		*2.27*	*0.89*	*5.77*	
Upstaging N	*no*	*51*	*1.00*			***0.03****	*1.00*			***0.02****
	yes	*12*	*2.80*	*1.08*	*7.25*		*3.08*	*1.25*	*7.60*	
Downstaging N	*no*	*36*	*1.00*			*0.48*	*1.00*			*0.27*
	yes	*27*	*1.39*	*0.56*	*3.43*		*1.64*	*0.68*	*3.97*	

Abbreviations:
CTV: clinical target volume *GTV: gross tumor volume*
OS: Overall survival *DFS: disease free survival*
** The P-values in bold represent the factors that were included in the multivariat analyses (P > 0.1).*
*** Mandard classification system Z ratio of viable residual tumor cells to the area of fibrosis (11).*

Discussion

The present study demonstrated that macroscopic tumor was located outside the GTV in 35% of the patients with macroscopic residual tumor. Furthermore, microscopic tumor was found outside the CTV in 14% of the patients, after neo-CRT.
The mismatch of the GTV and macroscopic tumor suggests inaccurate delineation. Accurate delineation of the GTV is a prerequisite for successful preoperative treatment of esophageal cancer with neo-CRT. However, it is well known that the intra- and interobserver variability for the tumor delineation of esophageal cancer can be rather large [12,13].
GTV delineation can be hampered by the poor discriminative value of the currently used CT and by the inability to relate endoscopic (ultrasound) information to CT images. Several authors have speculated about the incorporation of FDG-PET data to improve the accuracy of the tumor delineation by identifying a metabolic tumor volume [14],[6]. However, a recently published review showed that the evidence on pathologic and clinical validation is currently insufficient to support the use of FDG-PET/CT in the tumor delineation process for radiotherapy [15].
Microscopic tumor spread can easily be missed on CT, but also on FDG-PET. Moreover, FDG-PET is unable to identify T1-tumors, and it failed to identify microscopic residual tumor in 18% of cases in a study by Swisher et al [16].
The literature on the extent of submucosal spread in esophageal cancer is limited. Most surgical studies examined the resection margins of surgical specimens and did not report on the minimum margin that is required to encompass the microscopic tumor [17,18].
The only study that was performed explicitly to define the optimal CTV margin concluded that a CTV margin of at least 30 mm (proximal and distal) is required to cover the extent of microscopic spread within the esophagus in 94% of patients with SCC [19]. For AC located at the GEJ, a 30 mm proximal CTV margin would cover microscopic tumor in up to 100% of cases. However, for tumors along the GEJ and gastric cardia, a 50 mm distal CTV margin is required to cover microscopic tumor in 94% of cases [19].
In the current study, we used CTV margins of 35 mm in cranial and caudal directions. However, if the tumor had expanded into the gastric cardia, a 25 mm margin was used instead. In line with the findings of Gao et al. [19], this 25 mm margin appeared to be insufficient, since most cases of microscopic tumor outside the CTV were located caudally of the distal CTV margin into the gastric cardia. The amount of tumour extension beyond CTV borders was not measured in the current study. Therefore, no recommendation regarding the optimal CTV margins can be given. However, based on this study we currently use a caudal margin of 35 mm for all esophageal tumors.
The EORTC guidelines for neo-CRT of AC at the GEJ recommend a minimal CTV margin of 1.5 cm in caudal direction and a 1 cm margin in cranial direction. These margins seem insufficient. However, the authors advise to correct for target volume motion by the use of an internal target volume [20].
Another explanation for macroscopic or microscopic residual tumor outside the delineated GTV or CTV is persistent tumor growth. In the current study, half of the patients with microscopic extension beyond the CTV border were classified as non-responders to neo-CRT. For these relatively radiotherapy-resistant tumors, neo-CRT delays further treatment, i.e. the surgical resection, which gives the tumor the opportunity to grow, resulting in tumor extension beyond the radiotherapy target volumes. Several studies have described newly detected post-neoadjuvant metastases, also suggesting tumor

growth during or after the neoadjuvant treatment. In these studies, the incidence of post-neoadjuvant metastases varied from 8 to 17% [21-24]. Moreover, tumor progression can even be observed before the start of neo-CRT. Muijs et al. [25] found tumor progression – in terms of increased tumor length and/or more advanced TNM stage – in 31% and 27% of the patients, respectively, within a median time interval of 22 days between diagnostic imaging and imaging for radiotherapy planning.
Despite the limitations of the demarcation method, we demonstrated that the presence of microscopic tumor spread beyond CTV borders was associated with a significantly worse DFS and OS. Microscopic tumor spread beyond CTV borders might be a clinical sign of biologically more aggressive tumor behavior, suggesting that these tumors might be more progressive and tend to metastasize in an earlier stage and/or that they are less sensitive to (chemo)radiation.
Perineural growth was also an independent prognostic factor for OS, while ypN+ was an independent prognostic factor for DFS. However, the multivariate analysis in the current study, including all pre-treatment and pathological tumor characteristics, showed no other factors that were associated with DFS and/or OS.
A possible limitation to the current study is the number of patients and events, which are both relatively small for multivariate analysis. Nevertheless, these variables converge at a specific type of biological behavior. We therefore suggest that they should be the subject of larger prospective studies.

Conclusion

Macroscopic tumor outside the GTV and microscopic tumor outside the CTV were found in a substantial proportion of patients, suggesting inaccurate GTV delineation, inadequate CTV-margins, or tumor growth before, during or after the neo-CRT. Moreover, the presence of microscopic tumor spread beyond the CTV borders had a significantly adverse impact on DFS and OS. These findings emphasize either the importance of accurate delineation of the GTV or might indicate biologically more aggressive tumor behavior and should be subject of future studies.

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Chapter 6

Clinical validation of FDG-PET/CT in the radiation treatment planning for patients with esophageal cancer

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Abstract

Background

The aim of this prospective study was to determine the proportion of locoregional recurrences (LRRs) that could have been prevented if radiotherapy treatment planning for esophageal cancer was based on PET/CT instead of CT.

Materials and methods

Ninety esophageal cancer patients, eligible for high dose (neo-adjvuvant) (chemo)radiotherapy, were included. All patients underwent a planning FDG-PET/CT-scan. Radiotherapy target volumes (TVs) were delineated on CT and patients were treated according to the CT-based treatment plans. The PET images remained blinded. After treatment, TVs were adjusted based on PET/CT, when appropriate. Follow up included CT-thorax/abdomen every 6 months. If LRR was suspected, a PET/CT was conducted and the site of recurrence was compared to the original TVs. If the LRR was located outside the CT-based clinical TV (CTV) and inside the PET/CT-based CTV, we considered this LRR possibly preventable.

Results

Based on PET/CT, the gross tumour volume (GTV) was larger in 23% and smaller in 27% of the cases. In 32 patients (36%), >5% of the PET/CT-based GTV would be missed if the treatment planning was based on CT. The median follow up was 29 months. LRRs were seen in 10 patients (11%). There were 3 in-field recurrences, 4 regional recurrences outside both CT-based and PET/CT-based CTV and 3 recurrences at the anastomosis without changes in TV by PET/CT; none of these recurrences were considered preventable by PET/CT.

Conclusion

No LRR was found after CT-based radiotherapy that could have been prevented by PET/CT. The value of PET/CT for radiotherapy seems limited.

Introduction

During the last twenty years, the incidence of esophageal cancer in the Netherlands has increased dramatically [1,2]. Traditionally, surgery has been the primary treatment for esophageal cancer. More recently, chemoradiation has increasingly been used, either as definitive therapy or in the neoadjuvant setting prior to curatively intended surgical resection [3].
Accurate identification and delineation of the tumour volume is essential for adequate radiotherapy. Currently, computer tomography (CT) is the reference imaging modality for delineation of the gross tumour volume (GTV) for radiotherapy of esophageal cancer; it is combined with information derived from other diagnostic modalities, such as endoscopic ultrasonography (EUS). However, the discriminative value of CT is generally poor and it remains difficult to relate EUS information to CT-images.
Recent studies have speculated about the value ^{18}F-Fluoro-Deoxy-Glucose -positron emission tomography (FDG-PET) scans to improve the accuracy of tumour delineation by identifying a metabolic tumour volume [4,5]. However, the results of a recently published review [6] showed that the use of ^{18}F-FDG-PET/CT (PET/CT) in the tumour delineation process for radiotherapy is not supported with sufficient evidence. The addition of PET/CT resulted in changes in target volume delineation in a considerable proportion of patients (20-94%) [6,7]. However, it is unclear whether PET/CT-based target volumes provide a more accurate representation of the true tumour extension as compared to CT alone. Furthermore, there are no studies demonstrating the use of PET/CT in terms of improved locoregional control or survival.
Therefore, the aim of this study was to prospectively assess in what proportion of patients locoregional recurrences (LRR) – observed at 6, 12 or 18 months after treatment – could have been prevented if PET/CT-based treatment planning was used instead of CT-based treatment planning.

Materials and methods

Patients

The patients in this multicentre prospective observational cohort study had to meet the following inclusion criteria: (1) histologically confirmed esophageal cancer (adeno- or squamous cell carcinoma); (2) stage T2-4, N0-3, M0; (3) eligible for curative treatment consisting of radiotherapy alone (RT) or combined with concurrent chemotherapy(CRT) or neo-adjuvant chemoradiotherapy followed by surgery (neo-CRT); (4) no previous treatment or active infection, and (5) no other malignancies in the past 5 years.
All patients were staged according to the 7th TNM-system of the Union International Contre le Cancer (UICC) [8], based on the following diagnostic procedures: physical examination, EUS, cervical/ thoracic/ abdominal CT and whole body FDG-PET. Other additional investigations were carried out when indicated.
The study was approved by the Medical Ethical Committees of the participating centres and written informed consent was provided by all patients included in the study.

Imaging

For radiotherapy planning, PET/CT scans were acquired in treatment position using an integrated PET/CT scanner. CT-images (3 mm) including the tumour, lymph node areas, lungs and liver were obtained after administration of oral contrast agents.
The PET images were made for research purposes only and remained blinded for the treating physician during the preparation phase and actual treatment. All PET/CT scans were conducted according to a validated and standardised protocol [9], to minimize inter-subject and inter-institute variability of standardized uptake value (SUV) measures. Depending on body weight (5MBq/kg), ^{18}F-FDG was administered intravenously after the patients had fasted for at least 4 hours. Emission scans were obtained 60 minutes after injection of 18F-FDG and were performed for 2-3 minutes per bed position.

Target volume delineation

The GTV was delineated by experienced radiation oncologists on the planning CT scan, using all available diagnostic information, such as EUS, and reports of the CT and the diagnostic FDG-PET examinations. However, the planning PET/CT made for the purpose of this study was not co-registered with the planning CT.
The GTV contained the primary tumour and pathologic lymph nodes. The clinical target volume (CTV) was obtained by adding 1 cm margin in the transversal plane and 3.5 cm margin in cranial and caudal directions (2.5 cm margin if the tumour expanded into the stomach) to the primary tumour and 1 cm margin around pathologic lymph nodes. In addition, the CTV was adjusted to anatomical structures. The planning target volume (PTV) was generated by expanding the CTV with 5 mm margins to account for setup uncertainties.

Treatment

Primary RT consisted of a single fraction brachytherapy (6 Gy) followed by 60 Gy external radiotherapy, in 2 Gy fractions, five fractions a week. Patients who underwent primary CRT received a total radiation dose of 50.4 Gy, in daily fractions of 1.8 Gy. The chemotherapy regime contained 4 three-weekly cycles of cisplatin/5FU;two concurrent cycles followed by two adjuvant cycles. Neo-CRT consisted of 41.4 Gy, in daily fractions of 1.8 Gy, with concurrent 5 weekly cycles of carboplatin/paclitaxel [10].

GTV adjustment after completion of treatment

After completion of the radiotherapy, the original GTV and CTV were copied to minimize intra-observer variability, and adjusted by the treating physician based on visual interpretation of the integrated PET/CT information. The PET images were normalized to the physiological FDG uptake in the liver.
The conformality between CT-based and PET/CT-based target volumes were quantified using the conformality index, as described by Gondi et al. [12]. To quantify the proportion of PET/CT-based GTV or CTV that was omitted by the CT-based GTV or CTV, we calculated the Geographic-Miss-Index (GMI) by dividing PET/CT-GTV minus the intersection by the PET/CT-GTV in total [7]. Inadequate irradiation of these areas can result in possibly ineffective treatment with the risk of LRR.

Follow up

Patients who received neo-CRT underwent a transthoracic esophagectomy with 2-field lymphadenectomy followed by reconstruction, 6 weeks after completion of neo-CRT. After resection, the specimen was evaluated by the pathologist on tumour response to the neo-adjuvant treatment, using the Mandard classification system [11].
For all patients, routine follow up (FU) was carried out every 3 to 6 month depending on the postoperative years. Disease recurrence was established by CT every 6 months during the first 18 months, or earlier if indicated based on clinical suspicion. Histologic confirmation of locoregional recurrences was obtained whenever possible. In addition, other tests were performed when indicated to establish locoregional disease recurrence or metastasis.
If LRR was suspected, an additional integrated FDG-PET/CT was conducted in the original treatment position for recurrence analysis. For this purpose, these PET/CT images were compared with the pre-treatment PET/CT images and the corresponding delineations to determine the location of the recurrence reference to the CT-based CTV. If the physical condition of the patient did not allow PET/CT, the endoscopy or CT images were used for recurrence analyses.
In case the recurrence was located within the CT-based CTV, we considered this as not preventable by integrated PET/CT. If the recurrence was located outside or at the border of the CT-based CTV and inside the PET/CT-based CTV, we defined this as an potentially preventable event.

Statistical considerations and power analysis

The primary endpoint was LRR, located outside or at the border of the CT-based CTV and inside the PET/CT-based CTV. LRRs are most frequently observed in patients treated with (C)RT, with a LRR rate of 50%, within the first 2 years after treatment. Based on the results of a pilot study, we hypothesized that the LRR rate, outside the CT-based CTV but inside the PET/CT-based CTV (event) was 20%. Therefore, the overall expected event rate was 10%. To obtain a plus or minus 6% precision of the 95% confidence interval of the proportion, 90 patients had to be included in the study.
Survival and LRR curves were calculated according to the Kaplan-Meier method and were compared using the log rank test.

Results

Between May 2009 and April 2012, 90 patients were included in the trial. Most patients had an adenocarcinoma (76%) and most tumours were located at the distal esophagus (88%). Patients and tumour characteristics are listed in Table 1.

Table 1.
Patient characteristics

Characteristics	***n=90 (%)***
Sex	
Male	*69 (77)*
Female	*21 (23)*
Age (years)	
Median	*63*
Range	*39-85*
Histology	
AC	*68 (76)*
SC	*22 (24)*
Localization	
High	*4 (4)*
Mid	*7 (8)*
Distal/GEJ	*79 (88)*
Clinical stage	
TxN0M0	*2 (2)*
T2N0M0	*4 (4)*
T2N1M0	*8 (9)*
T3N0M0	*14 (16)*
T3N1M0	*43 (48)*
T3N2M0	*7 (8)*
T3N3M0	*2 (2)*
T4N0M0	*2 (2)*
T4N1M0	*8 (9)*

Tumour delineation

The addition of PET/CT information for RT planning resulted in a reduced delineation of the tumour length in 21 out of 90 patients (23%) with a mean reduction of 1.1 mm (SD: ± 0.7 mm), while an increased delineation of the tumour length was observed in 24 patients (27%) with a mean increase of 1.3 mm (SD: ± 0.9 mm). To avoid partial volume effects, differences <3 mm (slide thickness) were considered equal. Adjustments regarding the GTV were mainly seen at the caudal/cranial extent of the tumour. Volume modifications correlated with length modifications and were considered in the volume indexes.
The mean GTV Conformality Index (GTV-CI) was 0.87 (SD: ± 0.16), meaning that 87% of the PET/CT-based and CT-based GTVs overlapped. The mean CTV-CI was 0.93 (SD ± 0.10).
However, assuming that PET/CT represents the true extent of the tumour, it would be more interesting to determine the target tumour volumes that were omitted by CT-based delineation rather than the conformality of CT- and PET/CT-based volumes. The mean GTV-GMI was 0.07 (SD ± 0.12), i.e. 7% of the PET-avid disease was located outside the CT-GTV. In 32 patients (36%) >5% of the PET/CT-GTV was located outside the CT-based GTV. The mean CTV-GMI was 0.04 (SD ± 0.08). In 6 patients (7%) the PET/CT-GTV was also located outside the CT-CTV. In 4 of these patients this was caused by pathologic lymph node(s) located outside the CTV, while in 2 patients the PET/CT based delineation of the primary tumour extended beyond the CT-based CTV.

Treatment

Two patients underwent RT alone, 17 patients received CRT and 71 patients were treated with neo-CRT followed by surgery. All patients in the CRT or neo-CRT group received radiotherapy as planned, except for one patient who received a different regime, consisting of 50 Gy external radiotherapy combined with daily low dose cisplatin, followed by a single brachytherapy fraction of 10 Gy. For the patients treated with RT alone, one received 6 Gy brachytherapy followed by only 56 Gy external radiotherapy as a higher prescribed dose was considered to result in radiation doses beyond the dose constraints for normal tissues. The other patient, treated with primary RT did not receive the brachytherapy and died of esophageal bleeding during treatment (total dose 16 Gy).
Four patients treated with CRT (24%) did not receive adjuvant chemotherapy because of hematologic toxicity (n=2), treatment-related death (fistula followed by pneumonia) (n=1) and poor general condition (n=1).
Chemotherapy was not fully completed in 9 patients in the neo-CRT group (13%), because of hematologic toxicity (n=5), dyspnoea (n=1), cardiac chest pain (n=1), worsening general condition (n=1) and sudden deafness (n=1).
Tumour progression during or after neo-CRT was found in 5 patients (7%). Distant metastases were detected by pre-operative CT images in three patients (4%), while in two patients (3%) metastases were detected during transthoracic esophagectomy.
In total, 66 patients (93%) underwent an esophagectomy with 2-field lymphadenectomy followed by reconstruction. Thirteen (20%) patients showed a pathologically complete tumour response. Partial or non-response to neo-CRT was seen in 47 (71%) and 6 (9%) patients, respectively.
The 30-day mortality after resection was 6%. The perioperative deaths were related to septical complications resulting from necrosis of the interpositioned gastric tube (n=1) and cardiac (n=1) and pulmonary complications (n=2).

Pathology after surgery

Complete resection (R0) was achieved in 53 out of the 66 resected patients (80%). In 13 patients (20%) the resection was classified as incomplete at histopathological examination (R1), based on a tumour free margin including the circumferential margin (CRM) of <1mm, according to the Royal College of Pathologists (RCP) [12]. The smallest resection margin was found in most patients at the CRM. However, in 3 of these 13 patients (23%) tumour invaded the proximal and/or distal resection margin. Based on the PET/CT, the GTV was enlarged in 7 patients (54%) with a R1 resection as compared to the CT-based GTV. In these patients, the median geographical miss was 14% of the PET/CT-based GTV, but it remained within the CT-based CTV.

Primary endpoint

All non-metastasized patients underwent routine CT scanning every 6 months, except for 4 patients. Three of them refused further participation, while one patient declined FU due to poor physical condition. LRRs were seen in 10 patients (11%), with synchronic distant metastases in 3 patients. Most patients with LRR had been treated with (C)RT (60%). Three of these recurrences were located within the original radiation field and were considered not preventable, while 4 other patients showed regional recurrences outside the radiation field. These recurrences were also located outside the PET/CT-based CTV, so no event (preventable recurrence by PET/CT) was found. Two patients had a recurrence at the anastomosis, 18 and 35 months after R0-resection. Another patient had a recurrence at the anastomosis, 15 months after R1-resection. These three recurrences were also considered to be non-preventable as there were no changes in the target volume delineation by the use of PET/CT. Characteristics of these patients and their recurrences are listed in Table 2.

Table 2.
Characteristics of patients with locoregional tumour recurrences

	cTNM	*Type RT*	*CTV change based on PET/CT*	*Time to recurrence (months)*	*Type recurrence*	*Out-field recurrence located in PET/CT-based CTV (event)*
1	*T2N1M0*	*CRT*	*no*	*8*	*out-field*	*no*
2	*T4N1M0*	*RT*	*enlarged CTV*	*8*	*in-field*	*no*
3	*T4N0M0*	*CRT*	*no*	*16*	*in- and out-field*	*no*
4	*T2N1M0*	*neoCRT*	*reduced CTV*	*35*	*out-field (recurrence at anestomosis and lymph node hilair, despite R0 resection)*	*no*
5	*T3N1M0*	*CRT*	*enlarged CTV*	*7*	*out-field*	*no*
6	*T3N1M0*	*CRT*	*no*	*5*	*in-field*	*no*
7	*T3N1*	*neoCT*	*no*	*29*		*no*
8	*T2N0M0*	*neoCRT*	*no*	*18*	*out-field (recurrence at anestomosis, despite R0 resection)*	*no*
9	*T4N1M0*	*CRT*	*no*	*9*	*in-field*	*no*
10	*TxN0M0*	*neoCRT*	*no*	*15*	*lymph node recurrence and recurrence at anastomosis after R1 resection*	*no*

Secondary endpoints

At the time of analysis, FU of all patients was at least 18 months. At that time, 48 out of 90 patients (53%) had died after a median time of 12 months (range 0.3-36) after start of treatment. The median FU time was 29 months (95% CI 24.0-34.0).
The OS was 72%,48% and 40% at 1, 2 and 3 years, respectively, with a median OS of 23 months (95% CI 14.4-31.6). Tumour recurrences were seen in 41 patients (45%), after a median time of 8 months (range 1-35). The disease-free survival (DFS) was 56%, 45% and 36% at 1, 2 and 3 years, respectively, with a median DFS of 16 months (95% CI 3.8-28.2). The most frequently reported first site of recurrence was distant metastases in 32 patients (36%).

Discussion

This prospective observational study showed that the addition of FDG-PET to CT as reference imaging modality for the radiotherapy treatment planning for esophageal cancer patients resulted in an enlargement (23%) as well as a reduction (27%) of the GTV, which is in line with the results reported in literature [4-7]. The proportion of the PET/CT-based GTV which could be missed if the treatment planning was based on CT alone, was >5% in 32 patients (36%). Theoretically, these GTV and/or CTV mismatches, with subsequent inadequate irradiation of these areas, may result in LRR.
In the current study, LRR was found as first site of failure in 11% of the patients. All were considered not preventable by the use of PET/CT instead of CT, since half of them were located within the radiation-field, while in the other half the recurrences were located regionally, far from both the CT-based and PET/CT-based CTV. (C)RT patients accounted for 60% of the LRRs, which seemed related to the more locally advanced stages of these tumours at start of the treatment.
The most frequently reported first site of recurrence was distant metastases. This could be explained by the increased detection rate of asymptomatic distant metastases as a result of the routine CT scanning in FU. In the patients treated with CRT, distant metastases were the first site of recurrence in 8 patients (47%) of the current study. Button et al [13], who evaluated the recurrence pattern after CRT, found distant metastases in only 12% of the patients. In the RTOG 85-01 trial [14] the incidence of distant metastases was 22%. As a consequence, LRRs were less frequently seen as first site of failure in the current study. The LRR incidence was 29%, as compared to 49% and 52% in the studies by Button et al and the RTOG 85-01 trial.
Another explanation for distant metastases as predominant first site of recurrence is the relatively high percentage of patients who were treated with neo-CRT followed by surgery. After neo-CRT, distant metastases are the most frequently reported first site of recurrence [15]. Furthermore, the pattern of recurrence seems related to the histopathological response to the neo-adjuvant treatment. However, even after complete histopathological response, LRR can be seen in 13% of the patients, indicating that complete histopathological response is not synonymous with complete locoregional control [16].
R1 resections are significantly associated with a higher incidence of tumour recurrence. For these patients, the predominant pattern of failure is locoregional. In a study by Park et al. [17], 58% of the patients with a R1 resection developed LRR. The rate of R1 resections decreased significantly with the use of neo-CRT [10]. Therefore, it seems reasonable that a more accurate irradiation will

Table 3.
Characteristics of patients with a R1-resection (<1mm)

	cTNM	*Location smallest margin*	*Resection margin (mm)*	*Tumour outside CTV**	*CTV change based on PET/CT*	*GTV-GMI*	*Time to recurrence (months)*	*Time in FU (months)*	*Type recurrence*
1	*T3N1M0*	*Proximal and distal resection margin*	*0*	*Yes*	*increased GTV length (caudal)*	*0,15*	*7*	*8*	*regional and distant*
2	*T3N0M0*	*CRM*	*0,5*	*No demarcation*	*increased GTV length (cranial)*	*0,14*	*no recurrence*	*20*	
3	*T2N1M0*	*CRM*	*0,7*	*No demarcation*	*decreased GTV length (caudal)*	*0*	*8*	*15*	*distant*
4	*T3N0M0*	*CRM and proximal resection margin*	*0*	*No demarcation*	*increased GTV length (caudal)*	*0,07*	*9*	*12*	*distant*
5	*T3N1M0*	*CRM in GTV*	*<0.1*	*No*	*no difference*	*0,04*	*10*	*10*	*distant*
6	*T3N1M0*	*CRM in caudal CTV*	*0,9*	*No*	*decreased GTV length (cranial)*	*0,46*	*no recurrence*	*22*	
7	*T3N2M0*	*CRM in GTV*	*<1*	*No*	*no difference*	*0*	*12*	*13*	*distant*
8	*T3N1M0*	*CRM in GTV*	*0,5*	*No*	*decreased GTV length (cranial and caudal)*	*0*	*8*	*17*	*distant*
9	*T3N1M0*	*CRM*	*<1*	*Yes*	*increased GTV length (caudal)*	*0,03*	*no recurrence*	*5*	
10	*T3N1M0*	*CRM in CTV*	*0,4*	*No*	*increased GTV length (caudal)*	*0,21*	*no recurrence*	*18*	
11	*T3N0M0*	*CRM*	*0*	*No demarcation*	*no difference*	*0*	*no recurrence*	*15*	
12	*T3N2M0*	*CRM in cranial CTV*	*<0.1*	*No*	*no difference*	*0*	*17*	*17*	*distant*
13	*T3N2M0*	*CRM and proximal resection margin*	*0*	*Yes*	*no difference*	*0*	*no recurrence*	*16*	

** Based on in vivo demarcations of the GTV and CTV on the esophageal resection specimen as described by Muijs et al [18]*

decrease the risk of R1 resection even further, with consequently a lower risk of LRR. In the current study, 13 patients underwent an R1 resection. In 7 of these patients the GTV would have been larger when using PET/CT, with a median GTV mismatch of 14%. However, the closest resection margin was located outside the CTV in only two of these patients, of which one might have been prevented by the use of PET/CT for tumour delineation. In any case, the number of patients with a R1 resection is too small to draw any conclusions.
The current study was undertaken to evaluate the clinical relevance of the PET/CT-based changes in target volume delineation for the radiotherapy treatment of esophageal cancer. For this purpose, we chose a prospective cohort study design instead of a randomized controlled trial. This study design requires fewer patients to obtain the same statistical power, which is a major advantage. Furthermore, recurrence analyses allow safe evaluation of new (imaging) techniques, since the actual treatment remains unchanged. In the current study, no LRR was considered preventable by the use of a FDG-PET/CT treatment planning, suggesting that PET/CT-based radiotherapy treatment planning for esophageal cancer has no additional value over CT-based treatment planning, at least in terms of prevention of LRR. Given these findings, there is no rationale to perform a prospective randomised study.
Preventing distant metastases seems the major clinical challenge. It seems unlikely that patients with distant metastases as first site of recurrence, in absence of locoregional tumour recurrence, will benefit from a more adequate local treatment, which was expected of PET/CT-based radiotherapy planning.

Conclusion

Differences in radiotherapy target delineation of esophageal cancer based on the use of integrated FDG-PET/CT as compared to CT alone do not result in preventable LRRs. Therefore, the additional value of PET/CT for the radiotherapy of esophageal cancer remains limited in terms of prevention of LRRs.

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Chapter 7

General discussion and future perspectives

General discussion

Radiation oncology is changing rapidly. Several new technical developments have entered clinical practice, aiming at finding the optimal balance between tumour control and minimal toxicity for normal tissues. In recent decades, various types of radiation have been used. Cobalt-60 gamma-ir-radiation has been replaced by photon beams, which in turn may be replaced in the near future, at least partly, by proton therapy. Currently, many new developments in radiation delivery techniques have been introduced to the clinic. For example, intensity modulated radiotherapy (IMRT) and dynamic arc radiotherapy (VMAT and RapidArc) are increasingly being applied and have replaced 3D-conformal radiotherapy for patients with several tumour sites. With the use of these modern radiation delivery techniques, accurate delineation of various target volumes, including the tumour volume, has become increasingly important. 3D target volume definition and delineation using planning CT scans are now considered standard of care. Moreover, co-registration with (FDG)-PET and MR imaging is increasingly used for both target volume definition and the delineation of organs at risk [1,2].

To assure a safe and cost-effective introduction of new imaging techniques into the radiation treatment planning process, clinical validation of the accuracy and the possible consequences for clinical outcome is essential to determine the possible clinical relevance of these new techniques. This thesis focused on the potential added value of ^{18}F-FDG-PET/CT over CT for radiotherapy treatment planning in patients with esophageal cancer.

Detection of esophageal carcinoma by FDG-PET/CT

The first step in the validation of ^{18}F-FDG-PET/CT for radiotherapy planning was to evaluate the ability of this new technique to detect the gross target volume (GTV), i.e. the primary tumour and/or pathologic lymph nodes.

A systematic review, described in **Chapter 2**, showed that ^{18}F-FDG-PET is able to detect almost all tumours that are eligible for radiotherapy. Most undetected tumours are T1 tumours remaining within the submucosa. A significant association between the intensity of the primary tumour FDG uptake, expressed as standardized uptake value (SUV), and the depth of the tumour invasion was described by Kato et al. [3].

For the detection of pathologic lymph nodes, FDG-PET/CT has a higher sensitivity and specificity, as compared to CT or FDG-PET alone [4,5]. In a study by Yuan et al. [6], the sensitivity, accuracy and negative predictive value for the identification of pathologic locoregional lymph nodes were 94%, 92% and 98%, respectively, using integrated FDG-PET/CT, as compared to 82%, 86% and 95%, respectively, for the use of 1FDG-PET alone. However, although FDG-PET/CT improves the sensitivity for pathologic lymph node detection, Sihvo et al. [4] demonstrated that the sensitivity remained significantly lower than for endoscopic ultrasonography (EUS) (p=0.001).

Recently, Manabe et al. [7] demonstrated that the sensitivity of FDG-PET(/CT) to detect lymph node metastases is affected by the avidity of the primary esophageal cancer. The FDG uptake of pathologically confirmed lymph node metastases correlated positively with that of the primary lesions, which resulted in a lower sensitivity for the detection of lymph node metastases in patients with low FDG uptake in the primary tumour.

The addition of FDG-PET to planning CT changes tumour delineation and treatment planning.
The second step in the validation was an in silico planning study to evaluate the potential benefit of FDG-PET/CT as reference imaging modality for radiotherapy treatment planning in esophageal cancer patients as compared to CT. In **Chapter 4**, my colleagues and I demonstrated that the addition of FDG-PET to CT resulted in an enlargement of the GTV in 19% of the cases and in a reduction of the GTV in 43% of the cases. Similar results were found in the RESPECT trial, as described in **Chapter 6**. In that study, we found an enlargement of the GTV in 23% and a reduction in 27% of the patients, which corresponded well to the results described in other studies [8,9].
In Chapter 4 we also demonstrated that these changes in target volume delineation resulted in radiotherapy treatment plan modifications leading to significant differences in dose distributions to heart and lungs ($p < 0.04$). Corresponding changes in Normal Tissue Complication Probability (NTCP) values ranged from -3% to +2% for radiation pneumonitis and from -0.2% to +1.2% for cardiac mortality.
Furthermore, FDG-PET-avid tumour might be missed by CT-based tumour volumes, resulting in a potential geographic miss. The proportion of the PET/CT-based GTV which would have been missed if the treatment planning was based on CT as reference modality, was more than 5% in 13 patients (61%) in the study, described in **Chapter 4**. In the RESPECT trial, described in Chapter 6, this percentage was lower. In 32 patients (36%) more than 5% of the PET/CT-GTV was located outside the CT-based GTV. In 6 of these patients, the GTV was also located outside the CTV. These GTV and/or CTV mismatches for the radiotherapy treatment plans resulted in under dosing and possibly ineffective treatment. However, the question remains as to whether these potential geographical misses are of clinical importance.

Pathologic evaluation of the radiotherapy target volumes

Pathologic evaluation can provide information regarding the exact macroscopic and microscopic extension of the esophageal tumour. However, accurate validation is hampered by the difficulty of obtaining pathological tissue and comparing this with pre-surgical imaging. Therefore, reports on pathologic validation are limited. Most previous studies have reported on tumour length correlation rather than the accuracy of tumour localisation, as described in **Chapter 2**. However, Yu et al. [10] were the first to evaluated spatial conformity. In that study, various FDG-PET/CT-based and CT-based GTV delineations were compared to the gold standard of GTV delineation from pathology. They found that the mean conformity index (CI) of the GTVs was significantly higher for CT as compared to the best PET/CT delineation method (0.77 ± 0.17 vs. 0.52 ± 0.20), suggesting no additional value of PET/CT. Indeed, in that study CT alone appeared to be more accurate than PET/CT.

Chapter 5 describes how we developed a clinical useful method to demarcate the radiotherapy target volumes intra-operatively on the esophageal resection specimen in order to evaluate the accuracy of the currently used CT-based GTV and CTV. Using this method we gained information regarding the exact location of pathologic tumour in relation to these target volumes at pathologic examination. This type of quality control is essential and may provide suggestions for further improvement of the current radiotherapy treatment. We were able to show that in a substantial proportion of patients, macroscopic tumour was found outside the GTV and/or microscopic tumour was found outside the CTV. These GTV and/or CTV mismatches suggest inaccurate GTV delineation, inadequate CTV margins or tumour growth before, during or after neo-adjuvant chemoradiation (neo-CRT). Moreover, the presence of microscopic tumour spread outside the CTV had a significantly adverse impact on disease free survival (DFS) and overall survival (OS). This might indicate biologically more aggressive tumour behaviour. On the other hand, these findings emphasize the importance of accurate delineation of the GTV and the use of adequate CTV margins.
The literature on the optimal CTV margins to cover microscopic tumour spread in esophageal cancer is very limited. Only one study has been performed with the explicit aim of defining the optimal CTV margin for submucosal spread; the conclusion was that a cranial-caudal CTV margin of at least 30 mm is required to cover the extent of microscopic spread within the esophagus in 94% of patients with squamous cell carcinoma (SCC). However, for adenocarcinoma (AC) located at the gastro-esophageal junction (GEJ), a distal CTV margin of at least 50 mm is required to cover microscopic tumour in 94% of cases [11]. In our study described in Chapter 5, a CTV margin of 25 mm was used in caudal direction, if the tumour expanded into the gastric cardia. In line with the findings of Gao et al [11] this margin seemed insufficient, since most cases of microscopic tumour outside the CTV were located caudally of the distal CTV margin into the gastric cardia. Consequently, based on the results of this evaluation, we adjusted the caudal CTV margin for tumours at the GEJ at our institute.
Some studies have suggested that the CTV should also include elective (subclinical) lymph nodal areas. Huang et al. [12] investigated the pattern of lymph node metastases after esophagectomy in patients with SCC and demonstrated that microscopically positive lymph nodes were found in a substantial number of patients. Moreover, the number of microscopically positive lymph nodes was even higher than the number of macroscopically positive nodes (2737 vs. 1589). A meta-analysis concerning the pattern of lymph node metastasis in esophageal cancer patients was performed by Ding et al. [13]. The pooled estimates for lymph node metastasis rate in upper, middle and lower thoracic esophageal cancer were 31%, 17% and 11% cervical, 42%, 21% and 11% upper mediastinal, 13%, 28% and 20% middle mediastinal, 3%, 8% and 23% lower mediastinal, and 9%, 21% and 40% abdominal, respectively. Based on the observed pattern of lymph node metastases for the various tumour locations, the authors suggested that cervical and upper mediastinal nodes should be included in the CTV for tumours in the upper esophagus. The CTV for tumours in the lower esophagus should include the middle and lower mediastinal and upper abdominal lymph node regions. For mid-esophageal tumours, the CTV should cover all these lymph node areas.
Two major limitations of this meta-analysis were that 41 out of the 45 studies included were from Asia and 97% of the patients had SCC. Therefore, these results may not be valid for AC and/or the non-Asian population.
The clinical relevance of elective nodal irradiation is disputed. In a retrospective study by Hsu et al. [14], elective irradiation of the supraclavicular or celiac nodal area did not improve the overall or disease-free survival, despite a small difference in M1a-failure (11% vs. 3% at 3 years; $p = 0.05$). It seems questionable whether the possible benefits of elective nodal irradiation outweigh the disadvantage of larger irradiation fields. These larger irradiation fields will consequently increase the risk of normal tissue toxicity, while even with the currently used CTV margins the radiation dose to the heart and/or lungs is relatively high; serious complications, both acute and late, have been described [15-17]. The potential survival benefit of elective nodal irradiation would likely be counteracted by these serious complications. This is probably why elective treatment of uninvolved nodes is not recommended in the current guidelines for non-small cell lung cancer (NSCLC). Therefore,

further research is required to determine the actual value of elective nodal irradiation.

Clinical validation

The final step in the validation of FDG-PET/CT for radiotherapy treatment planning is the evaluation of the clinical relevance and outcome. The RESPECT trial was the first to evaluate the clinical relevance of the FDG-PET/CT based changes in the target volume delineation for the radiotherapy treatment of esophageal cancer. In this study, described in **Chapter 6**, we did not find any locoregional recurrences (LRRs) that were considered preventable by the use of PET/CT based treatment planning, despite a mean CTV geographical mismatch index (GMI) of 0.04, i.e. 4% of the PET/CT-based CTV was located outside the CT-based CTV. However, none of these patients developed a recurrence in these areas. Therefore, we concluded that FDG-PET/CT-based radiotherapy treatment planning for esophageal cancer has no additional value over CT-based treatment planning in terms of prevention of LRR.
The RESPECT study was a prospective observational cohort study. Although clinical randomized trials (RCTs) are considered the golden standard to evaluate the potential of a new intervention, they are not always practically feasible and/or the most suitable methodology. Prospective observational cohort studies require fewer patients to obtain the same statistical power and are therefore less time consuming than RCTs. Consequently, information regarding the primary endpoint - the value of PET/CT for preventing LRRs - is available sooner. Furthermore, prospective observational cohort studies with recurrence analyses allow safe evaluation of new (imaging) techniques, since the actual treatment remains unchanged. Direct introduction of a new technique in the study cohort is not advisable, unless the expected gain is relatively large. In that case, proper stopping rules should assure a safe introduction.
The results of the RESPECT study, i.e. that PET/CT has no additional value of PET/CT for radiotherapy of esophageal cancer in terms of preventing LRRs, confirmed that this type of study design can be used reliably for these purposes. On the other hand, as a prospective observational cohort study it focussed on the evaluation of FDG-PET/CT-based enlargements of the radiotherapy target volumes only, and did not evaluate the justification of FDG-PET/CT-based target volume reductions. The latter information might have been available after a RCT.

Future perspectives

Optimal timelines in care paths might improve target volume delineation

Even though the value of PET/CT for radiotherapy planning seems limited in terms of prevention of LRR, FDG-PET/CT might still play a role in the detection of pathologic lymph nodes and patient selection.
As shown in **Chapter 3**, esophageal cancer can progress rapidly. The FDG-PET/CT for radiotherapy planning revealed new pathologic lymph nodes and new distant metastases as compared to the diagnostic FDG-PET(/CT), within a median time interval of 30 days. The detection of the new pathologic lymph nodes will influence the radiation fields, which emphasizes the importance of recent state-of-the-art imaging and underlines the necessity to minimize the time interval to start

of treatment. For other tumour sites, this was already demonstrated in a systematic review by Chen et al. [18]. They found a significant association between an increased waiting time for radiotherapy and the risk of local recurrence, which may translate into decreased survival.
Furthermore, the detection of distant metastases has important implications for the treatment intent, which switches from curative to palliative. Therefore, time-limited imaging (≤ 4-6 weeks) is essential for adequate patient selection. Curatively intended treatment can be accompanied by treatment related toxicity and subsequent decreased quality of life [19]. Moreover, the costs of curative treatment for esophageal cancer are high [20].
This rapid esophageal tumour progression requires more optimal timelines in care paths than are currently available, which contributes to a better patient selection and might increase the accuracy of target volume delineation by improved detection of pathologic lymph nodes.

MRI for target volume delineation of esophageal cancer

The use of magnetic resonance imaging (MRI) seems more promising for target delineation of the primary esophageal tumour. MRI is a minimally invasive imaging technique that provides excellent soft-tissue contrast, and can therefore improve the visualisation and target volume delineation in esophageal cancer. In recent years, MRI has increasingly been used for target volume delineation of several other tumour sites, and currently provides excellent results for prostate cancer and head and neck cancer [21-24]. Until recently, no studies have supported the use of MRI for the detection of esophageal cancer. Van Rossum et al. [2] suggested that this might be explained by technical shortcomings of the conventional MRI. Increased field strength, faster sequences and cardiac and respiratory gating might yield better imaging quality. These authors suggested that MRI will soon have the potential to improve the detection of local tumour extension and to identify pathologic lymph nodes.
Recently, De Cobelli et al. [25] also analysed the role of diffusion weighted MRI (DWI-MRI) for tumour response evaluation after neo-CRT. Their results were very promising. Responders (tumour regression grade (TRG) 1-2-3) showed lower apparent diffusion coefficients (ADC) ($p<0.01$) at the pre-neo-CRT DWI-MRI, and higher ADC ($p<0.01$) at the post-neo-CRT DWI MRI than non-responders (TRG 4-5). Furthermore, ADC increased in responders (ΔADC; $p<0.01$) and ΔADC inversely correlated with the TRG at pathology ($r=-0.71$, $p<0.01$). Distinction between responders and non-responders seemed possible at an ADC increase threshold of 13.6 % (sensitivity=88.2%, specificity=86.7%, accuracy=87.5%; AUC=0.90; $p<0.01$). Therefore, the authors suggested that ΔADC can be used to assess gastroesophageal tumour response to neo-CRT. Whether DWI-MRI can also be useful for early tumour response monitoring to distinguish the responders from the non responders, is a subject for future research.

Dose escalation

Radiation dose escalation in the treatment of esophageal cancer has been debated for many years, especially since the Intergroup trial (INT 0123 – RTOG 94-05), which randomized between CRT up to 50.4 Gy vs. CRT up to 64.8 Gy (in daily fractions of 1.8 Gy), did not find a significant difference in survival or locoregional tumour control. Even in a separate survival analysis, which included only patients who received the assigned radiation dose, no survival advantage was found in the high dose arm [26]. However, this trial used a 3D-CRT technique

without lung inhomogeneity corrections, resulting in higher doses to normal tissues.
Despite these disappointing results, subsequent studies have investigated the potential use of a simultaneously integrated boost (SIB) delivered with a IMRT technique, with the aim of improving local tumour control by increasing the dose to the GTV [27,28]. However, this type of dose escalation seems useful only if it is possible to delineate the gross tumour volume correctly, since wide margins are no longer there to compensate for uncertainties.
Furthermore, dose escalation is accompanied by an increased irradiation dose to normal tissues, with a subsequent risk of toxicity. Even with the current radiation regimes without a boost, the radiation dose to the heart and/or lungs is relatively high and symptomatic cardiac and pulmonary toxicity had been described in several retrospective studies and seems related to cardiac and/or lung doses (MHD, V40, MLD, V5, V20) [15,17,29,30].
Konski et al. [15] found treatment related cardiac toxicity (RTOG grade III and IV) in 12 out of 102 patients who were treated with primary chemoradiotherapy. The 12-month actuarial incidence of any observed cardiac toxicity was 20.4%, and 8.5% when only symptomatic toxicities were considered. In these patients, the mean heart V20, V30 and V40 were significantly higher as compared to patients without symptomatic cardiac toxicity.
Cardiac toxicity no longer appears to be only a late effect of radiotherapy and could therefore counteract the potential survival benefit of dose escalation [31]. The highest increased risk of ischemic heart disease was found in the first 4 years after treatment, as described by Darby et al. [31], who evaluated the cardiac toxicity in a large group of breast cancer patients treated with radiotherapy. Moreover, Hatakenaba et al. [29] evaluated the acute cardiac toxicity in 30 esophageal cancer patients who received CRT. In this prospective trial, MRI was used to analyze the functioning of the left ventricle (LV). After CRT, the LV end-diastolic volume index, stroke volume index, ejection fraction (EF) and wall motion in segments 8-10 decreased significantly in the group receiving a relatively high LV dose (3.6-29.4 Gy).

IMRT, and in the future proton beam irradiation, improves target conformality. As a result of the more conformal dose delivery, IMRT, and to an even larger extend proton beam irradiation, can reduce the radiation dose to organs at risk, which decreases the risk of toxicity. Recently, two studies retrospectively compared 3D-CRT vs. IMRT in esophageal cancer patients treated with (neo-adjuvant) CRT. Lin et al. [32] found a greater incidence of documented cardiac-related deaths in the 3D-CRT group (5-year estimate 11.7% vs. 5.4%). Furthermore, OS was significantly worse in the 3D-CRT group (median OS 25 months vs. 43 months). No difference was seen in cancer-specific mortality. For the nonsurgical patients, the LRR rate was higher after 3D-CRT as compared to after IMRT. However, 3D-CRT and IMRT patients were mostly treated in 2 different periods, with imbalances resulting from, for example, the introduction of PET scans for staging, which were performed in 54% vs. 96% of the patients. FDG-PET/CT improves the staging and selection process [33], which can be a major bias for treatment outcome. Moreover, in this study by Lin et al.[32], the diagnostic PET was significantly associated with a lower incidence of LRR.
Wang et al. [30] focused on post-operative complications after neo-adjuvant CRT followed by surgical resection. They demonstrated that the risk of pulmonary complications was significantly increased using 3D-CRT as compared to IMRT (odds ratio (OR), 2.02; 95% confidence interval (CI), 1.10-3.69). Furthermore, the pulmonary complication rate was even lower in the patients treated with proton beam irradiation (p=0.019). However, the difference between IMRT and proton beam

irradiation was not significant, which might be explained by the relatively low number of patients treated with protons (OR, 2.228; 95% CI, 0.863-5.755). The mean lung dose (MLD) was strongly associated with pulmonary complications and might explain the differences in toxicities between the radiation modalities.
Lin et al. [34] were the first to prospectively evaluate the results of proton chemo-radiotherapy and found promising results. The treatment was well tolerated, with relatively low acute treatment-related toxicities and perioperative morbidities. Furthermore, tumour response and disease related outcomes were good, with a nearly complete tumour response in 50% of the patients treated with neo-adjuvant CRT followed by a surgical resection.
However, for safe use of the conformal dose delivery of IMRT and especially proton beam irradiation, accurate target volume delineation is essential and reliable target volumes are a prerequisite. Furthermore, protons can be quite sensitive to density changes along their path. Therefore, range errors due to diaphragm motion, stomach gas-filling and cardiac activity must be considered to assure target coverage, as they can manifest themselves in beam overshoot or undershoot [35].
Esophageal tumors can move up to 10 mm due to respiratory motion [36,37,38]. 4D-CT can be used to evaluate the dosimetric impact of this respiration motion [35]. On the other hand, respiratory gating can be used to reduce the intra-fraction respiratory motion, while adaptive radiotherapy might minimize the influence of inter-fraction motion [39].
One thing seems clear: imaging of tumour and/or normal tissue (movement) will play increasingly an important role in the radiotherapy of esophageal cancer in the near future.

Adjuvant treatment

Distant metastases are frequently reported as first site recurrence after (neo-adjuvant) CRT. Preventing these distant metastases is a major clinical challenge [40,41]. However, the role of chemotherapy in an adjuvant setting in patients with esophageal cancer is still controversial, so most studies have not been based on neo-adjuvant CRT [42,43].
The role of targeted therapy in the treatment of esophageal cancer remains to be determined. For patients with metastasized Her2-postive GEJ and gastric AC, the TOGA-trial showed a benefit from the addition of trastuzumab, a monoclonal antibody against Her2, to the standard chemotherapy of 5-FU (capcetabin) and cisplatin. Median OS was 13.8 months (95% CI 12-16) for those receiving trastuzumab and chemotherapy vs. 11.1 months (10-13) for the patients receiving chemotherapy alone (hazard ratio 0.74; 95% CI 0.60-0.91; p<0.01)[44]. Her2/Neu overexpression was reported in a wide range of patients with esophageal AC (0-73%) [45].
Currently, the RTOG is conducting 2 trials in which targeted agents are added to the CRT regime [43][46]. The RTOG 1010 trial randomizes Her2-positive GEJ AC patients to neo-adjuvant CRT, consisting of carboplatin/paclitaxel and radiotherapy, with or without trastuzumab, followed by surgery. The trastuzumab will be continued adjuvant for one year.
For patients who are ineligible for surgery, the RTOG 0436 trial randomizes patients with SCC or AC for primary CRT with or without cetuximab, a monoclonal antibody against EGFR. The results of these trials will indicate whether these targeted agents have additional value in the curative treatment of esophageal cancer.

Conclusion

Although the addition of FDG-PET to planning-CT in esophageal cancer results in changes in target volumes and thus different radiation treatment plans, the added value of PET-CT for preventing locoregional recurrences is limited. These findings underline the importance of a proper validation of new imaging modalities for target volume definition before introducing them into routine clinical practice.

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Appendices

Summary and conclusion

Summary

The incidence of esophageal cancer is substantially rising and it is the seventh most common cause of cancer-related death worldwide [1-3].
Traditionally, surgery has been the primary treatment modality for esophageal cancer. More recently, chemoradiation has been increasingly applied, either as definitive therapy or in the neo-adjuvant setting prior to curatively intended surgical resection [4].
Accurate identification and delineation of the gross tumour volume (GTV) is the basis of adequate irradiation. However, tumour delineation is one of the difficulties in oesophageal cancer, which is shown by the rather large intra- and interobserver variability [5,6] for the delineation of the GTV.
Computer tomography (CT) is the current reference imaging modality for delineation of the GTV for radiotherapy of oesophageal cancer, integrated with information derived from other diagnostic modalities, such as endoscopic ultrasound (EUS). However, the discriminative value of CT is generally poor, and it remains difficult to relate endoscopic (ultrasound) information to the CT images. Therefore, the use of other currently available imaging methods may be useful in determining adequate target volumes.
Incorporation of metabolic data from ^{18}F- Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scans might improve the accuracy of tumour delineation. FDG-PET already showed to be very useful in the staging process of oesophageal tumours [7], in particular with regard to the detection of distant metastases and nodal staging.
The main and general objective of this thesis was to determine the value of the (PET/)CT-scan for radiotherapy of oesophageal cancer and its potential to improve the treatment outcome, in terms of efficacy and toxicity.

Tumour detection by FDG-PET/CT

The first step in the validation of FDG-PET/CT for radiotherapy planning was a systematic review to evaluate the ability of FDG-PET/CT to detect the primary tumour and/or pathologic lymph nodes. The systematic review, described in **Chapter 2**, showed that FDG-PET detects almost all esophageal tumours. T1 tumours, remaining within the submucosa, are the most undetected tumours. Furthermore, PET/CT can be used very well for the detection of pathologic lymph nodes, especially for non-adjacent lymph nodes. Moreover, integrated PET/CT has a higher sensitivity and specificity, as compared to CT or FDG-PET alone [8,9].
A planning PET/CT can also be used to intercept fast tumour progression. **Chapter 3** described a study in which the findings of the diagnostic PET/CT were compared to the findings of PET/CT for radiotherapy planning. Tumour progression was seen in a substantial proportion of the patients, within a median time interval of 30 days. The PET/CT for radiotherapy planning revealed 18 new pathologic lymph nodes, which resulted in a changed N-stage in 8 patients (18%). The detection of new pathologic lymph nodes will influence the radiation fields, which emphasizes the importance of recent state-of-the-art imaging and underlines the necessity of minimizing the time interval to start of treatment.
Newly detected distant metastases (M) were seen in 6 patients (13%), whichhas important implications for the treatment intent, which switches from curative to palliative. Therefore, time-limited imaging (≤ 4-6 weeks) is essential for adequate patient selection.

In-silico planning study

The second step in the validation was an in-silico planning study to evaluate the potential advantage of PET/CT over the current use of CT for the radiotherapy planning for patients with esophageal cancer, which is described in **Chapter 4**.
The addition of PET to the currently used CT resulted in an enlargement of the GTV as well as a reduction. Adjustment of the GTV with more than 10% was seen in 62% of the cases; 9 patients (43%) showed a GTV reduction, while in 4 patients (19%) the addition of PET resulted in an enlargement of the GTV. Adjustments regarding GTV were mainly seen at the caudal/cranial extent of the tumour. Similar results were found in the RESPECT trial, as described in **Chapter 6**. In that study, we found an enlargement of the GTV in 23% and a reduction in 27% of the patients. This corresponded well to the results described in other studies [10,11].
PET-positive disease which was omitted by the CT-based GTV and/or CTV can result in a geographical miss. Chapter 4 showed a mean geographical mismatch index (GMI) for the GTV of 0.16 (SD ±0.24), meaning that 16% of the PET-avid disease was located outside the CT-GTV. In 13 patients (61%) more than 5% of the PET/CT-based GTV was omitted by the CT-based GTV. Geographical misses will lead to underdosing and possibly ineffective treatment. Furthermore, treatment plan modifications resulted in significant changes ($p < 0.04$) in dose distributions to heart and lungs. Corresponding changes in NTCP values ranged from -3% to +2% for radiation pneumonitis and from -0.2% to +1.2% for cardiac mortality.
However, the question remains as to whether these potential geographical misses are of clinical relevance.

Pathologic evaluation of the radiotherapy target volumes

More information regarding the exact macroscopic and microscopic extension of the esophageal tumour can be provided by a thorough pathologic evaluation. In **Chapter 5** we developed a method to demarcate the radiotherapy target volumes intra-operatively on the esophageal resection specimen in order to evaluate the accuracy of the currently used CT-based GTV and CTV at pathologic examination. This type of quality control is essential and may provide suggestions for further improvement of the current radiotherapy treatment.
Using this method, we were able to show that after neo-adjuvant chemoradiotherapy (neo-CRT) and resection, macroscopic tumour was located outside the GTV in 7 patients (11%), while microscopic tumour was located outside the CTV in an even larger number of patients (n=9; 14%). These GTV and/or CTV mismatches suggest inaccurate GTV delineation, inadequate CTV margins and/or tumour growth before, during or after neo-CRT.
Most cases of microscopic tumour outside the CTV were located caudally of the distal CTV margin into the gastric cardia, where only a 25mm margin was used, suggesting that this margin was insufficient.
The presence of microscopic tumour spread beyond the CTV borders had a significantly adverse impact on disease free survival (DFS; HR 5.92, 95%CI 1.89-18.54) and overall survival (OS; HR 4.96, 95%CI 1.03-15.36). The one year DFS was 23% vs. 77% for patients with or without tumour outside the CTV($p<0.01$). These findings emphasize either the importance of accurate delineation of the GTV and CTV. On the other hand, tumour outside the CTV might also indicate biologically more aggressive tumour behavior and might be subject of future studies.

Clinical validation

The final step was the clinical validation, which was described in **Chapter 6**. The RESPECT-trial was a prospective observational cohort study with the aim to determine the proportion of locoregional recurrences (LRRs) that could have been prevented if the radiotherapy treatment planning for esophageal cancer was based on PET/CT instead of CT.
GTV and/or CTV mismatches, with subsequent inadequate irradiation of these areas, may result in LRRs. After a follow up of at least 18 months, LRRs as first site of failure were seen in 10 patients (11%).
All were considered not preventable by the use of PET/CT instead of CT, since 3 recurrences were located within the original radiation field. In 4 other patients regional recurrences were located far from both PET/CT- and CT-based. Three other patients developed a recurrence at the anastomosis, which were also considered non-preventable as there were no changes in the target volume delineation by the use of PET/CT.
The results of the RESPECT study showed that differences in radiotherapy target delineation of esophageal cancer based on the use of integrated FDG-PET/CT as compared to CT alone did not result in preventable LRRs.

Conclusion

Although the addition of FDG-PET to planning-CT in esophageal cancer results in changes in target volumes and thus different radiation treatment plans, the added value of PET-CT for preventing locoregional recurrences is limited. These findings underline the importance of a proper validation of new imaging modalities for target volume definition before introducing them into routine clinical practice.

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Samenvatting en conclusie

Samenvatting

De incidentie van het oesofaguscarcinoom in Nederland neemt toe en is in de afgelopen 20 jaar zelfs verdubbeld [1]. Deze stijging komt met name door een toename in de incidentie van het adenocarcinoom. De incidentie van het plaveiselcelcarcinoom is nagenoeg gelijk gebleven. Het adenocarcinoom had in 2010 in Nederland een incidentie van 10,8 per 100.000 inwoners [2].
De prognose van het oesofaguscarcinoom is matig. Dit komt doordat de tumor relatief laat klachten geeft en daardoor vaak bij presentatie al in een vergevorderd stadium of zelfs gemetastaseerd blijkt te zijn.
Chirurgie is jarenlang de behandeling van eerste keus geweest bij het oesofaguscarcinoom met een beperkt stadium. In de afgelopen decennia echter wordt (chemo)radiotherapie als primaire behandeling maar ook als neo-adjuvante therapie steeds vaker toegepast.
Recent werd in een Nederland uitgevoerde prospectief gerandomiseerde trial (de CROSS-studie) aangetoond dat neo-adjuvante chemoradiotherapie gevolgd door chirurgie zowel de ziektevrije overleving (HR 0.50, 95% CI 0.36-0.69) als de algehele overleving (HR 0.66, 95% CI 0.50-0.87) significant verbetert ten opzichte van chirurgie alleen. De mediane overleving was 49.4 maanden in de groep met neo-adjuvante chemoradiotherapie gevolgd door chirurgie tegenover 24 maanden in de groep die alleen met chirurgie behandeld was [3].
Voor patiënten die niet geopereerd kunnen worden, is primaire chemoradiotherapie een goed alternatief, en heeft de voorkeur boven radiotherapie alleen. De RTOG 85-01 studie, waarin chemoradiotherapie (50Gy in 25 fracties met cis/5FU) werd vergeleken met alleen radiotherapie (64 Gy in 32 fracties), liet een betere overleving zien na chemoradiotherapie (mediane overleving 14.1 vs. 9.3 maanden) [4].
In vroege stadia van het oesofaguscarcinoom kunnen echter ook goede resultaten met alleen radiotherapie worden bereikt [5-7].
Bij een behandeling met radiotherapie zijn een nauwkeurige identificatie van de tumor en vervolgens een accurate intekening van het doelvolume essentieel. In de praktijk blijkt het echter moeilijk om vooral de craniale en caudale uitbreiding van het oesofaguscarcinoom nauwkeurig te bepalen met behulp van CT. Daarnaast is het lastig om de informatie van endoscopie te vertalen naar CT-beelden. Het gebruik van FDG-PET/CT zou het intekenen van het doelvolume mogelijk kunnen verbeteren, doordat naast de anatomische beelden ook gebruik gemaakt wordt van metabole informatie van de tumor.

Dit proefschrift richt zich op de validatie van het gebruik van FDG-PET/CT bij de radiotherapeutische behandeling van het oesofaguscarcinoom. Wij hopen hiermee te kunnen vaststellen of het gebruik van PET/CT daadwerkelijk resulteert in een meer adequate bestraling en of dit vervolgens leidt tot een verbeterde behandeluitkomst.

Detectie van het oesofaguscarcinoom door PET/CT

De eerste stap in de validatie van het gebruik van FDG-PET/CT bij de radiotherapeutische behandeling van het oesofaguscarcinoom is het evalueren van de beeldvormende eigenschappen van de techniek. Is FDG-PET/CT in staat om de tumor en eventuele pathologische lymfklieren beter af te beelden? Uit een systematische review van de literatuur, zoals beschreven in **hoofdstuk 2**, blijkt dat FDG-PET/CT in staat is om vrijwel alle tumoren die in aanmerking komen voor radiotherapie te detec-

teren. Vrijwel alleen T1-tumoren, die beperkt blijven tot de submucosa, kunnen worden gemist. Daarnaast blijkt FDG-PET/CT ook bruikbaar voor de detectie van pathologische lymfklieren [8]. De systematische review in **hoofdstuk 2** laat zien dat PET/CT een hogere sensitiviteit en specificiteit heeft dan PET of CT afzonderlijk.
FDG-PET/CT is bij het oesofaguscarcinoom superior m.b.t. de detectie van afstandsmetastasen en speelt daardoor een belangrijke rol bij de stagering. Het oesofaguscarcinoom kan echter zeer snel progressief zijn. **Hoofdstuk 3** beschrijft een studie waarin de stagerings-PET(/CT) vergeleken wordt met de PET/CT scan voor de radiotherapeutische planning. Binnen een mediaan tijdsinterval van 30 dagen werden bij 6 patiënten (13%) afstandsmetastasen ontdekt op de plannings-PET/CT, die op de diagnostische PET(/CT) nog niet zichtbaar waren, zelfs niet in retrospectie. Daarnaast werden ook 18 nieuwe pathologische lymfklieren gezien, die bij 8 patiënten (18%) resulteerde in een veranderde N-status. Deze snelle tumorprogressie benadrukt de noodzaak om de tijd tussen diagnostiek en start van de behandeling te beperken. Daarnaast kan recente beeldvorming, in de vorm van een plannings-PET/CT, bijdragen aan verbeterde patiënten selectie en een verbeterde intekening van pathologische lymfklieren.

In-silico planningsstudie

De tweede stap in de validatie was een in-silico planningsstudie om het potentiële voordeel van PET/CT voor de radiotherapeutische planning te evalueren bij patiënten met oesofaguscarcinoom, in vergelijking met het oorspronkelijk gebruik van CT. In **hoofdstuk 4** worden de uitkomsten van deze studie beschreven, waarin zowel naar het verschil in intekening als naar de gevolgen voor de radiotherapie planning is gekeken.
Toevoeging van de PET aan de CT resulteerde in een vergroting van het GTV (Gross Tumour Volume) bij 19% van de patiënten en in een verkleining van het GTV bij 43% van de patiënten. Vergelijkbare resultaten werden beschreven in de RESPECT-studie, te vinden in **hoofdstuk 6**. In deze studie, werd bij 23% een vergroting van het GTV gezien en een verkleining bij 27% van de patiënten.
Hoofdstuk 4 laat zien dat de deze veranderingen in doelvolume ook resulteren in aangepaste bestralingsplannen, met als gevolg significante veranderingen in de dosisverdeling in hart en longen ($p<0.04$). Bijbehorende veranderingen in NTCP (Normal Tissue Complication Probability) waarden varieerde van -3% tot +2% voor radiatie pneumonitis en van -0.2% tot 1.2% voor cardiale mortaliteit. Daarnaast kan tumoractiviteit op PET worden gemist door het CT-gebaseerde doelvolume, resulterend in een potentiële geografische missmatch, wat kan leiden tot inadequate bestraling. Bij 13 patiënten (61%) zou meer dan 5% van het PET/CT-gebaseerde GTV worden gemist door het CT-gebaseerde GTV. In **hoofdstuk 6** is dit percentage lager. Daar valt bij 32 patiënten (36%) meer dan 5% van het PET/CT gebaseerde GTV buiten het CT-gebaseerde GTV. In 6 (7%) van deze 32 patiënten ligt het PET/CT-gebaseerde GTV ook buiten het CT-gebaseerde CTV. Het gevolg hiervan voor de bestralingsplanning is een mogelijke onderdosering ter plaatse van de tumor. Het blijft echter de vraag of deze potentiële verschillen ook daadwerkelijk een klinische betekenis hebben.

Pathologische evaluatie

Uiteindelijk kan alleen een pathologische evaluatie informatie geven over de exacte macroscopische en microscopische tumoruitbreiding van het oesofaguscarcinoom.

Accurate pathologische validatie blijkt in de praktijk echter moeizaam, omdat het lastig blijft om pathologisch weefsel te vergelijken met prechirurgische beeldvorming. **Hoofdstuk 2** laat zien dat er dan ook erg weinig studies zijn over dit onderwerp en in de studies die er zijn wordt veelal gekeken naar een correlatie in tumorlengte en niet naar de exacte tumorlocatie.
In **hoofdstuk 5** wordt een methode beschreven ter evaluatie van de radiotherapeutische doelvolumina. Hierbij worden de grenzen van deze doelvolumina intra-operatief zo nauwkeurig mogelijk gemarkeerd op de te resecteren slokdarm. Deze methode stelt ons in staat om bij de pathologische evaluatie informatie te verkrijgen over de exacte locatie van het macroscopisch en/of microscopisch tumorresidu in relatie tot de huidige CT-gebaseerde radiotherapeutische doelvolumina (GTV en CTV). Dit type evaluatie is een belangrijk onderdeel van de kwaliteitscontrole en kan helpen bij de verdere verbetering van de huidige radiotherapeutische planning.
In een substantieel deel van de patiënten werd macroscopische tumor gevonden buiten het GTV (7 patiënten; 11%) en/of microscopisch tumor buiten het CTV (9 patiënten; 14%). Dit kan duiden op een inaccurate GTV intekening, inadequate CTV marges, of tumor groei voor, tijdens of na de neo-adjuvante behandeling. Daarnaast bleek de aanwezigheid van microscopisch tumor buiten het CTV een onafhankelijke negatieve prognostische factor te zijn voor zowel de ziektevrije (HR 5.92, 95%CI 1.89-18.54) als de algehele overleving (HR 4.96, 95%CI 1.03-15.36). De 1-jaars ziektevrije en algehele overleving was respectievelijk 23% en 20% voor patiënten met tumor buiten het CTV tegenover 77% en 86% voor patiënten zonder tumor buiten het CTV ($p<0.01$). Tumor buiten het CTV zou dus kunnen duiden op een agressiever beloop bij deze patiënten. Aan de andere kant onderstreept het ook het belang van een accurate intekening van het GTV en het gebruik van adequate CTV marges.

Klinische validatie

De laatste stap in de validatie van de PET/CT voor radiotherapeutische planning is het vaststellen van de klinische relevantie en uitkomsten. De RESPECTstudie is de eerste studie waarin gekeken is naar de klinische relevantie van de op PET/CT gebaseerde veranderingen bij de intekening van het doelvolume en vervolgens de radiotherapeutische planning bij het oesofaguscarcinoom. In deze studie, die beschreven wordt in **hoofdstuk 6**, was het eindpunt een door PET/CT te voorkomen locoregionaal recidief, gelegen buiten het CT-gebaseerde CTV en in het PET/CT gebaseerde CTV. Locoregionale recidieven werden gezien bij 10 patiënten (11%). Recidief analyse liet echter zien dat geen van deze locoregionale recidieven te voorkomen was geweest door het gebruik van PET/CT voor de radiotherapeutische planning. Bij 3 patiënten ging het om een recidief in het oorspronkelijk bestralingsveld. Vier regionale recidieven bleken zowel buiten het CT- als het PET/CT gebaseerde CTV te liggen. Tot slot waren er 3 patiënten met een recidief ter plaatse van de anastomose. In deze patiënten waren de CT- en PET/CT-gebaseerde doelvolumina gelijk.
Afstandsmetastasen werden het meest frequent gezien als eerste presentatie van recidief ziekte (32 patiënten; 36%).
Op basis van deze bevindingen lijkt de toegevoegde klinische waarde van PET/CT voor de radiotherapeutische planning ter voorkoming van locoregionale recidieven beperkt.

Toekomstige ontwikkelingen - MRI

Hoewel de toegevoegde waarde van PET/CT beperkt lijkt voor de radiotherapeutische planning bij het oesofaguscarcinoom, zou MRI wel eens veelbelovend kunnen zijn voor de intekening van de

primaire tumor. MRI, een minimaal invasieve techniek, levert een uitstekend weke delen contrast, wat juist de beperking is van de huidige CT. In de afgelopen jaren is MRI bij tal van anderen tumorsoorten, zoals het prostaatcarcinoom [9,10] en hoofd/hals tumoren [11], een steeds belangrijkere rol gaan spelen bij het intekenen van het doelvolume.
Tot dusver zijn er echter nog geen studies die het nut van MRI bij de detectie van het oesofaguscarcinoom laten zien. Van Rossum et al [12] suggereert dat dit komt door de technische tekortkomingen van de conventionele MRI. Toegenomen veldsterkte, snellere sequenties en cardiale en respiratoire gating zouden de beeldkwaliteit aanzienlijk kunnen verbeteren.

Toekomstige ontwikkelingen - dosis escalatie

Dosisescalatie bij de radiotherapeutische behandeling van het oesofaguscarcinoom is al jaren een punt van discussie.
De Intergroup trial (INT 0123 – RTOG 94-05), waarin patiënten werden gerandomiseerd tussen chemoradiotherapie tot 50.4 Gy en chemoradiotherapie tot 64.8Gy, vond geen significant verschil in overleving en locoregionale controle. In deze studie werd echter gebruik gemaakt van een 3D-CRT techniek zonder inhomogeniteitscorrectie, met relatief hoge dosis voor normale weefsels. Sommige studies hebben daarom in planningsstudies toch gekeken naar de potentie dosisescalatie door middel van IMRT met een simultaneous integrated boost (SIB) techniek, ter verbetering van locale tumor controle[13,14]. Voorwaarde voor deze vorm van dosisescalatie is dat het boostgebied (GTV) correct gedefinieerd kan worden. De relatief grote CTV marges zijn er namelijk niet langer om de onzekerheden op te vangen.
Een ander risico van dosisescalatie is de verhoogde dosis op de normale weefsels, met bijbehorende toegenomen toxiciteitsrisico's. Zelfs met de huidige bestralingsschema's is de dosis op het hart en/of de longen al hoog met een relatief hoog risico op symptomatische cardiale of pulmonale toxiciteit. Verschillende retrospectieve studies laten zien dat deze risico's dosisafhankelijk zijn (MHD, V40, MLD, V5, V20) [15-18].
Het is evident dat deze levensbedreigende toxiciteit een negatieve stempel kan drukken op de potentiële overlevingswinst van dosisescalatie.

IMRT en in de toekomst wellicht protonen therapie verbeteren echter de conformaliteit van de dosis rondom het doelgebied, waardoor de dosis op de kritieke organen met het bijbehorende toxiciteitrisico kan worden verminderd. Recent zijn 2 studies verschenen die retrospectief de radiotherapeutische technieken 3D-CRT en IMRT bij patiënten met het oesofaguscarcinoom met elkaar hebben vergeleken. Lin et al. [19] zag meer cardiale dood in de patiëntengroep die met 3D-CRT behandeld was in vergelijking tot de IMRT-groep (11.7% vs 5.4% na 5 jaar). Dit had zijn weerslag op de algehele overleving (mediane OS 25 maanden vs. 43 maanden), die ook lager bleek te zijn. Wang et al. [18] richtte zich op postoperatieve complicaties na neo-adjuvante CRT gevolgd door chirurgische resectie. Zij lieten zien dat het risico op pulmonale complicaties significant hoger was na 3D-CRT in vergelijking tot de patiëntengroep die met IMRT behandeld waren (odds ratio (OR): 2.02; 95% CI 1.10-3.69). De protonengroep liet echter een nog lager kans op pulmonale complicaties zien. Dit verschil was echter niet significant.
Om veilig gebruik te kunnen maken van IMRT en protonen therapie wordt een betrouwbare methode voor het vaststellen van doelgebieden een absolute voorwaarde. Dit onderstreept het

belang van een accurate intekening van het doelvolume. Daarnaast zijn protonen meer gevoelig voor dichtheidveranderingen. Range errors door diafragma beweging, maag-gasvulling en cardiale activiteit moeten worden meegenomen om uiteindelijk adequate dekking van het doelgebied te kunnen garanderen.

Eén ding is duidelijk; beeldvorming van tumor en normale weefsels zal in de toekomst een steeds belangrijkere rol gaan spelen bij de radiotherapeutische behandeling van het oesofaguscarcinoom.

Conclusie

De toevoeging van PET aan de CT voor de radiotherapeutische planning bij het oesofaguscarcinoom resulteert in een verandering van doelvolumina en veranderingen in de bijbehorende bestralingsplannen. Ondanks deze veranderingen lijkt de toevoegde waarde van PET/CT beperkt als het gaat om het voorkomen van locoregionale recidieven.
Dit onderstreept het belang van validatie van een nieuwe (beeldvormende) techniek voordat het standaard geïmplementeerd kan worden in de klinische praktijk.

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Dankwoord

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Curriculum vitae

Curriculum Vitae

Chrisina T. Muijs was born on the 16th of December 1983 in Zwolle, The Netherlands and grew up in Nunspeet. In 2002, she graduated from secondary school at Nuborgh College in Elburg. In the same year she started her medical training at the University of Groningen.
To perform her internships, she went to Deventer between 2006-2007. In 2008, she returned to Groningen to participate in a research project at the department of radiation and cell biology, concerning the histological and functional changes in lung tissue after radiation. During this period, she developed a growing interest for scientific research.
She performed her final internship at the department of Radiation Oncology in Groningen and obtained her medical degree in October 2008. Thereafter she started her PhD-project on the value of PET/CT for radiotherapy of esophageal cancer at the department of Radiation Oncology at the University Medical Center Groningen.
At the same department she started her residency Radiation Oncology in January 2010 and was enabled to combine her residency with her PhD-project.

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