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Systematic review

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 TVs 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.

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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. ^{18}F-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 Fig. 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
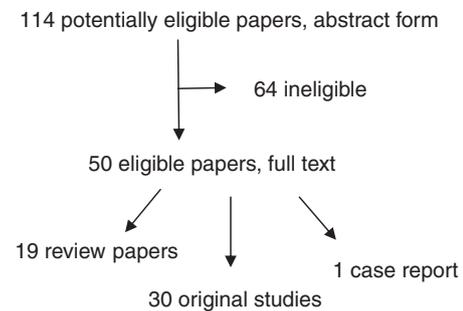

Fig. 1. The study selection process, both search strategies combined.

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.

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,

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

Author	N	Primary tumour		Lymph node metastases						Remarks
		Detection rate on CT (%)	Detection rate on PET (%)	Sensitivity of PET for LN (%)	Specificity of PET for LN (%)	Sensitivity of CT for LN (%)	Specificity of CT for LN (%)	Sensitivity of PET/CT for LN (%)	Specificity 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	

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. Conformality index (CI) is recommended 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-Zabotto et al. [25]	34	Fusion	Visual	PET/CT had impact on treatment 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 variability 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	TVs based on CT might exclude PET-avid disease. Consequences are under dosing. The addition of PET in radiation planning might result in clinically important changes in NTCP
Comparison tumour length PET based vs. pathology				
Mamede et al. [22]	17	Integrated	SBR (liver activity), different SUV-thresholds	FDG-PET-tumour length of untreated esophageal carcinomas correlates well with surgical pathology results
Zhong et al. [47]	36	Integrated	⩾2.5 SUV/40% SUV$_{max}$/visual	The optimal PET method to estimate the length of gross tumour varies with tumour length and SUV$_{max}$, an SUV cutoff of 2.5 seems best
Han et al. [12]	22	Integrated	Visual/SUV-values for autocontouring	A standardised 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 SUV$_{bgd}$ + 20% (SUV$_{max}$(slice) − SUV$_{bgd}$) method optimally estimated gross tumour length, but only reached an unsatisfactory CI for GTV

Abbreviations: GTV, gross target volume; SBR, source-to-background ratio; SUV, standard uptake value.

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 ($p < 0.05$).

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. found that the addition of FDG-PET resulted in GTV reduction with more than 5% in 10 of 16 patients (62.5%). The mean overlap between FDG-PET/CT- and CT-based GTVs was low, only 46%. The observers delineated the GTVs 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 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 speci-

mens 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 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- (SUV_{cutoff}: $SUV_{background} + 20\%$) and pathology-based tumour lengths. However, regarding the spatial conformity index, the conformity index (CI) of pathology and $PET_{SUV+20\%}$ 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 three 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 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 $29.1\% \pm 5\%$ (range 5–69.8%). The V20 was increased in 13 patients, with a mean increase of $25.3\% \pm 4\%$ (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 (Table 3) were used: (1) 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 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

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/ integrated PET/ CT
	Overall	Increase		Decrease					
	Proportion	Proportion	Size	Proportion	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 > 1 cm	–	Δ sup/inf extent > 1 cm	GTV	Visual/ ⩾ mean liver activity + 2SD	II	Integrated
Moureau-Zabotto et al. [25]	56 (19/34) 53 (18/34)	21 (7/34) 21 (7/34)	20% ± 8.7 22% ± 11	35 (12/34) 33 (11/34)	21.3% ± 4.7 9.8% ± 7.4	GTV PTV2	Visual	I	Fusion
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-GTVs were delineated separately and blinded.

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 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, localisation 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.

Conflict of interest statement

The authors state that the research presented in this manuscript is free of conflicts of interest.

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