Tumour delineation in oesophageal cancer – A prospective study of delineation in PET and CT with and without endoscopically placed clip markers

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Oesophageal cancer (both adenocarcinoma and squamous cell carcinoma) is the 8th most common cancer worldwide and the sixth most common cause of death from cancer [1]. Because of rapid tumour progression in this type of cancer, time between diagnostic imaging and start of therapy should be minimized [2]. Radiotherapy (RT) plays a vital role in curative treatment of oesophageal cancer: besides surgery, RT is a potential curative treatment option, mostly in combination with chemotherapy [3–5]. In case of surgical treatment, neoadjuvant radiochemotherapy is a guideline-recommended standard of care [6].

In RT, the precise delineation of the target volume is essential. Computed tomography (CT) is most widely used for radiation treatment planning [7]. In oesophageal cancer, definition of the cranio-caudal tumour extent is demanding in CT images, therefore the target volume of the primary tumour is preferably retrieved using endoscopic clipping with metallic markers [8]. However, endoscopic clipping is invasive and associated with the risk of bleeding, especially in patients with inflammatory or other pre-existing diseases.

Over the past years, positron emission tomography (PET) has proven a useful tool for treatment planning in several tumour

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entities [9–12]. In lung cancer [^{18}F] fluorodesoxyglucose(FDG)-PET/CT can help to differentiate between atelectasis and active tumour tissue [13,14]. It has also proven its value in the detection of involved lymph nodes as well as distant metastases [15,16]. Also in other tumour entities PET/CT can add essential information for radiation treatment planning [17–19].

In oesophageal cancer PET/CT was found to be useful for diagnosis and staging [20–22]. Advantages of metabolic imaging include a better differentiation between tumour tissue and adjacent soft tissue structures [23]. In addition, PET allows the detection of involved lymph nodes and distant metastases. Mamede et al. reported on a good correlation between the oesophageal tumour metabolic length and the tumour length as assessed by histopathology [24].

However, accurate delineation of the tumour volume in PET is challenging and the method of choice is still unclear. One option is the manual delineation in the PET images similar as performed in CT data. This can lead to good results as long as the parameters to display the images are standardized [10]. In addition, the application of a suitable and accurate segmentation algorithm is beneficial for exact GTV delineation [25]. Many semi-automatic algorithms have been discussed as well. Simple threshold based algorithms using a fixed value appear not to be useful in PET data, while at least in some cases, as in the lung, algorithms based on a relative threshold can lead to good results, especially when taking into account the background activity [26]. Recently gradient-based algorithms were reported to present good results [27]. As PET acquisition can take several minutes, patient movement is an important factor as well. Motion artefacts can severely influence tumour volume estimation and require correction algorithms like respiratory gating [28,29].

The objective of this study was to evaluate the potential of FDG-PET/CT to delineate the Gross Tumour Volumes (GTVs) of primary oesophageal cancer by means of different delineation methods. The GTVs were compared with the reference volume retrieved from endoscopic clipping with CT visible clip markers (CT-clip). In addition for registration between PET and CT data non-rigid registration was compared to a rigid registration.

Material and methods

Patients and CT/PET-CT examination

Twenty consecutive patients (13 male, 7 female; mean age, 68 year, range, 51year–82year) with histologically proven oesophageal cancer (12 squamous cell carcinoma, 8 adenocarcinoma) were included in this prospective study. This prospective exploratory feasibility study was designed according to the declaration of Helsinki. Further steps are described in the Discussion Section. All patients gave written and informed consent to the study. The study was approved by the local ethics committee.

Prior to radiation therapy, all patients underwent routine F-18-fluorodesoxyglucose (FDG)-PET/CT for exclusion of distant metastasis and analysis of the nodal status; this (FDG)-PET/CT study was acquired in treatment position. Subsequently, patients underwent structured endoscopy for "clipping" of their tumours, which were marked with CT-visible metal markers followed directly by a CT-scan (planning CT). Clipping covered all endoscopically visible macroscopic tumour.

PET/CT

PET-scans were performed 60–90 min after the intravenous injection of about 5 MBq per kg body weight with a duration of 2 min per bed position. PET/CT examinations were performed on a Siemens biograph mCT, equipped with a 64 slice CT-scanner (Siemens Medical Solutions, Erlangen, Germany). Images were reconstructed using the attenuation-weighted ordered subsets expectation maximization algorithm (OSEM) provided by the manufacturer using the CT data for attenuation as well as scatter correction. PET image were reconstructed in 200 × 200 matrices with a voxel size of 4 mm × 4 mm × 5 mm and a post-reconstruction 2 mm Gauss filter was applied.

After the PET examination, a diagnostic CT-scan in free breathing using intravenous contrast agent (Imeron 300, 1.5 mg per kg body weight, Bracco Imaging, Konstanz, Germany) and oral contrast agent (PERITRAST®CT-Lösung, 30 mL per 1 l water, Dr. Franz Köhler Chemie, Bensheim, Germany) was acquired. CT-images were reconstructed in 512 × 512 matrices with a voxel size of 0.76 mm × 0.76 mm × 5 mm.

Standard of reference

In order to receive reference tumour volumes, proximal and distal ends of the tumour were endoscopically marked with titan markers. These markers were visible in the subsequent free-breathing contrast-enhanced CT scan for treatment planning preparation on a Siemens Somatom 20 CT scanner (Siemens Medical Solutions, Erlangen, Germany). CT-images were reconstructed in 512 × 512 matrices with a voxel size of 0.97 mm × 0.97 mm × 5 mm.

The reference tumour volume is then defined based on the CT-visible markers, which mark the proximal and distal ends of the tumour. In lateral direction tumour boarders are difficult to define, so the GTV should contain the complete oesophagus and any additional tumour tissue. As described later in the discussion section, this reference method is handled as "gold standard" in this study because there were no surgical specimens as real gold standard available. CT scans under free breathing has been established in the treatment planning to overcome the problem of acquisition the CT in an extreme breathing position, while motion artefacts are rare with recent multi-slice CT scanners.

Segmentation

Data analysis was done with the software MIMVista® (MIM Software Inc., Cleveland, Ohio, USA). The GTV was delineated manually in the PET-dataset (PET-manual) by one single experienced nuclear medicine physician. Additionally, the GTV was defined by one single CT-experienced radiation oncologist in the contrast enhanced CT component of the (FDG)-PET/CT (CT-manual) as well as the planning CT with endoscopic clips (CT-clip). The tumour volume was delineated on the basis of these markers, defining the cranio-caudal borders. Laterally, the complete oesophagus as well as any additional tumour tissue was enclosed in the target volume (Fig. 1). In addition to manual delineation, the tumour was defined with different segmentation algorithms in the PET dataset. The accuracy of the different PET-segmentation algorithms was tested by choosing a variety of absolute and relative thresholds for segmentation. A wide range of segmentation thresholds was covered by choosing the following percentual thresholds: 20%, 35%, 40%, 45% [24] of the maximal standard uptake value (SUV) and absolute threshold of SUV 2.0; 2.5; 3.0 [22].

The SUV was calculated with $SUV = \frac{A[Bq/l] \cdot W[kg]}{A_{in}[Bq]}$ in which A = measured cumulated activity, W = body weight, A_{in} = injected activity, decay corrected to the time of acquisition. With the assumption that the density of human tissue is 1 kg/L the SUV is a dimensionless factor.

A contrast-orientated target-to-background-algorithm ($PET_{T/B}$) and a gradient based algorithm (PET_{Edge}) provided in MIM-Vista (MIM Software Inc., Cleveland, Ohio) [30,31] were applied. The

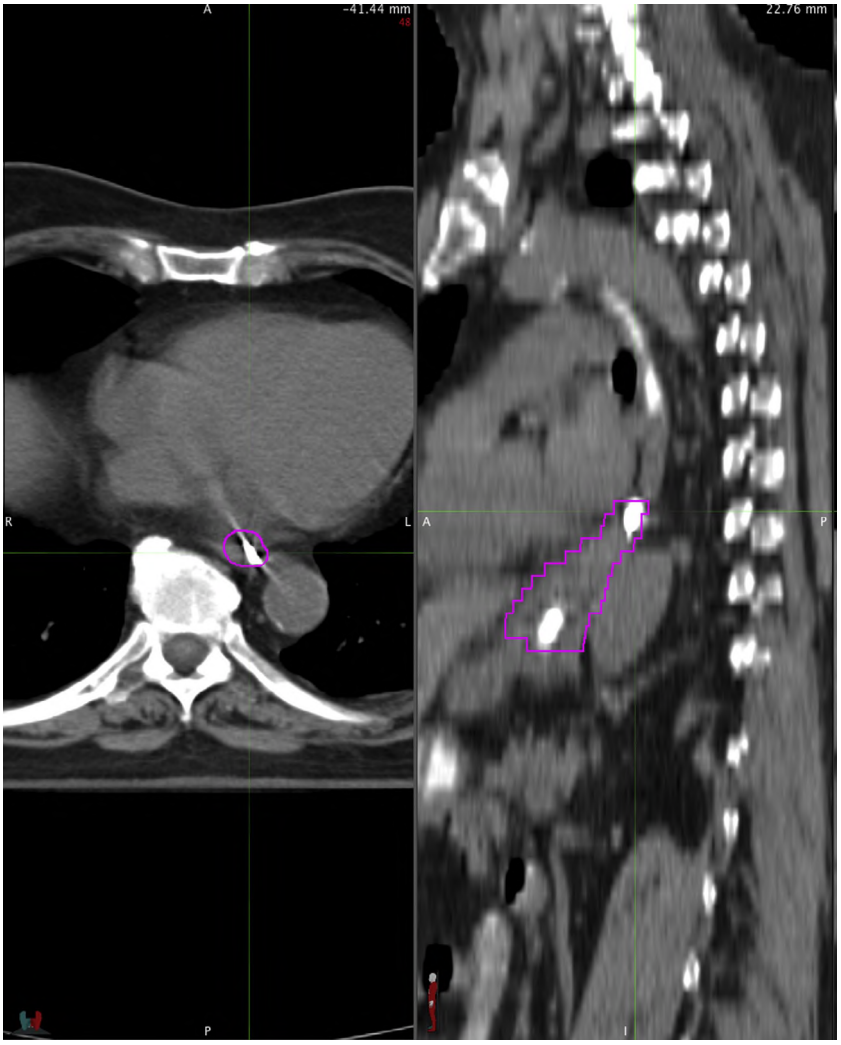

Fig. 1. GTV delineation based on the CT-visible Clips. Clips were marking the proximal and distal boarders of the tumour. Laterally the complete oesophagus is enclosed in the GTV.

target-to-background-algorithm used [34] is based on the assumption that the optimum method to determine the threshold for auto-contouring a volume in FDG-PET is influenced by the background activity and FDG accumulation of the lesion. For every lesion, a single threshold in consideration of the background near that lesion was computed, thus receiving specific threshold values for every lesion. The calculation from [32] is modified with appropriate parameters for the Siemens mCT according to Preylowski et al. [33].

The gradient-based algorithm identifies tumour on basis of a change in count levels at the tumour borders. The segmentation is done based on changes in intensity/activity concentration. Through calculation of spatial gradients the highest change in the intensity was detected. There the algorithm defined the tumour borders [34]. The absolute volumes [cc] and the absolute length/extent [cm] of the tumour in cranio-caudal direction were determined and compared to the volume/length assessed by the reference volume (CT-clip). The analysis was done separately for proximal and distal tumours.

Registration and overlap

For an accurate definition of the overlap between the reference–volume (CT-Clip), derived from the planning CT and the volumes derived by the segmentation algorithms in the PET, robust registration methods are required. In a first step the CT-component of the PET/CT was registered to the planning CT (reference). The PET-dataset was automatically co-registered with the same registration vector as the CT, because of the integrated scan on the hybrid PET/CT-scanner. A rigid- and a non-rigid registration (intensity-based free-form deformable registration algorithm) were applied. Adequate co-registration between CT and PET was checked visually. In none of the cases misalignment was found between the CT acquired at the PET/CT and PET, so no further correction was applied.

Registration was also performed in MIMVista®. After the fusion of all datasets the contours were copied to the reference dataset for further analysis. For the overlap-analysis the software Artistruct (© 2010 AQUILAB SAS, Lille, France) was used.

The overlap (OV) was calculated with $OV = \frac{c_n \cap c_R}{c_R}$, in which c_n = contour of the operator n (PET-contours or CT-manual) and c_R = reference contour (CT-clip). In addition we performed the analysis of Mean Contour Distance (MCD) and calculated the Dice-coefficient for volume comparison.

Statistics

Pearson correlation coefficient was used to assess statistical significance of linear correlation, P values less than 0.05 were

considered to indicate statistical significance. Statistical analysis using the two sided t-test was performed with the software package R 3.0.2).

Results

In 6 of the 20 patients, previously unknown tumour manifestations were found in the whole-body FDG-PET/CT examination. In one patient lung metastases were found, in 4 cases lymph node metastases (2 supraclavicular, 1 mammaria interna, 1 cervical) and in two cases bone metastases. In one patient a breast tumour was discovered as secondary carcinoma. Consequently, the target volume (irradiated nodal areas) or intent of treatment (curative to palliative) changed in three and three patients, respectively.

A total of 20 lesions in 20 patients were analysed. In one patient (non-)rigid registration was not necessary because the patient was clipped before the PET/CT examination, so CT-Clip and CT-manual were delineated in the same dataset. In another patient the distal clip was lost before the CT-examination, so the tumour was defined on basis on the proximal clip and on the lower end based just on the visible tumour tissue.

The diagrams in Fig. 2 illustrate the high variability and standard deviations in the mean values for tumour volumes, tumour length and overlap.

When using rigid registration for the analysis of the absolute GTV volumes of all, proximal and distal tumours, the reference volume (CT-clip) showed the best correlation with the gradient-based segmentation algorithm (PET-edge) ($R^2 = 0.84$, $p = 1.5 \cdot 10^{-8}$) and the manual delineation in the CT (CT-manual) ($R^2 = 0.89$, $p = 4.4 \cdot 10^{-10}$). When comparing CT-manual (PET-Edge) with reference volume an overlap of 68 ± 19% (48 ± 19%) was found while the MCD is 0.36 ± 0.24 cm (0.6 ± 0.55 cm) and the Dice 0.68 ± 0.2 (0.55 + 0.21).

The GTV length in cranio-caudal direction of the manual CT-delineation achieved a correlation coefficient of $R^2 = 0.69$, $p = 6.06 \cdot 10^{-6}$. The correlation coefficient of manual delineation in PET (PET-manual) and PET 3.0 was $R^2 = 0.57$, $p = 0.0001$.

When using the overlap analysis with the reference volume as quality parameter, best results were found for manual CT delineation (CT-manual) and the absolute threshold based PET 2.0 algorithm achieved both a mean overlap of (68 ± 20)%. When rating according to the MCD, best results were obtained for CT-manual with MCD = 0.36 ± 0.24 cm and for PET-manual with MCD = 0.48 ± 0.23 cm. According to the DICE coefficient CT-manual gave best result with 0.68 ± 0.20 followed by PET 20% with 0.58 ± 0.16.

When comparing proximal and distal lesions average overlap values were smaller in distal lesions for all segmentation algorithms while the MCD was on average larger in all cases. The Dice coefficient was on average smaller in distal lesions for 9 of the 11 segmentation methods. However no statistical significance was reached in this comparison. There was also no tendency for the relative volume difference in GTV according to tumour location.

No statistical significant differences for GTV volumes, DICE and MCD analysis were observed after non-rigid registration. Consequently, non-rigid image registration did not improve correlation results even visual difference was very strong as seen in Fig. 2 and Table 1).

In Table 1 the correlation coefficients of the GTVs with the associated overlap values, MCD values and Dice coefficients are shown separately for proximal and distal tumours as well as for rigid and non-rigid co registration for the three segmentation algorithms showing the best correlation with the reference volume.

Discussion

The main finding in our study is that GTV definition in oesophageal carcinoma showed a high variability in all three imaging modalities. Neither CT without clips nor any PET segmentation algorithm provided close agreement with the "gold standard" in our study: a planning CT showing the tumour extension after endoscopic clip placement. This was the fact from all analysed parameters of tumour length, absolute volume overlap, MCD and DICE with the reference parameters.

Currently, according to our results none of the tested segmentation algorithms can replace the reference method of endoscopic clip placement. However it is questionable whether endoscopic clipping can really be considered as gold standard. A real gold standard like surgical resection of the tumour followed by histopathological examination of the specimen was not available in patients who underwent radiotherapy. Due to lack of a real gold standard pseudo gold standards such as endoscopic clipping or endoscopic ultrasound are used as reference. There are only few studies using histopathological specimens as gold standard like those by Daisine et al. [35] in head and neck cancer, Bundschuh et al. [36] in prostate cancer or Stroom et al. in lung cancer [37]. In rectal cancer Buijsen et al. found the best correlation between FDG-PET compared to surgical specimens [38].

Other groups tried to improve pseudo gold standards like contouring volumes in CT more accurate using effervescent powder for volumetric in CT-imaging. An effervescent powder, distends the oesophagus directly before the CT-examination. In oesophageal evaluation they found multidetector CT using effervescent powder for oesophagus analysis a promising technique with an accurate longitudinal and axial evaluation [39].

Wanet et al. [40] showed when the primary lung tumour was surrounded by modifications of the lung parenchyma the gradient-based method outperformed the threshold-based ones in terms of accuracy and robustness. Zhang et al. [41] found in their study that the gradient-based method provided the closest estimation of GTV length in delineation of primary GTVs in PETs in oesophageal cancer. The radiotherapy planning based on the gradient-based segmentation reduced the irradiated volume in the lung, heart and other normal tissues.

The algorithms we used, even the manual delineation did not provide good overlap values. Despite good correlation coefficients in the comparison of absolute volumes the associated mean overlap values did not reach more than 78%, which was achieved in the manual CT delineation of proximal tumours after non-rigid registration. Only the gradient-based segmentation algorithm for PET-images seems appears to have some potential to contribute to the GTV delineation in oesophageal cancer. The mean overlap provided by PET-Edge was (48 ± 19)% after rigid registration and (49 ± 18)% after non-rigid registration. This is in good accordance to Niyazi et al. They described, that the best agreement was found for the region growing threshold segmentation method. Using Conformity Index ($CI = \frac{BTV \cap GTV}{BTV \cup GTV}$) for overlap calculations the median overlap was 56% [42].

It is likely that the respiratory-induced movement of the oesophagus influenced the analysis and affected comparability of the different imaging modalities [43,44]. Fast spiral CT and slow PET imaging are additionally different in displaying breathing motion during very different image acquisition times. According to Yamashita et al. the movement of the metal markers in the oesophagus can range up to 13.8 mm in the lower oesophageal region [44]. Our results indicate that especially the overlap values for distal tumours are mostly <50%. Dieleman et al. reported that the distal oesophagus shows more mobility compared to the proximal region [45]. This is also indicated by our results in the separate analysis for proximal and distal tumours. In both volumes as well as overlap analysis the results for distal tumours are worse than for proximal tumours, also it was not statistically significant. The lower third of the oesophagus is affected in a stronger way by respiratory induced motion [44] or nonspecific changes like

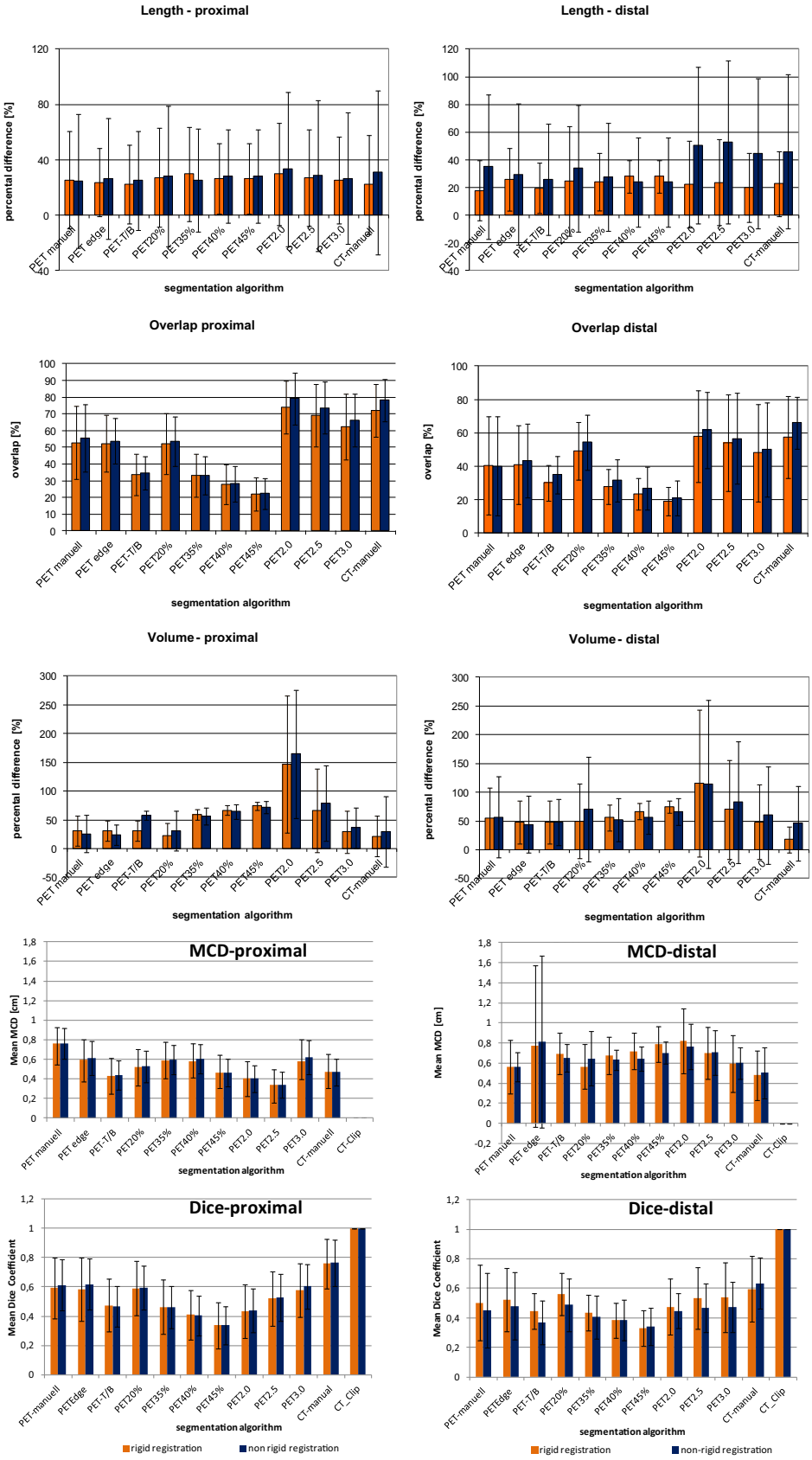

Fig. 2. Mean deviations $\left(\frac{(\text{segmented volume}-\text{reference volume})}{\text{reference volume}} \cdot 100\right)$ from the reference value of the tumour volumes, length in cranio-caudal direction, values of the tumour overlap between the volume assessed by the segmentation algorithm with the reference volume CT-Clip, mean, Dice coefficients and Mean MCD with standard deviation, separate graph for proximal and distal tumours.

Table 1
Results for volume and overlap for distal and proximal lesions.

	Volume											
	After rigid registration						After non-rigid registration					
	R^2	p	Algorithm	OV (%)	DICE	MCD	R^2	p	Algorithm	OV (%)	DICE	MCD
Proximal	0.93	$7.6{\cdot}10^{-6}$	CT-manual	72 ± 15	0.76 ± 0.17	0.25 ± 0.17	0.93	$2.7{\cdot}10^{-5}$	PET-Edge	53 ± 14	0.62 ± 0.17	0.39 ± 0.15
	0.89	$4.6{\cdot}10^{-5}$	PET-Edge	52 ± 17	0.58 ± 0.22	0.44 ± 0.21	0.89	0.00011	CT-manual	78 ± 12	0.76 ± 0.16	0.26 ± 0.19
	0.88	$6.02{\cdot}10^{-5}$	PET 35%	33 ± 13	0.46 ± 0.19	0.56 ± 0.21	0.85	0.0004	PET-T/B	34 ± 9	0.47 ± 0.47	0.51 ± 0.15
Distal	0.87	$8{\cdot}10^{-5}$	CT-manual	57 ± 24	0.60 ± 0.22	0.48 ± 0.25	0.87	$8.3{\cdot}10^{-5}$	CT-manual	66 ± 15	0.63 ± 0.17	0.50 ± 0.25
	0.85	0.00015	PET-Edge	41 ± 23	0.52 ± 0.22	0.77 ± 0.80	0.78	0.0007	PET-Edge	43 ± 22	0.48 ± 0.48	0.81 ± 0.86
	0.84	0.00021	PET-manual	40 ± 29	0.50 ± 0.26	0.56 ± 0.27	0.75	0.0011	PET-manual	40 ± 29	0.45 ± 0.25	0.56 ± 0.15

inflammation around the tumour. A respiratory gated planning CT and PET/CT are therefore expected to improve the accuracy of the treatment planning as it provides information about respiratory-induced motion of the thorax and the oesophagus.

Variable filling of the stomach may also have influenced the position of the distal oesophagus and thereby have affected the results of our study.

Another problem is the limited specificity of FDG. Thus, target definition in oesophageal cancer in the PET-images was very difficult due to inflammation around the tumour, which very often occurs in this type of cancer. A standard FDG-PET cannot differentiate between inflammation and increased glucose uptake due to cancer. However, there are other radiopharmaceuticals available which could potentially aid in differentiation, for example [^{18}F] fluorothymidine (FLT) [43]. In addition to exact tumour delineation with PET-specific segmentation algorithms it is a challenge to use an accurate image registration method to register images from non-hybrid scanners under preferably the same conditions.

In the volume analysis the manual PET-delineation, the PET-Edge, the T/B-algorithm and the percentual threshold algorithms appear smaller than the reference volume (CT-clip) for distal and proximal tumours after rigid and non-rigid-registration. There is evidence that GTV delineation based on clips leads to a bigger GTV than based on PET. This smaller PET-positive volume can be treated as boost volume in the therapy planning process. Konski et al. compared only tumour length and found that tumour length in CT was significant longer compared with PET scans which is in good agreement with our results [22]. Mamede et al. found a significant correlation for PET in tumour length compared with pathology in contrast to a non-significant correlation when compared with tumour length determined by endoscopic ultrasound [24].

The worse correlation coefficients and overlap values in the overlap comparison despite good correlations in the volume analysis can be explained by inaccuracy in the exact repositioning of the patient for the second CT scan resulting in complexity during the registration process or breathing artefacts resulting in misalignments between CT and PET. To cope with this challenge the reference CT (CT-Clip) should be acquired on the same scanner as the PET images best in combination with a gated PET/CT.

Despite FDG-PET appears to have limited value in GTV definition, the primary objective of our study, FDG-PET staging was of tremendous relevance for staging of the patients. Previously unknown tumour locations were found in 6 of 20 patients and in one case a secondary carcinoma of different histology was detected. In the three cases distant metastases were detected and therefore patients were upstaged to stage IV which resulted in a change of the treatment regimen from curative to palliative intent. In another three cases, the target volume was substantially enlarged to cover newly detected FDG-PET active lymph nodes which were not suspicious in other imaging modalities. Therefore FDG-PET/CT proved as an important tool for initial staging and decision of treatment for the individual patients. This finding agrees with a study by Mac Manus which found essential changes in the treatment of non-small cell lung cancer by FDG-PET [46]. In addition in this prospective study also the treatment planning using FDG-PET/CT was "associated with excellent survival". Also not in context with radiotherapy treatment planning FDG-PET has proven to be successful in finding of distant metastasis in patients with oesophageal carcinoma. Purandare et al. found in 25 of 156 patients with oesophageal carcinoma previously unknown distant metastasis leading to an upstaging to stage IV [47]. However in local lymph node staging FDG-PET/CT is discussed controversially [48] and further studies need to be performed, especially in the context with radiation treatment.

Conflict of interest statement

The authors declare that they have no conflict of interests.

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