Better Assessment of Nodal Metastases by PET/CT Fusion Compared to Side-by-Side PET/CT in Oesophageal Cancer*

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Abstract. *Background: Recently, positron emission tomography/computed tomography (PET/CT) has been introduced in the staging of oesophageal cancer. The impact of PET/CT fusion in comparison with side-by-side PET/CT in these tumours, was analyzed. Patients and Methods: In 61 patients, 18-F-fluorodeoxyglucose (FDG)-PET and multidetector (md)-CT were performed within a two week interval. Software-fusion of md-CT and FDG-PET was correlated with side-by-side FDG-PET/CT reading by two independent investigators. The gold standard was the pathological outcome or clinical evidence of progression during the first year of follow-up. Results: In 18 patients (18/61; 30%), nodal staging improved with software-fusion. The number of nodal metastases increased in five patients and decreased in four patients, leading to up-staging in one patient (2%) and down-staging in three patients (5%). In nine cases (15%), certainty and localization of metastases improved. However, the number of distant metastases did not change and software-fusion did not have an influence on resectability. Conclusion: PET/CT fusion substantially improves detection and localization of nodal metastases and may have an impact on locoregional treatment options.*

In cancer of the oesophagus and gastro-oesophageal junction (GOJ) curatively intended resection, eventually with neoadjuvant chemoradiation, is the most effective treatment option (1). As cure is only possible in the absence of distant metastases or local invasion into vital surrounding structures, optimal staging is indispensable for adequate preoperative patient selection preventing unnecessary surgical exploration. Endoscopic ultrasonography (EUS) in combination with fine needle aspiration (FNA), multidetector computed tomography (md-CT), and ultrasound (US) of the cervical region are commonly used staging methods (2). EUS-FNA is the most accurate in detecting nodal involvement and gross mediastinal invasion, whereas CT is the best imaging technique in detecting distant metastases (3). In the last decade, positron emission tomography with 18-F-fluorodeoxyglucose (FDG-PET) has become a frequently used staging technique (4-7). FDG-PET is especially applied for the detection of regional lymph node and distant metastases not visible on CT or EUS. Hence, pre-therapeutic FDG-PET alters assessment of the tumour stage in 15-22% of the patients (8-12).

Despite the improvements in preoperative staging, it is still difficult to determine resectability accurately. Depending on the pre-operative work-up, local invasion and distant metastases are found in 10-60% of patients during exploration (13-20). A combination of PET/CT images is thought to increase significantly the accuracy of staging because it correlates functional PET information with high resolution anatomical CT results (21-26). Previously, it was common practice to correlate FDG-PET with CT visually, but recently hybrid PET/CT or PET/CT fusion have gained more support. In this study the accuracy of PET/CT fusion in staging patients with cancer of the oesophagus or GOJ was evaluated and compared with visual correlation of PET and md-CT.

Patients and Methods

Patient characteristics. Retrospectively the medical records of 85 patients, who were staged by FDG-PET and md-CT and treated for cancer of the oesophagus or GOJ between January 2001 and November 2004 were analyzed. Exclusion criteria were, treatment

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with neoadjuvant chemoradiation or a history of other malignancies. Twenty-four patients were excluded, either because the CT data from rural hospitals were missing (n=10) or the CT-slices were too thick (n=14). All the other patients were staged with EUS, 16-64 md-CT with slices of at least three mm and FDG-PET within two weeks of the time of presentation. In these 61 patients, it was feasible to perform a software-based PET/CT fusion. The mean age was 63.4 (SD±8.0; range 48-80) years (Table I). Fifty patients (82%) presented with an adenocarcinoma of the oesophagus. Most of the tumours (87%) were localized in the distal part of the oesophagus (n=40) or at the GOJ (n=13). Depending on tumour invasion and lymph node involvement, the tumours were divided into stage I-IV according to the tumour-node-metastasis (TMN) staging system of the Union Internationale Contre Le Cancer (UICC) (27).

Computed tomography. Multidetector row CT imaging was performed with a 16-64 md-CT scanner (Somatom Sensation, Siemens Medical Systems, Erlangen, Germany). The CT scans (collimation 16×1.5 mm) were performed from the neck to the upper abdomen with both intravenous and oral contrast. The reconstructed slices had a thickness of 3 mm with a 1.5 mm effective section thickness.

Positron emission tomography with 18-fluorodeoxyglucose. FDG-PET was performed with an ECAT HR+ positron camera (Siemens/CTI, Knoxville, TN, USA) acquiring 63 planes over a 15.8 cm axial field-of-view with retractable septa that enable 2D or fully-3D data acquisition. All patients fasted for at least 4 hours before 400-580 MBq FDG (depending on body weight) was administered intravenously. The transmission scans were performed for 3 minutes per bed position allowing attenuation correction. The scans were corrected for decay, scatter and randoms, whilst the ordered subset expected maximization with two iterations and 16 subsets was used for reconstruction. A Gaussian filter of 5 mm full width at half maximum was used for post-smoothing of the reconstructed images (28). Data acquisition started in whole body mode 90 minutes after injection, for 5 minutes per bed position from the crown to the mid-femur.

Diagnostic evaluation of CT and PET findings. The images of the md-CT, EUS and FDG-PET techniques were reviewed independently by two experienced nuclear physicians. Round hypo-dense lymph nodes larger than 5 mm and lymph nodes measuring 10 mm or more on CT were determined to be pathological. Pathological lymph nodes at the celiac axis were classified as M1a metastases in the case of distal oesophageal cancer or as M1b metastases in the mid or proximal tumours. Cervical metastases were classified as M1a in the case of proximal cancer and as M1b for mid or distal tumours. The FDG-uptake was scored on a four-point intensity scale: 'normal' (physiological), 'slightly increased', 'moderately increased' and 'intensely increased'. These lesions were interpreted as: 'absolutely benign', 'probably benign', 'indeterminate', 'probably malignant' and 'definitely malignant'. All the 'indeterminate', 'probably malignant' and 'definitely malignant' lesions were identified as hotspots. Suspect lesions were occasionally confirmed by FNA cytology, by pathological examination during or after surgery, or by radiological and clinical follow-up of at least one year. The lymph nodes were defined according to the Naruke lymph node stations (Table II).

Table I. *Patient characteristics*.

Characteristics	N (%)
Gender	
Male	51 (83.6)
Female	10 (16.4)
Age (years)	
Median (Range)	63.4 (48-80)
Histology	
Adenocarcinoma	50 (82.0)
Squamous cell carcinoma	11 (18.0)
Localization	
High	8 (13.1)
Low	40 (65.6)
GOJ	13 (21.3)
Clinical staging	
Stage I (T1N0M0)	4 (6.6)
Stage II (T2-3N0M0/T1-2N1M0)	18 (29.5)
Stage III (T3N1M0/T4N0-1M0)	32 (52.5)
Stage IV (T1-4N0-1M1)	7 (13.7)
Total	61

Clinical stage: staging without software based FDG-PET/CT; GOJ: gastro-oesophageal junction.

PET/CT fusion compared with side-by-side PET/CT reading. Together with an experienced radiologist all the reviewed FDG-PET and CT results were visually correlated (side-by-side) and scored by the same nuclear medicine physicians. Lymph nodes >1 cm on CT imaging without FDG-uptake on PET imaging, were scored as negative on visually correlated FDG-PET/CT staging. The rigid software-based PET/CT fusion was accomplished on a Siemens Leonardo Workstation using the Syngo 3D Fusion program. Fusion was carried out and PET/CT images were scored by the same experienced nuclear physician and radiologist. Disagreement was resolved in a consensus meeting. The outcomes of software fusion were compared with visually correlated PET/CT and the differences between these two methods were scored as shown in Table III.

Enlarged lymph nodes >1 cm on CT with negative PET findings were defined as negative. In the cases where fusion detected nodes that were initially not seen at all on md-CT or seen but not classified as physiological lymph nodes, these PET positive nodes were retrospectively defined as positive lymph nodes.

The grade of certainty increased (outcome 2), when: the lymph nodes were detected retrospectively at the anatomic location of FDG-accumulation; the lymph nodes with a moderate suspect diameter or appearance turned out to be PET positive; the nodes at fusion were defined at another anatomical location than that seen by side-by-side review, but within the same TNM stage or when fusion revealed FDG accumulation in a suspicious node located in the proximity of the primary tumour which was unclear for PET positivity on side-by-side correlation .

Follow-up. The follow-up data of all the patients were available. The patients were followed according to a standardized programme consisting of an examination at the outpatient department every three months for the first two years and every six months thereafter for a total period of five years.

Table II. *Locoregional and distant lymph node stations according to Naruke.*

Station	Name	Location
1	Supraclavicular nodes	Above suprasternal notch and clavicles
2R	Right upper paratracheal nodes	Between intersection of caudal margin of innominate artery with trachea and the apex of the lung
2L	Left upper paratracheal nodes	Between top of aortic arch and apex of the lung
3P	Posterior mediastinal nodes	Upper para-oesophageal nodes, above tracheal bifurcation
4R	Right lower paratracheal nodes	Between intersection of caudal margin of innominate artery with trachea and cephalic border of azygos vein
4L	Left lower paratracheal nodes	Between top of aortic arch and carina
5	Aorto-pulmonary nodes	Subaortic and para-aortic nodes lateral to the ligamentum arteriosum
6	Anterior mediastinal nodes	Anterior to ascending aorta or innominate artery
7	Subcarinal nodes	Caudal to the carina of the trachea
8	Para-oesophageal nodes	From the tracheal bifurcation to the diaphragm
9	Pulmonary ligament nodes	Within the inferior pulmonary ligament
10R	Right tracheobronchial nodes	From cephalic border of azygos vein to origin of RUL bronchus
10L	Right tracheobronchial nodes	Between carina and LUL branches
15	Diaphragmatic nodes	Lying on the dome of the diaphragm, and adjacent to or behind its crura
16	Paracardial nodes	Immediately adjacent to the gastro-oesophageal junction
17	Left gastric nodes	Along the course of the left gastric artery
18	Common hepatic nodes	Along the course of the common hepatic artery
19	Splenic nodes	Along the course of the splenic artery
20	Celiac nodes	At the base of the celiac artery

L: left, R: right, RUL: right upper lobe, LUL: left upper lobe.

Statistical analysis. Sensitivity, specificity and accuracy were calculated for both visual correlation and PET/CT fusion. Both the techniques were compared in nonparametric paired analysis using the McNemar test and p-values <0.05 were considered statistically significant.

Results

In 18 patients (30%), an improvement in the detection of locoregional and/or distant lymph node metastases was observed on fused PET/CT compared to visually correlated CT and PET (Table III). Details of these 18 patients are summarized in Table IV.

Increased certainty of localization and number of metastases. In patients 1 to 9, the certainty of suspicious lymph nodes increased on PET/CT fusion without altering the clinical nodal staging. In patients 1 and 2, enlarged nodes were seen on md-CT in the paracardial region (patient 1) and near the left gastric artery (patient 2). On side-by-side correlation it was not possible to distinguish whether these nodes were PET positive or not, but fusion revealed FDG-uptake in these nodes. In one patient (3), the lymph nodes were visible on CT at Naruke 4/5 and 17 without FDG accumulation on primary PET review. However, FDG-uptake was noted in two nodes after correction for the difference in height of the diaphragm vault. Only two nodes (Naruke 4/5 and 20) were eventually submitted for pathological examination as

Table III. *Improvements of software based FDG-PET/CT fusion compared to visual side-by-side correlation.*

	Outcomes	N=61 (%)
1	No improvement	43 (70)
2	Staging unaltered, increased certainty of suspicion or location	9 (15)
3	Staging unaltered, number of metastases increased	4 (7)
4	Staging unaltered, number of metastases decreased	1 (2)
5	Staging unaltered, localization altered	0 (0)
6	Upstaging, not leading to changes in resectability	1 (2)
7	Upstaging, change in resectability from resectable to irresectable	0 (0)
8	Downstaging, not leading to changes in resectability	3 (5)
9	Downstaging, change in respectability from irresectable to resectable	0 (0)

resection was abandoned because of tumour invasion in the pericardium (T4 stage). In patient 4, two nodes both >1 cm (mean 1.6×1.1) at Naruke 16, did not show any FDG uptake, indicating a benign enlargement. Fusion revealed that there was indeed nodal FDG-uptake but that it was assimilated by FDG accumulation from the primary tumour. In patient 5, local and distant lymph nodes were detected by CT, as well as skeletal and lung metastases by PET. With precise anatomical correlation, PET/CT fusion could identify exactly the Naruke stations that were involved. Cytological proof was taken only from Naruke 18 and the six month

Table IV. *Details of the 18 patients with differences in staging between software PET/CT fusion and visual correlation.*

Pts	Lpt	H	S	I	L_{EUS} (n)	L_{visual} (n)	$L_{software}$ (n)	L_{path} (n)
1	Distal	AC	III	2	16, 17 (2)	16 (1)	16 (1)	7,8,16,17 (22)
2	GOJ	AC	III	2	- (0)	17 (1)	17 (1)	17 (3)
3	Distal	SC	III	2	4/5,17 (5)	4/5, 17 (10)	4/5, 17 (12)	4/5, 20 (2)
4	GOJ	AC	III	2	4/5, 7, 8, 16, 17 (8)	7, 8, 16 (6)	7, 8, 16 (6)	8,16 (2)
5	Distal	AC	IVB	2	8, 16, 18 (4)	8, 16, 17, 18, 20 (13)	8, 16, 17, 18, 20 (13)	18 (1)
6	Distal	AC	III	2	16 (1)	4/5, 16, 17 (7)	4/5, 16, 17 (7)	-
7	Distal	AC	III	2	8 (1)	8 (1)	8 (1)	8,16 (2)
8	Distal	AC	IVA	2	7, 18 (3)	8, 17 (4)	8, 17 (4)	8, 17 (4)
9	GOJ	AC	IVA	2	20 (3)	17, 20 (3)	20 (3)	20 (2)
10	Distal	AC	IIB	3	8 (1)	17 (1)	8, 16, 17 (3)	8, 16, 17 (3)
11	Distal	SC	III	3	8 (1)	7 (1)	4/5, 7 (2)	4/5, 8 (8)
12	GOJ	AC	III	3	16 (3)	19 (1)	19, 16 (2)	16 (1)
13	Distal	AC	III	3	8 (1)	- (0)	8 (1)	4, 5, 8, 16
14	Distal	AC	III	4	8 (1)	8 (5)	8 (4)	-
15	Distal	AC	IIA	6	- (0)	- (0)	8, 16 (2)	8, 16, 17
16	Distal	AC	IVA	8	16 (2)	16, 20 (2)	16 (1)	16, 17 (2)
17	Distal	AC	IIA	8	- (0)	4/5, 7 (3)	- (0)	- (0)
18	Distal	AC	III	8	17 (3)	17, 20 (3)	17 (2)	8, 16, 17

Lpt: location of primary tumour, GOJ: gastro-oesophageal junction, H: histology, AC: adenocarcinoma, SC: squamous cell carcinoma, S: clinical stage based on staging without PET/CT fusion, I: improvements 2-9: see Table II, L: localization of lymph node station(s) according to Naruke by endoscopic ultrasound (EUS), visual correlation (visual), software fusion (software) or on pathological examination (path), 4/5: paratracheal, 8: para-oesophageal, 16: paracardial/curv. minor, 17: left gastric artery, 20: celiac trunk, n: number of lymph node metastases.

clinical/radiological follow-up was taken as validation. In patients 7 and 8 a small paracardial (patient 6) and para-oesophageal node (patients 7) was missed on CT, although these lesions were suspected on PET and EUS. In patients 8 and 9, PET, CT and EUS did not agree on the localization of suspected lymph nodes. PET/CT fusion enabled accurate identification and localization in the four nodes.

Number of metastases altered, stage unaltered. In four patients (10 to 13), the total number of nodal metastases increased as more pathological lymph nodes were observed on PET/CT fusion, though the TNM stage remained unaltered. In patient 10, PET/CT fusion revealed lymph node metastases close to the tumour (Naruke 8 and 16) which were not suspect on CT and were thought to be primary tumour tissue at first PET diagnosis. In patient 12, an initially missed node metastasis at Naruke 16 was detected on PET/CT fusion. Two other enlarged lymph nodes >1 cm at Naruke 8 and 17 did not show any FDG-uptake on visual correlation. In patient 13, no nodal involvement was observed on PET scanning, but on PET/CT fusion there was indeed FDG- uptake in the para-oesophageal lymph nodes.

In one patient (patient 14), the number of metastases decreased. CT detected three lymph nodes >1 cm, but on side-by-side fusion it was impossible to determine whether these nodes were involved due to their close proximity. PET/CT fusion clearly showed that one of these nodes did not absorb any FDG. Unfortunately, at exploration, pathologically proven cervical metastasis was found and resection was abandoned. Hence, PET/CT findings of enlarged lymph nodes at Naruke 8 were verified by the 12-months follow-up.

Altered staging. The TNM classification was altered by PET/CT fusion in 4 patients (patients 15 to 18; 6.6%). Upstaging was found in one patient (15), but had no impact on the resectability. There was a low suspicion on PET for nodal (Naruke 8 and 20) and skeletal metastases, not confirmed by CT or EUS. After software PET/CT fusion pathologically confirmed metastatic lymph nodes were clearly visible at Naruke 8 and 16 (Figure 1a). Downstaging by PET/CT fusion was found in three patients (patient 16, to 18). In patient 16 an enlarged node at Naruke 16 was staged as N1 on CT, but as FDG-uptake was visible at the celiac trunk it was staged as M1a. At PET/CT fusion both findings appeared to be the same lesion, staged as N1 (Figure 1b). In patient 17, three lymph nodes >1 cm were found on CT and during visual correlation it was unclear whether a slightly diffuse accumulation of FDG-uptake was attributable to these nodes or to a Barrett oesophagus segment. PET/CT fusion showed undeniably that these nodes were clear. In patient 18, a suspicious celiac node metastasis (Naruke 20) was noted on visual correlated FDG-PET, but software PET/CT fusion enabled precise localization of increased FDG-uptake at Naruke 17.

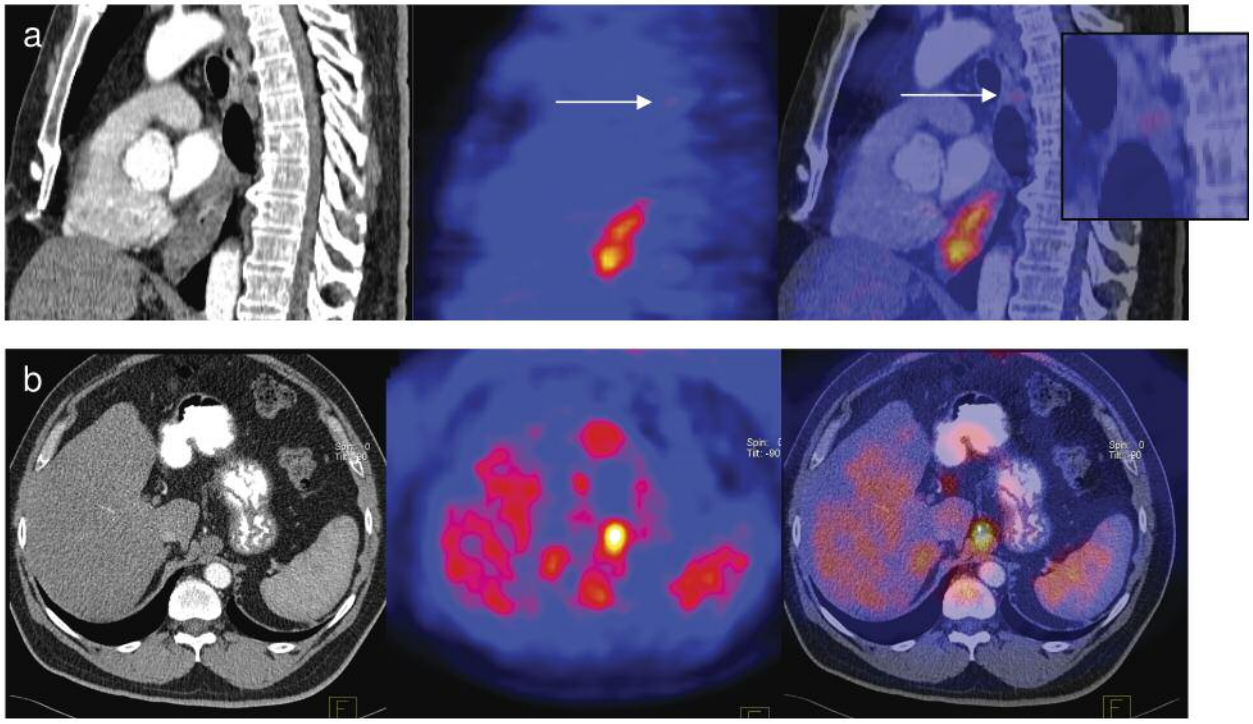

Figure 1. *Upstaging (a) and downstaging (b). (a) Patient 15: FDG-PET, low suspicion for both nodal and skeletal metastases, but without suspicion on md-CT or EUS. Software fusion clearly showed metastatic nodal metastasis in the para-oesophageal region. Magnification shows the involved lymph node. (b) Patient 16: enlarged lymph node in the paracardial region staged as N1 on md-CT. On FDG-PET, FDG-uptake was seen in the celiac region, staged as M1a. After software PET/CT fusion both findings appeared to be the same lesion in the paracardial region.*

Sensitivity, specificity and accuracy. Although not statistically significant (p=0.250), the diagnostic accuracy of PET/CT fusion (87%; 53/61) was slightly better than side-by-side visualization (82%; 50/61) in the assessment of locoregional metastases. Sensitivity and specificity of side-by-side visualization were 80% (12/15) and 83% (38/46), respectively. The sensitivity and specificity of PET/CT fusion in the assessment of nodal metastases were both 87%; 13/15 and 40/46, respectively.

Discussion

This study showed that software-fused PET/CT had a supplementary value over visually correlated FDG-PET and md-CT in the assessment of nodal metastases in 30% of the patients with cancer of the oesophagus. Improved assessment of locoregional tumour foci is necessary for appropriate surgical treatment, but also for more accurately planned target volumes, particularly in the neoadjuvant chemoradiation treatment of these tumours (29, 30). Refinement of the nodal assessment was found by PET/CT fusion compared to the side-by-side visualisation method, even though the N-stage itself was not significantly affected. It is this refinement that is of major importance in radiotherapy planning.

However, there are some potential pitfalls in the interpretation of PET/CT fusion images. Although md-CT has a high accuracy in detecting enlarged lymph nodes, its specificity for metastases is low. Previous studies showed that lymph nodes of >1 cm on CT without FDG-uptake on PET are usually benign (23, 31, 32). Visual correlation between PET and CT is usually sufficient to determine this difference. Therefore, improvements in staging were not taken into account when summarizing improvements of software fusion compared to visual fusion. This statement should be interpreted with caution as it was difficult to visualize the regional lymph nodes near the primary tumour. In many cases, FDG-uptake in the primary tumour may mask nearby lesions, due to the assimilation of FDG-uptake in both. The para-oesophageal and paracardial areas are particularly difficult to interpret in this way. The lymph nodes can be categorized only as benign on the aforementioned criteria when they are not in the proximity of the primary tumour. Software fusion can be helpful in identifying whether these lymph nodes are located near the primary tumour. Another pitfall in the determination of nodal metastases on PET/CT fusion is the difficulty in exact pathological localization. Only meticulous marking during surgery with mapping of all visible or palpable nodes region

by region in the resected specimen according to the Japanese method makes correct identification possible.

There are also some inherent difficulties in software PET/CT fusion. Firstly, the outlining in software fusion depends, to a certain extent, on human expertise and appraisal, as does its evaluation. Therefore, small inter-observer variation is inherent to this kind of science (31). To overcome this problem in the present study, all the fusion images were studied and scored separately by an experienced nuclear physician and a radiologist. Disagreements were solved in a consensus meeting. Secondly, the software-fused images consist of two images from two different techniques at different times. Consequently body posture and position differ between the md-CT and PET. Fortunately, structures close to the spine, like the oesophagus, show only minimal movements and are therefore very suitable for fusion, though the position of the diaphragm often does not match as md-CT is conducted at maximum inspiration and PET during moderate respiration. Therefore, it is difficult to fuse PET and CT images below the vault of the diaphragm. Some authors have reported a failure of 30-39% in software PET/CT fusion of the evaluated cases (32, 33). However, these studies also described an increased success rate if the PET transmission data were incorporated in the fusion process for attenuation correction.

Recently hybrid PET/CT scanners have become available. The use of hybrid scanners partly overcomes these above mentioned limitations because PET and md-CT are performed simultaneously, in the same body posture and nearly at the same diaphragm position. Several studies comparing hybrid PET/CT with visually correlated FDG-PET/CT have reported an improvement of 22-49% in the detection, localization and characterization of malignant lesions with an accuracy of 90-96% (21-23, 34-36). Nevertheless, hybrid FDG-PET/CT scanners still consist of two separate scanners in one combined device, and difficulties may occur in the application of these scanners. The quality of the md-CT scan as part of a hybrid scan is frequently inferior to the quality of a separate md-CT scan, because md-CT is primarily based on anatomical mapping for precise localization of structures for FDG-PET. Additionally, oral contrast fluid is not administered, accurate imaging of pulmonary and hepatic lesions might be problematic due to respiratory movements and timing for arterial/venous imaging are not optimal. Furthermore, as earlier research has revealed no benefit of FDG-PET in stage I and II disease, hybrid scanning seems to be of limited value compared to md-CT in this group of patients (37). It is a relatively expensive investigation used in a whole population, while PET scanning will have no additional value in some subgroups.

In conclusion, fusion of FDG-PET and md-CT images improves the detection and/or localization of locoregional metastases in oesophageal cancer cases with a more accurate differentiation between physiological and pathological lesions.

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