

Combined PET/CT in the follow-up of differentiated thyroid carcinoma: what is the impact of each modality?

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Abstract

Purpose ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) is a well-established method in the follow-up of patients with differentiated thyroid carcinoma (DTC), elevated thyroglobulin (Tg) and negative ^{131}I scans. This retrospective clinical study was designed to evaluate the impact of computed tomography (CT) and that of FDG-PET in combined FDG-PET/CT examinations on the restaging of DTC patients.

Methods Forty-seven FDG-PET/CT scans of 33 patients with a history of DTC, elevated Tg levels and negative ^{131}I uptake or additionally suspected ^{131}I -negative lesions were studied. PET and CT images were analysed independently by an experienced nuclear medicine specialist and a radiologist. Afterwards a final consensus interpretation, the gold standard in our department, was provided for the fused PET/CT images and, if available, for supplementary investigations.

Results Thirty-five investigations (74%) revealed pathological FDG-PET/CT findings. In summary, 25 local recurrences, 62 lymph node metastases and 122 organ metastases (41 lung, 60 bone, 21 other organs) were diagnosed. In 36 out of 47 examinations (77%), the original PET diagnoses were modified in the final consensus interpretation owing to the CT assessments. In 8 of the 35 pathological FDG-PET/CT examinations (23%), the final consensus interpretation of the PET/CT images led to an alteration in the treatment plan.

Conclusion PET/CT is a powerful fusion of two pre-existing imaging modalities, which not only improves the diagnostic value in restaging DTC patients with elevated Tg and negative ^{131}I scan, but also provides accurate information regarding subsequent treatment options and may lead to a change in treatment management.

Keywords FDG-PET/CT · Differentiated thyroid carcinoma · Thyroglobulin · Local recurrence · Metastases

Introduction

In the follow-up of differentiated thyroid carcinoma (DTC) after thyroidectomy and radioiodine remnant ablation, elevated serum levels of thyroglobulin (Tg) with absence of Tg antibodies is most likely an indicator for local recurrence (LR) or metastases. In such cases, ultrasonography of the neck for localisation of LR or local lymph node metastases (LNMs) is recommended. Additionally, whole-body scans with various tracers may be helpful in detecting distant metastases. Usually ^{131}I is the tracer of choice, especially for post-therapeutic scans, because of its high specificity in visualising DTC metastases or LRs which have not lost their ability to store iodine. However, ^{131}I scans have been found to have a sensitivity of only 50–69% for the detection of thyroid malignancies [1–3]. The approximately 40% of lesions without any iodine uptake seem to be metastases with dedifferentiation, which worsen the prognosis and have to be detected early by other imaging modalities [1, 2, 4–7]. Computed tomography (CT), magnet resonance imaging and bone scanning are valuable tools in investigating such patients. Furthermore, scans using less specific tracers such as ^{201}Tl chloride, $^{99\text{m}}\text{Tc}$ -2-methoxyisobutylisonitrile, $^{99\text{m}}\text{Tc}$ -tetrofosmin or

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^{18}F -fluorodeoxyglucose (FDG) have been used for detection of DTC metastases [1, 2, 4, 8–11]. In comparison with other tracers, FDG has shown equal or superior sensitivity [1, 2, 4, 8, 9].

Because of its relative sensitivity, FDG positron emission tomography (PET) has become a well-established method in the follow-up of DTC patients with elevated Tg and negative ^{131}I scans. Depending on the Tg level, its sensitivity may reach 94% and its specificity 90%, in the detection of DTC metastases or LRs [1–6, 12–15]. At the 3rd German interdisciplinary consensus conference, FDG-PET was graded as a 1a indication (“established clinical use”) in restaging radioiodine-negative lesions and as a 1b indication (“clinical use probable”) in radioiodine-positive lesions if additional LR or metastases are suspected on the basis of elevated Tg levels [16]. The latter conclusion has been justified by studies revealing both iodine storage and FDG uptake in a number of DTC patients [1–6, 9].

The recent development of combined PET and CT imaging using so-called PET/CT scanners has improved the diagnostic information in the follow-up of DTC. Visualising the pathological glucose metabolism in the context of the detailed anatomical structure in one setting assists in planning surgical treatment or radiation therapy [17–19]. Studies using FDG-PET/CT scans to detect DTC metastases have revealed similar sensitivity to FDG-PET alone, but have not been able to answer the question of whether the additional information provided by the CT scan may lead to a change in diagnosis [17–19].

The aim of this retrospective clinical study was to evaluate (a) the impact of CT and that of FDG-PET in combined FDG-PET/CT examinations on the restaging of DTC patients and (b) the changes in therapy that resulted from the FDG-PET/CT scans.

Materials and methods

Patients

Forty-seven FDG-PET/CT scans of 33 patients with a history of histologically confirmed DTC and markedly elevated Tg levels were studied. All except five of the patients had negative post-therapeutic ^{131}I scans. These five patients showed only slight ^{131}I storage correlated with the elevated Tg levels, so that additionally ^{131}I -negative and FDG-positive lesions were suspected. Tg, measured by a radioimmunoassay, was <20 ng/ml in nine (median 4.36 ng/ml, range 1.78–10.37 ng/ml) and >20 ng/ml in 38 (median 480 ng/ml, range 23.9–7,712,300 ng/ml) examinations. The Tg recovery ranged from 72% to 127% (mean 92%) and Tg antibody levels were found to be below 50 mU/l in all patients except one (1,427 mU/l).

All patients had undergone thyroidectomy and ^{131}I radioablation of the remnants and were investigated between one and four times. The 47 FDG-PET/CT scans were performed in 32 women and 15 men, of whom 15 had papillary and 32, follicular DTC (mean age 63 ± 12 years, range 22–89 years). Thirty scans were performed under suppressive L-thyroxine therapy (thyroid stimulating hormone levels: median 0.011 mU/l, range 0.001–0.19 mU/l), four under euthyroid thyroid stimulating hormone levels (median 0.53 mU/l, range 0.39–0.84 mU/l) and 13 under elevated thyroid stimulating hormone levels (median 80 mU/l, range 24.5–80 mU/l). In our institution, the assay used to measure thyroid stimulating hormone levels is limited at 80 mU/l. In 11 of the 13 studies performed under elevated thyroid stimulating hormone levels, recombinant human thyroid stimulating hormone was injected intramuscularly to stimulate Tg production and to enhance the radioiodine and FDG uptake. In the remaining two cases, L-thyroxine had been withdrawn 4 weeks before the investigation started. As indicated above, usually the scans were performed under suppressive L-thyroxine therapy; elevated thyroid hormone conditions were induced only in patients with planned radioiodine application. Euthyroid conditions reflected limited compliance of patients in taking the L-thyroxine medication.

Protocol for FDG-PET/CT

Imaging was performed with a PET/CT scanner (Siemens Biograph LSO, Erlangen, Germany) which combines a helical CT system with a full ring lutetium oxyorthosilicate PET scanner. After overnight fasting and with blood glucose levels below 150 mg/dl, FDG was injected intravenously (mean activity 6.4 MBq/kg body weight, range 4.5–8.4 MBq/kg). Ninety minutes after tracer administration, scanning was initiated. The total acquisition time was about 20 min, consisting of 40 s CT scanning followed by CT-attenuation-corrected PET scanning. The whole-body PET images were acquired from the proximal femur to the base of the skull (axial field 90 cm; six bed positions, each lasting for 3 min). In 29 investigations, no further radioiodine therapy was planned and the CT scans were done as full contrast medium-enhanced scans (Visipaque 270).

Image analysis

An experienced radiologist interpreted the CT scans without information on the PET results, and an experienced nuclear medicine specialist independently assessed the PET scans without knowledge of the CT findings. Tracer uptake was defined as abnormal if it was visually higher than in the surrounding tissue and if no physiological uptake was

Table 1 Correlation of pathological PET results considered true positive on the basis of the consensus interpretation with thyroid stimulating hormone and Tg levels

	PET true positive investigations		PET true positive lesions/total lesions in consensus interpretation
	Tg< 20 ng/ml	Tg> 20 ng/ml	
TSH< 1 mU/l	1/4	27/30	123/149 (83%)
TSH> 20 mU/l	1/5	6/8	50/57 (88%)

TSH thyroid stimulating hormone

suspected. After these separate analyses, the radiologist and nuclear medicine specialist reviewed their own assessments and read the fused PET/CT images together, drawing up a fusion image report. Finally, a consensus interpretation that included consideration of pathological findings from other diagnostic investigations (¹³¹I whole-body scintigraphy in five cases, ^{99m}Tc-tetrofosmin scintigraphy in two cases, ultrasonography in two cases, magnetic resonance imaging in one case, ^{99m}Tc-depreotide scintigraphy in seven cases) was made by the two specialists. These supplementary diagnostic investigations were done if additional findings were suspected or in order to evaluate further treatment options. The results described LR, LNMs, organ metastases and additional pathological findings which were not due to the DTC history. Based on this final consensus interpretation, the subsequent management of the patient was determined.

Table 2 Results regarding pathological findings in the nuclear medicine report and the radiologist’s report compared with the consensus interpretation

	Report I			Report II			Report III
	True pos.	False pos.	False neg.	True pos.	False pos.	False neg.	
Local recurrences	19	4	6	20	2	5	25
Lymph node metastases	59	5	3	56	19	6	62
Organ metastases	95	2	27	108	8	14	122
Detailed organ metastases:							
Lung	26	–	15	41	6	–	41
Bone	50	2	10	48	2	12	60
Soft tissue	9	–	1	10	–	–	10
Vein tumour thrombosis	3	–	1	2	–	2	4
Adrenal gland	2	–	–	2	–	–	2
Pleura	2	–	–	2	–	–	2
Liver	1	–	–	1	–	–	1
Kidney	1	–	–	1	–	–	1
Spleen	1	–	–	1	–	–	1

Report I nuclear medicine report (FDG-PET), report II radiologist’s report (CT), report III consensus interpretation (mainly based on fused FDG-PET/CT image report)

Data analysis

In our retrospective clinical study we analysed the assessments of the different investigations in three categories: report I, nuclear medicine report; report II, radiologist’s report; report III, consensus interpretation, our gold standard, which was based on imaging modalities, and primarily on the FDG-PET/CT fusion image report. In each report the number of different pathological localisations of LR, LNMs and organ metastases was counted. Lesions in reports I and II were divided into true positive, false positive and false negative findings compared with the lesions which were considered as pathological in report III, the gold standard. Disseminated organ metastases, mainly in the lung, were counted as one metastasis or as one more metastasis if further lesions were identified by another imaging modality. Additionally we registered changes in the therapy, if there were any, and pathological findings which were unrelated to the DTC history and had to be treated or further investigated.

Results

Out of the 47 investigations, pathological FDG uptake was observed in 35 cases, yielding a sensitivity of 74%. Correlation of pathological PET results with thyroid stimulating hormone and Tg levels is shown in Table 1 and discussed below. In our series, 38 patients had Tg levels >20 ng/ml at the time of the investigation. Pathological FDG uptake was found in 33 of these investigations

(sensitivity 87%). Scans performed in the context of only slightly elevated Tg levels, namely <20 ng/ml, yielded pathological PET findings in just two out of nine cases (sensitivity 22%). Patients with elevated thyroid stimulating hormone levels revealed a lesion detection rate of 88% (50/57; true positive in nuclear medicine report/consensus interpretation). Patients with thyroid stimulating hormone-suppression or thyroid stimulating hormone levels in the normal range revealed a lesion detection rate of 83% (123/149; true positive in nuclear medicine report/consensus interpretation).

The total number of identified lesions (report III: 25 LRs, 62 LNMs and 122 organ metastases) is listed in detailed form in Table 2. Apart from five LRs and two bone metastases, all lesions which were considered as pathological in the consensus interpretation were diagnosed or confirmed in the FDG-PET/CT fusion image report. Four of the five patients with positive ^{131}I scans (these findings were considered as pathological) revealed additional pathological findings on FDG-PET/CT. As expected, most

metastases were diagnosed in lymph nodes (62), the lung (41) and the bone (60). Twenty-one metastases were found in other organs (ten in soft tissue, two in adrenal glands, two in pleura, one in the liver, one in kidneys, one in the spleen and four cases of vein tumour thrombosis).

The 25 distinct localisations of LR were detected by FDG-PET/CT (20 lesions), by $^{99\text{m}}\text{Tc}$ -depreotide scintigraphy (four lesions in two examinations) and by ^{131}I scan (one lesion). Nineteen LRs were detected as true positive on the PET scans (76%) and 20 true positive LRs were found on CT (80%).

In the diagnosis of LNMs, all malignancies identified in the consensus interpretation were detected by FDG-PET/CT. We found an overall sensitivity of 95% (59/62) for PET and 90% (56/62) for CT. The positive predictive value in identification of LNMs was 92% (59/64) on PET and 75% (56/75) on CT.

Regarding lung metastases, PET findings revealed only 26 of the 41 pathological localisations in the lung

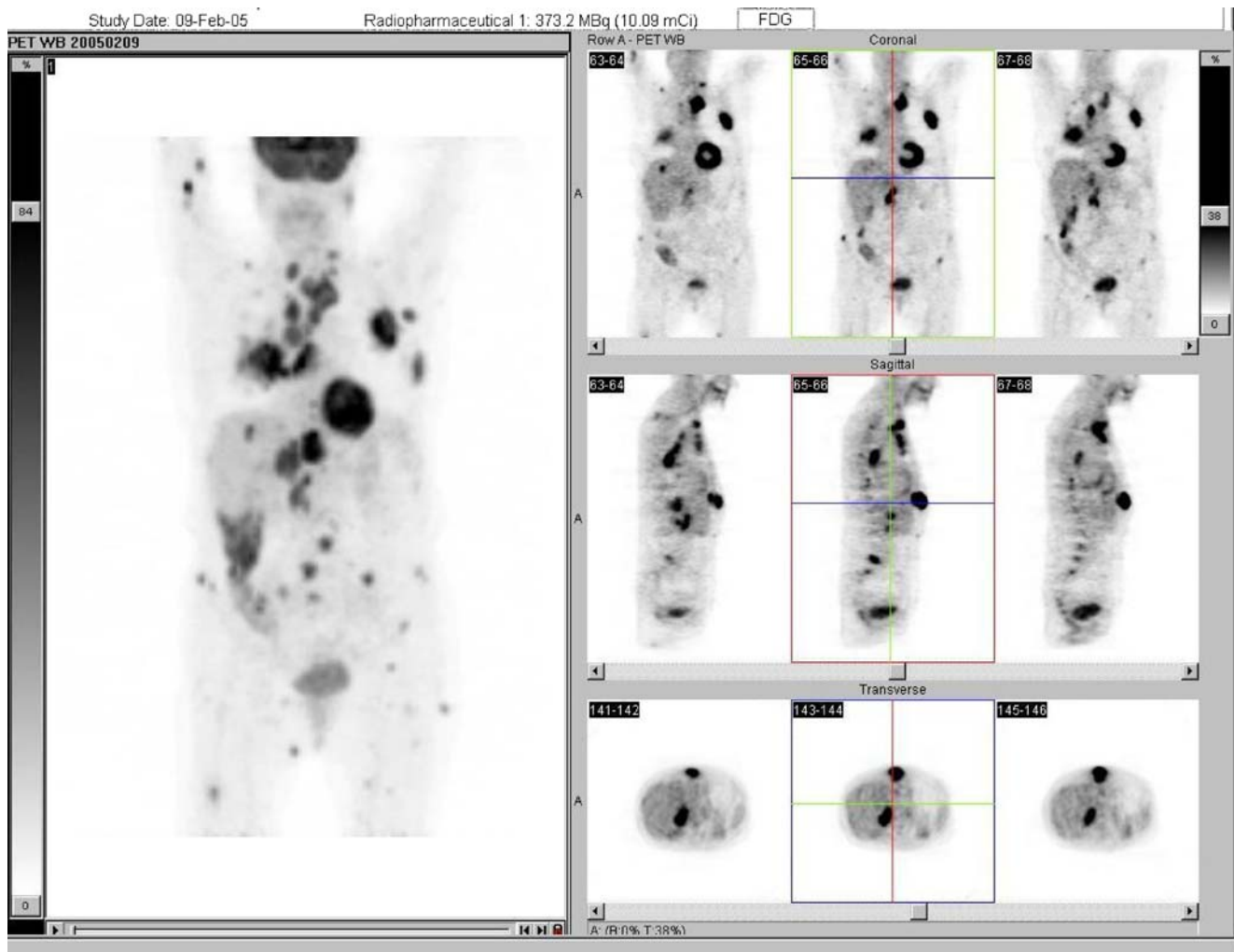


Fig. 1 A 71-year-old woman with follicular DTC (Tg 1.78 ng/ml, thyroid stimulating hormone 24.5 mU/l). FDG whole-body scan reveals multiple pathological lesions (lung, mediastinum, right adrenal gland, liver, bone, subcutaneous tissue)

(sensitivity 63%), but PET had a positive predictive value of 100%. On the CT component of FDG-PET/CT, all 41 localisations were recognised (sensitivity 100%), with a positive predictive value of 87% (41/47). In most cases in which more lesions were detected on the CT images, there was disseminated cancer involvement of the lung. Owing to its higher resolution, CT was able to reveal a larger number of small metastases. Such constellations were counted as one false negative and one true positive lesion on PET and as two true positive lesions on CT.

In one examination, two ^{131}I -positive bone metastases could not be confirmed by FDG-PET/CT. Fifty true positive and two false positive bone metastases were detected on PET, yielding a sensitivity of 85% (50/60) and a positive predictive value of 96% (50/52). CT revealed similar results, with a sensitivity of 80% (48/60) and a positive predictive value of 96% (48/50). Although PET and CT demonstrated almost the same statistical values, they differed in the detection of bone lesions. In 25% (15/60) of true positive bone metastases on the consensus interpretation, the findings could not be confirmed by one of the components of PET/CT, i.e. either PET or CT.

In 36 investigations (77%) the suspected diagnosis made by the nuclear medicine specialist based on PET images differed from the radiologist's assessment of the CT scan and had to be modified in the fusion image report.

In eight of the 35 FDG-PET/CT positive examinations (23%), therapy (radiation therapy, lymph node resection, excision of bone metastases, nephrectomy, excision of LRs and initiation of antithrombotic therapy) was changed on the basis of the final consensus interpretation of the PET/CT images, and in 11 cases (31%) retinoid therapy was started.

In 26 cases, additional findings unrelated to DTC were noted. Four of these findings (9%) had to be further investigated or treated (histologically confirmed oesophageal cancer, histologically confirmed breast carcinoma, aortic aneurysm, uterine tumour).

Discussion

The correlation of pathological FDG-PET findings and histopathological analyses has been demonstrated in previous studies [1–3, 5, 6, 8, 13, 15, 17–19, 24, 27]. In light of these results, our interpretations were based on a gold standard comprising only imaging modalities without histological confirmation. This can be perceived as a limitation of our study. A second limitation is that our data were analysed retrospectively, and so our patients had different initial situations and different further investigations. We have tried to clarify this situation in our exposition.

As in other studies, we found that the sensitivity of FDG-PET rose in conjunction with an elevated Tg level (Table 1) [2, 3, 6, 12, 18, 19]. To date, a Tg cut-off level for an FDG-PET examination has not been defined. However, FDG-PET or FDG-PET/CT is proposed to be a useful tool in patients with a Tg level of >10 ng/ml and negative ^{131}I scans, irrespective of the thyroid stimulating hormone level [6, 19]. Patients with no rise in Tg level after stimulation with recombinant human thyroid stimulating hormone and patients with an undetectable basal serum Tg level (<1 ng/ml) can be considered disease free [20]. Dietlein et al. reported that a low Tg level under thyroid stimulating hormone

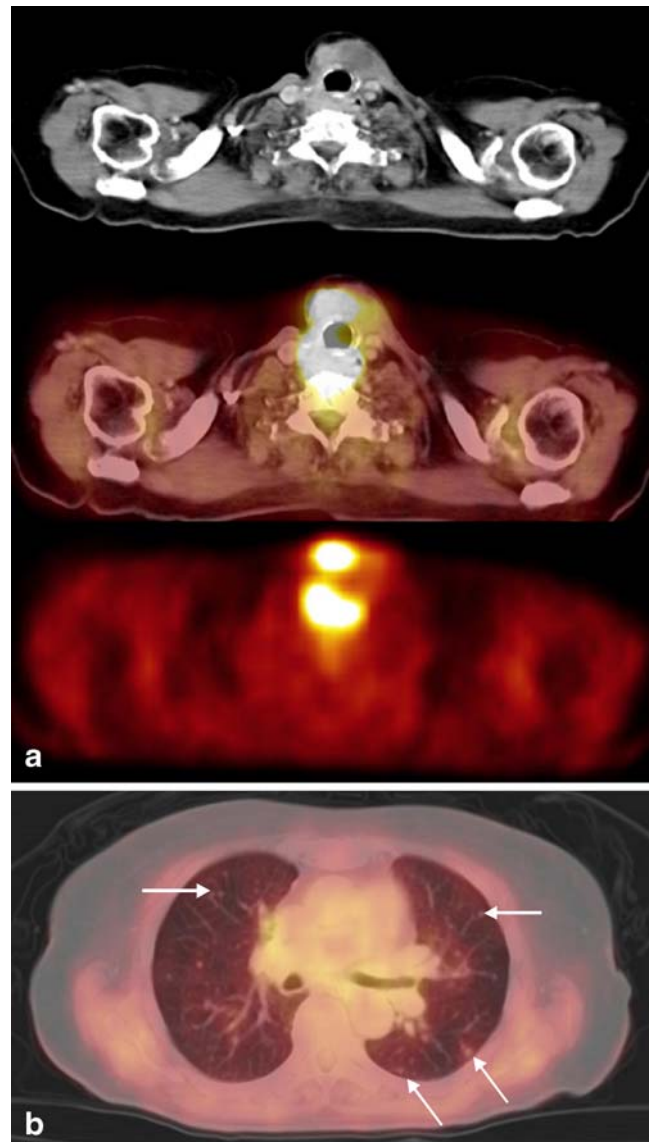


Fig. 2 A 75-year-old woman with papillary DTC (Tg 84.5 ng/ml, thyroid stimulating hormone 0.02 mU/l). **a** Axial images of the neck (from top to bottom: CT, fused PET/CT, PET) with pre- and retrotracheal extension of LR, infiltrating the oesophagus. **b** Fused axial PET/CT image of the lung with FDG-negative metastases because of their size (arrows)

suppression did not exclude vital tumour or FDG uptake, but that a low Tg level under stimulation, together with an undisturbed recovery test, makes FDG-PET redundant [3]. We observed that only two out of nine patients with Tg <20 ng/ml (6.88 ng/ml and 1.78 ng/ml) showed pathological FDG uptake. However, as shown in Fig. 1, one of these patients had multiple FDG-positive metastases under elevated thyroid stimulating hormone conditions and in the absence of Tg antibodies (Tg 1.78 ng/ml, thyroid stimulating hormone 24.5 mU/l); nevertheless, such cases seem rare.

Elevated thyroid stimulating hormone levels have a positive effect on the uptake of FDG in DTC recurrences or metastases and have been recommended for FDG-PET examinations [21–23]. We can confirm this thesis with our findings, which demonstrate a slight increase in lesion detection on FDG-PET, from 83% to 88%, in the presence of an elevated thyroid stimulating hormone level (Table 1).

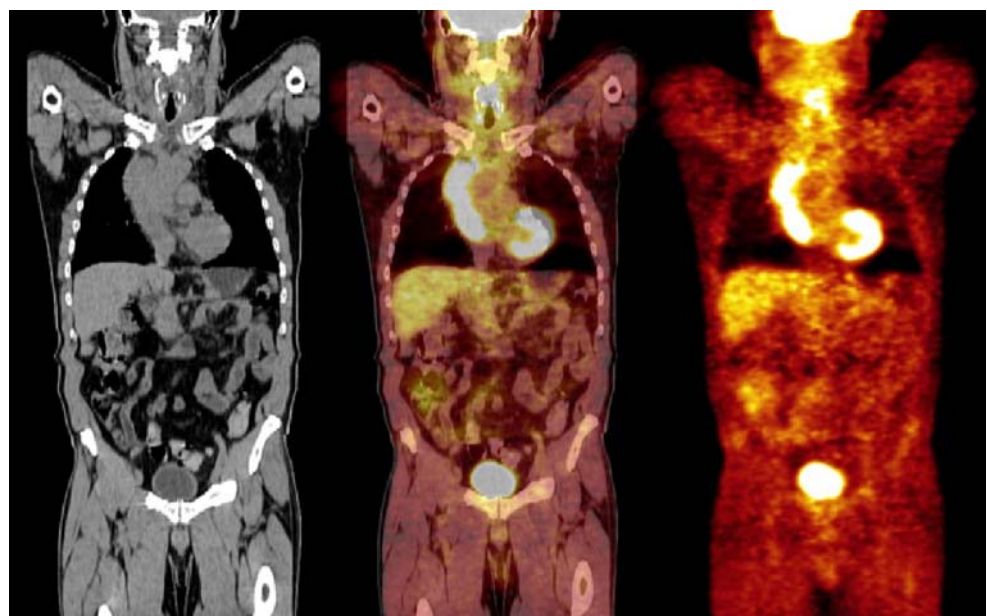
It needs to be stressed that, even if PET and CT yield equivalent results, the combination of these techniques always improves the diagnostic assessment by providing more accurate information. Our comparison between PET and CT findings showed that the two techniques resulted in nearly the same assessments in respect of LRs. PET revealed a sensitivity of 76% (19/25) and CT, 80% (20/25) in identifying distinct LRs. CT was very helpful in distinguishing LRs from local LNMs and in providing detailed depiction of tumour extension and organ infiltration, e.g. of the larynx, trachea, vessels or prevertebral fascia (Fig. 2a). On the other hand, PET was helpful in differentiating vital tumours from scar tissue in the thyroid bed. Nahas et al. reviewed 33 patients with suspected recurrent papillary thyroid cancer who were investigated by

FDG-PET/CT. FDG-PET/CT correlated with histopathological analysis after surgery in 25 of 36 distinct anatomical sites. FDG-PET/CT was found to have a sensitivity of 66%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 27% [19]. Zimmer et al. reported FDG-PET/CT to have a positive predictive value of 75% (six of eight cases) based on histopathological confirmation of local DTC recurrences [18]. Both studies revealed that positive findings of FDG-PET/CT regarding LR are likely to be indicative of malignancy.

Alongside ultrasonography, FDG-PET is a powerful tool in detecting LNMs, even in lymph nodes with a diameter of less than 1 cm, and it is a supplementary aid in discriminating between unspecific lymph node enlargement and LNMs [2, 3, 24]. The metabolic information visualised on PET seems to have a higher impact on the detection of LNMs on FDG-PET/CT than the morphological presentation on CT. We found that, based on the consensus interpretation, PET and CT had positive predictive values of 92% and 75%, respectively. PET analyses markedly reduced the number of false positive findings on CT, but on the other hand CT assessments were able to reveal false positive PET findings in a few cases, e.g. tracer uptake in brown fat tissue.

Previous studies have revealed that FDG-PET has shortcomings in detecting miliary lung metastases, especially in small pulmonary lesions (<1 cm). In such cases spiral CT is necessary [1, 3, 25]. In the present study, a total of 41 lung metastases were reported in the FDG-PET/CT consensus interpretations. Only 26 (63%) of these lesions were found on PET, but PET had a positive predictive value of 100%. As in other studies, small pulmonary metastases were often overlooked by PET (Fig. 2b). In these cases the

Fig. 3 A 61-year-old man with follicular DTC (Tg 2,210 ng/ml, thyroid stimulating hormone 80 mU/l). Coronal images (from left to right: CT, fused PET/CT, PET) of a tumour thrombosis of the right brachiocephalic vein and the superior vena cava with significant FDG uptake. The tumour thrombosis was overlooked on this non-contrast-enhanced CT scan



CT scan was very helpful in detecting malignancies (sensitivity 100%, positive predictive value 87%). False positive findings on CT were due to non-vital residuals. In conclusion, CT plays the major role in diagnosing lung metastases and raises the sensitivity of PET in combined PET/CT scanners to a high level.

Schirrmester et al. demonstrated that FDG-PET is clearly more sensitive than planar radionuclide bone scanning in the detection of osseous lesions [26]. On the other hand, Feine et al. reported multiple bone metastases that exhibited ^{131}I uptake and had a typical appearance on radiographs but were not visible on $^{99\text{m}}\text{Tc}$ -methylene diphosphonate bone scans or FDG scans, possibly owing to low malignancy [5]. In the present study, only two out of 60 bone metastases were ^{131}I positive and FDG-PET/CT negative. PET and CT revealed similar sensitivities and positive predictive values, but the combination of both modalities improved diagnostic sensitivity exceptionally. It has to be mentioned that 25% of the diagnoses were made by PET or CT alone. A recent FDG-PET/CT study concerning bone metastases revealed that only half of the true positive metastases detected on PET were perceived as morphological changes on CT (four out of six DTC metastases were detected by CT); however, CT was able to reduce the number of false positive findings on PET [27].

In our series, DTC metastases were not found very often in other organs, except in soft tissue. In these cases, PET and CT seem equally adept at detecting malignancies, except for vein tumour thrombosis, which was overlooked on our non-contrast-enhanced CT images (Fig. 3).

In addition to providing morphological and anatomical information, CT changed the suspected diagnosis based on PET in 36 investigations (77%) owing to its higher resolution and the visualisation of FDG-negative metastases. CT also helped in avoiding pitfalls, e.g. tracer uptake in brown fat tissue. On the other hand, in many cases PET was able to detect bone metastases at an early stage and to distinguish enlarged reactive lymph nodes from LNMs and post-therapeutic alterations from vital tumours in many cases.

In a study on recurrent papillary thyroid carcinoma, the treatment plan was altered in 40% of patients and supported in 27% by the FDG-PET/CT information [19]. In our patient group, eight out of 35 (23%) FDG-PET/CT-positive investigations led to changes in therapy. This is less than the figure reported by Nahas et al. [19], but like descriptions of overall sensitivity, statements on therapeutic impact are highly dependent on the included patient group. It has previously been reported that in approximately 20% of cases, retinoids lead to redifferentiation in thyroid carcinomas, re-induce radioiodine uptake in dedifferentiated tumour cells, induce apoptosis and have a growth-inhibiting effect [28, 29], and accordingly, in our study Roaccutan therapy was started in 11 (31%) cases .

Two additionally detected malignancies (oesophageal carcinoma, breast carcinoma), which were unexpected and were not linked to the history of DTC, were found in our 47 investigations (Fig. 4). Ishimori et al. reviewed 1,912 patients with confirmed cancer who had been scanned by FDG-PET/CT. In 4.1% a second unexpected primary was suspected; in 1.2% the suspected lesion had been pathologically proven to be malignant, in 2% it had not yet been

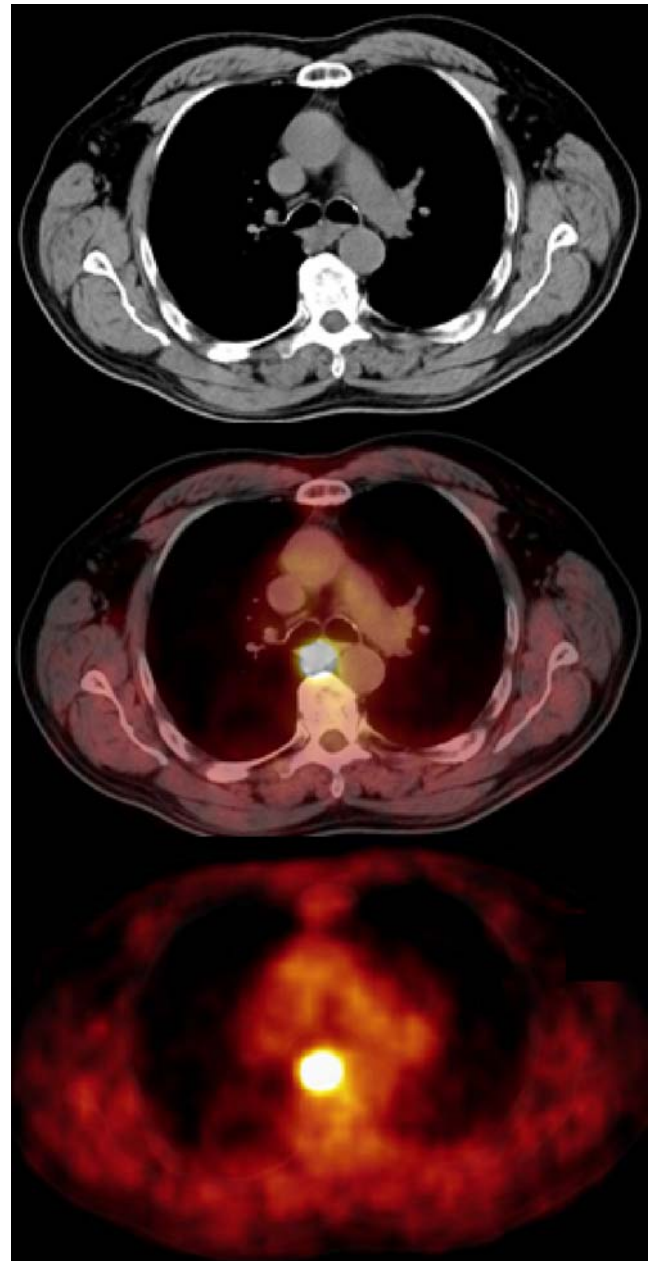


Fig. 4 A 68-year-old man with a history of follicular DTC (Tg 2.29 ng/ml, thyroid stimulating hormone 0.5 mU/l). Axial images (from top to bottom: CT, fused PET/CT, PET) of an oesophageal carcinoma, unrelated to DTC. According to the PET image report, a lymph node metastasis was suspected. In the CT image report and final consensus report, the oesophageal tumour localisation was diagnosed (it was subsequently confirmed histologically)

confirmed and in 0.9% it had proven benign [30]. In summary, FDG-PET/CT frequently leads to necessary management alteration which is unrelated to the expected primary cancer.

This study cannot answer the question of whether independent acquisition of PET and CT would have led to diagnostic differences in the consensus interpretation. However, it can be assumed that diagnosis would have been less accurate owing to the use of two bed positions at different times of investigation and the lack of availability of a fused FDG-PET/CT image.

In conclusion, PET/CT should be preferred to PET in the follow-up of DTC patients with ^{131}I -negative whole-body scans and elevated Tg levels. FDG-PET/CT markedly improves upon the diagnostic value of FDG-PET in such cases, can result in the modification of treatment plans and may reveal unexpected pathological findings. It integrates the strengths of CT in visualising lung metastases and detailed morphological changes and of PET in detecting vital tumour tissue, especially in lymph nodes, LR and bone.

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