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Value of ^{124}I-PET/CT in staging of patients with differentiated thyroid cancer

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Abstract The aim of this study is to evaluate the clinical significance of ^{124}I positron emission tomography (PET) using a combined PET/CT tomograph in patients with differentiated thyroid carcinoma and to compare the PET/CT results with ^{131}I whole-body scintigraphy (WBS), dedicated PET and CT alone. Twelve thyroid cancer patients were referred for diagnostic workup and entered complete clinical evaluation, including histology, cytology, thyroglobulin level, ultrasonography, fluorine-18 fluorodeoxyglucose (FDG)-PET, FDG-PET/CT and CT. Lesion-based evaluation showed a lesion delectability of 56, 87 and 100% for CT, ^{124}I-PET, and combined ^{124}I-PET/CT imaging, respectively. Lesion delectability of ^{131}I-WBS was 83%. We conclude that ^{124}I-PET/CT imaging is a promising technique to improve treatment planning in thyroid cancer. It is particularly valuable in patients suffering from advanced differentiated thyroid cancer prior to radio-iodine therapy and in patients with suspected recurrence and potential metastatic disease.

Keywords Dual-modality · Thyroid cancer · Staging · PET · PET/CT · Iodine-124 · Iodine-131 · WBS

Introduction

Patients with well-differentiated thyroid cancer (DTC) generally have a good prognosis. However, widespread metastatic disease or tumor recurrence can be associated with significant morbidity, and even mortality. Proper staging is crucial for appropriate therapy planning. Treatment options involve radio-iodine therapy and, in advanced disease, external beam radiotherapy and chemotherapy [1].

In addition, thyreoglobulin (TG), ^{131}I-WBS, ultrasonography (US), US-guided fine-needle biopsy and FDG-PET are useful diagnostic tools in the follow-up of thyroidectomized patients with DTC [1–5], of which ^{131}I-WBS was shown to be most sensitive procedure in follow-up of DTC [6]. Recent studies showed that FDG-PET results lead to changes in approaches to surgical treatment plans in a significant number of patients, especially in cases with poor tumor differentiation, where reduced or lost iodine-accumulating ability leads to false-negative ^{131}I-scanning results [1–3].

In the majority of patients, however, iodine uptake in the tumor is adequate for scintigraphy and radio-iodine therapy. Therefore, patients with DTC may benefit from technical improvements in tumor scintigraphy with iodine.

Iodine-124, an isotope with a half-life of 4.2 days, is suitable for PET imaging and has already been used for dosimetry [7–13]. Although PET is a superior imaging system with physical advantages compared to planar gamma cameras and SPECT, it has not been established for routine imaging of thyroid cancer with iodine for several reasons: first, because of the complex decay scheme of ^{124}I that includes several high-energy gamma rays and makes ^{124}I imaging a challenge for a gamma camera. In addition, the limited availability of ^{124}I, which needs a high-MeV cyclotron for production, together with the somewhat limited availability of PET scanners further limit the widespread acceptance of ^{124}I imaging. However, upon availability measurements with ^{124}I made under realistic scan conditions using different

PET scanner models have shown that satisfactory imaging results can be achieved [12]. However, ^{124}I will only be made available for satellite PET sites if it can be established as a superior radiopharmaceutical for thyroid cancer imaging.

Second, a major challenge when interpreting PET or SPECT images with highly specific tracers such as ^{124}I is the lack of identifiable anatomical structures, thus making an accurate localization of foci of tracer uptake highly problematic [14]. By correlating the PET information with the available anatomical background information such as obtained from a dual-modality PET/CT exam, the spatial localization of lesions may be much improved. By acquiring both PET and CT data sets in a single scan session using a combined PET/CT tomograph, the PET and CT data can be acquired in a single session and the resulting imaging sets are intrinsically co-registrated [14, 15]. Until now, only a few case-reports concerning ^{124}I-PET/CT have been published showing the potential of this new and innovative imaging tool [16–18].

The purpose of this study was for the first time to evaluate ^{124}I-PET/CT scanning in patients with differentiated thyroid carcinoma by comparing diagnostic imaging results of established imaging procedures with the results of ^{124}I-PET and CT alone.

Material and methods

Patients

Twelve patients (five female and seven male, age: 31–76 years, mean 59 years) with DTC who where admitted to the Department of Nuclear Medicine at the University Hospital, Essen, for radioiodine therapy were included in this study. All patients gave informed consent. Eleven patients were examined during the postoperative phase after thyroidectomy under maximal thyroid-stimulating hormone (TSH) stimulus (52±21 mU/l). One patient with known pulmonary metastasis was examined following an exogenous TSH stimulation by recombinant human TSH (rhTSH). Iodine excretion in the urine was within physiological limits in all patients (128±50 µg/l), excluding an iodine contamination. The tumor classification in these patients according to the Union Internationale Contre le Cancer (AJCC) system [19] is shown in Table 1. Six patients presented with elevated TG, and no patient had pathologically elevated TG antibodies (Table 2). Surgical intervention was performed in three patients after completion of the diagnostic imaging; two patients received external radiation beam therapy in addition to radio-iodine therapy. During routine clinical staging, computed tomographic imaging (CT), ^{124}I-PET, combined ^{124}I-PET/CT, US and separate FDG-PET were performed. All imaging procedures were completed within 2 weeks.

Table 1 Tumor classification according to the AJCC system [16] in 12 patients with DTC

AJCC stage	No. of patients
pT1	0
pT2	4
pT3	2
pT4	6

pT1, <1 cm; pT2, <4 cm; pT3, >4 cm; pT4, tumor of any size not confined to the thyroid; pTx, tumor size not available.

Methods

Radiopharmaceutical preparation of ^{124}I

[^{124}I] Iodide was produced using the CV28 cyclotron by means of a [^{124}Te] Tellurium (*d*, 2*n*) [^{124}I] Iodine reaction. A platinum-iridium target plated with 99.8% [^{124}Te] Telluriumdioxide was irradiated with 14 MeV deuterons at 15 µA. Subsequently, the [^{124}I] Iodine was distilled at 745°C in an quartz apparatus and the [^{124}I] Iodide was inserted in 0.2 ml of 0.01 N NaOH. [20] About 100 MBq (70–90 µl) of this solution was applied to a commercially available capsule (Amersham, Brauschweig, Germany) just before administration to the patient.

^{124}I-PET/CT data acquisition

Data acquisition was performed using a combined PET/CT system (Biograph, Siemens Medical Solutions Hoffman Estates, USA manufactured by CPS, Knoxville, TN). The biograph consists of a single-slice spiral CT (Somaton Emotion) and a dedicated PET scanner based on ECAT EXACT HR+.

PET/CT imaging commenced 24 h postoral administration of 84±15 MBq ^{124}I. The patient was positioned on the table and a topogram (scout scan) was used to define the axial imaging range. Typically, patients were scanned from the head to the abdomen, thus yielding four to seven contiguous bed positions. First, a single-spiral CT scan was acquired covering the entire axial imaging range. All CT scans were acquired with a tube voltage of 130 kVp, 160 mAs, a slice width of 5 mm and a pitch of 1.6. As all patients were scheduled for radio-iodine-therapy, no intravenous CT contrast agent was applied due to the potential iodine blockade. The CT data were used for PET attenuation correction [21]. After completion of the CT scan, the patient was advanced automatically to the PET (to the rear of the combined gantry), and emission scanning started. Whole-body emission data were acquired in 3D mode for 5 min per bed position. Image reconstruction of the corrected emission data was performed after Fourier rebinning (AW-OSEM at two iterations and eight subsets with a 5 mm post-reconstruction Gaussian filter). Total scan time was 25–40 min depending on the number of beds scanned.

Interpretation of the ^{124}I-PET examinations

Validation of ^{124}I-PET findings was not possible in all lesions since most lesions were not biopsied. Therefore, we introduced the following diagnostic criteria for reading the ^{124}I-PET images:

(1) Intense focal tracer accumulation exceeding normal regional tracer uptake by at least a factor of five was rated as tumor or thyroid remnant, depending on the location and morphology (Fig. 1 shows the weakest positive lesion interpreted as tumor, with a tumor/background ration of 6.2).
(2) Focal tracer accumulation in the pelvis of the kidney or bladder was considered to be physiologic.
(3) Non-focal linear uptake following the intestine was rated as non-specific, non-pathological uptake.

These criteria were confirmed in 6 lesions (of 69 total lesions) by histology.

Table 2 Number of tumor lesions in comparison to the standard of reference (consensus)

Patient no.	Age	Gender	Previous surgery	Histology	pT	N	M	TG (ng/ml)	Recovery (%)	TSH (mU/l)	urine-iodine (µg/l)	^{131}I-Uptake (%)	Nature of tumor	^{124}I-PET	CT	Combined PET/CT	^{131}I-WBS	Cerv. & abd. US	18 F-FDG-PET	Others	Consensus
1	42	Male	Yes	Papillary	2	0	0	>0.3	58	42	58	6	PT	2	3	2	1[a]	2			2
													LNM	0	0	0	0	0			0
													OM	0	0	0	0	0			0
2	57	Female	Yes	Papillary	2	0	0	62	103	31	113	9	PT	3	0	3	1[a]	0		MRT	3
													LNM	0	0	0	0	0			0
													OM	0	0	0	0	0			0
3	71	Male	Yes	Papillary	4	0	1	1	104	47	143	12	PT	2	0	2	1[a]	1			2
													LNM	0	0	0	0	0			0
													OM	3	0	3	2	0			3
4	62	Male	Yes	Papillary	4	1	0	5	96	54	126	8	PT	2	0	2	1[a]	1			2
													LNM	1	0	1	0	0			1
													OM	0	0	0	0	0			3
5	58	Female	Yes	Papillary	3	0	0	2.2	108	>80	90	2	PT	1	0	1	1[a]	1			1
													LNM	0	0	0	0	0			0
													OM	0	0	0	0	0			0
6	63	Male	Yes	Follicular	4	2	1	4,758	97	10	134	16	PT	1	1	1	1	1		Histology	1
													LNM	1	1	1	1	0		Bone	1
													OM	11	9	14	12	0		Scintigraphy	14
7	76	Female	Yes	Papillary	4	0	0	0.4	109	>80	231	3	PT	3	0	3	1[a]	0			3
													LNM	0	0	0	0	0			0
													OM	0	0	0	0	0			0
8	31	Female	Yes	Follicular	4	1	1	216	91	>80	104	1	PT	0	0	0	0	0			0
													LNM	0	0	0	0	0			0
													OM	1	4	4	1	0			4
9	54	Male	Yes	Papillary	2	1	0	122	76	37	92	4	PT	1	1**	1	1	0	2		1
													LNM	1	1**	1	1	1[b]	2		1
													OM	0	0	0	0	0	0	Histology	0
10	48	Female	Yes	Papillary	2	0	0	0.4	104	>80	214	3	PT	0	0	0	0	0			0
													LNM	1	0	1	1	0			1
													OM	0	0	0	0	0			0
11	73	Male	Yes	Papillary	4	2	1	1,324	89	64	107	11	PT	1	1	1	1	1	1		1
													LNM	1	1	1	1	1	1		1
													OM	19	13	21	17	0	14		21
12	69	Male	Yes	Follicular	3	2	1	2,410	113	54	121	9	PT	1	1	1	1	1	0		1
													LNM	1	1	1	1	1	1		1
													OM	3	4	4	3	0	4	Histology	4

PT, primary tumor; LNM, lymph node metastasis; OM, organ metastsis.
[a] WBS was not able to determine different foci of thyroid remnants.
[b] Additional secondary oropharyngeal tumor with lymph node metastasis.

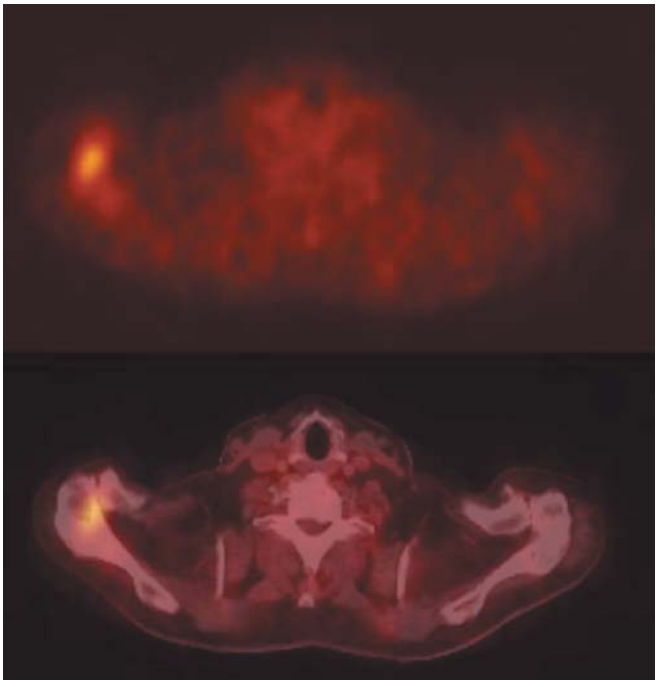

Fig. 1 ^{124}I-PET (*top*) and fused ^{124}I-PET/CT (*bottom*) show the exact localization of an iodine avid bone metastases of follicular thyroid carcinoma in the capsula with a tumor/background ration of 6.2 (patient 11)

I-131 WBS

High-dose WBS was performed 5–8 days after oral administration of 3,000 MBq ^{131}I using a dual-head gamma camera (BodyScan, Siemens, Erlangen, Germany) with a high-energy collimator.

Ultrasound

Lymph node staging was performed in all 12 patients by Ultrasound (Sonoline Elegra, Siemens, Erlangen, Germany) as part of morphological diagnostic imaging. Lymph nodes were called metastatic according to the criteria of Görges et al. that include the Solbiati-Index (ratio of largest to smallest diameter), internal structure and vascular pattern yielding a sensitivity of 90% and specificity of 82% [22].

Data analysis

Two experienced radiologists (GA, JFD) assessed the results of anatomical imaging procedures. Two experienced nuclear medicine specialists (LSF, RG), without knowledge of the CT findings, or clinical data, evaluated the PET images. Finally the PET/CT-images were read by two nuclear medicine specialists (LSF, RG) and two radiologists in consensus (GA, JFD). Except for six cases where histological results were available, a consensus reading based on the sum of all clinical data and imaging procedures was established by a committee consisting of the two radiologists and the two nuclear medicine specialists. A consensual verdict was reached for each patient with respect to the presence or absence of disease and the number and localization of malignant lesions. This consensus, combined with results of US and ^{131}I-WBS, served as the standard of reference and reflected the final clinical diagnosis.

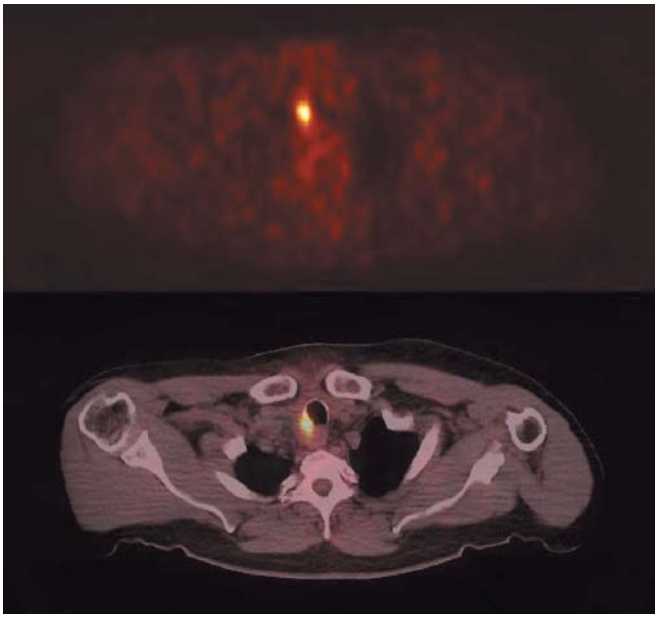

Fig. 2 ^{124}I-PET (*top*) and fused ^{124}I-PET/CT (**bottom**) show the exact localization of thyroid remnant of papillary thyroid carcinoma (CT was read as normal) (patient 5)

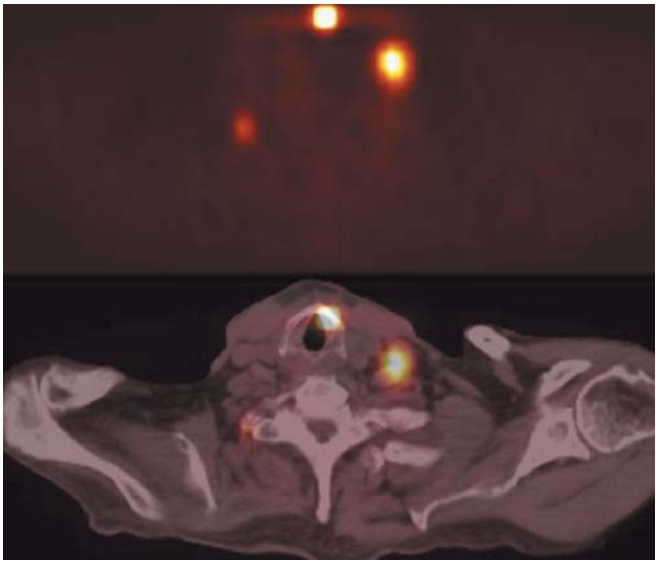

Fig. 3 ^{124}I-PET (*top*) and fused ^{124}I-PET/CT (*bottom*) show the exact localization of thyroid remnant of papillary thyroid carcinoma and cervical lymphnode metastasis (patient 4)

This consensus procedure resulted in a set of data for each patient with respect to primary tumor/local recurrence, lymph node status and metastasis. Lesion delectability of the individual procedures was calculated from these data.

Table 3 Results of the different imaging modalities in comparison to the gold standard (consensus)

	^{124}I-PET				CT				^{124}I-PET/CT				^{131}I-WBS				Ultrasonography				Consensus
	TP	FP	FN	LesD	TP	FP	FN	LesD	TP	FP	FN	LesD	TP	FP	FN	LesD	TP	FP	FN	LesD	
Primary tumor	17	0	0	100	6	1	11	35	17	0	0	100	17	0	0	100	8	0	9	47	17
Lymph node metastases	6	0	0	100	3	1	3	50	6	0	0	100	5	0	0	83	2	0	4	33	6
Organ metastases	37	0	9	80	30	2	16	65	46	1	0	100	35	2	11	76					46
Total	60	0	11	87	39	4	30	56	69	1	2	100	58	2	11	83					69

TP, true-positive; TN, true-negative; FP, false-positive; LesD, lesion detectability in persentage.

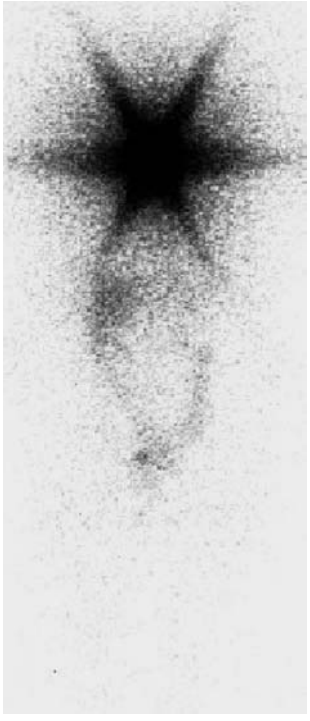

Fig. 4 ^{131}I-WBS compared to ^{124}I-PET/CT (patient 4, see Fig. 3) does not allow differentiation between thyroid remnant and cervical lymph node metastasis

Results

The summarized findings of the individual diagnostic techniques are shown in Table 2. ^{131}I-WBS did not allow any differentiation of multiple foci in thyroid remnants in all patients as shown in Fig. 2. Besides evaluation of thyroid remnants the clinical readings from ^{124}I-PET and ^{131}I-WBS agreed in 10/12 (83%) patients. The discrepancies in three patients can be described as follows.

(1) A cervical lymph node, which was close to thyroid remnant metastasis was not detected in ^{131}I-WBS (patient 4, see Figs. 3, 4).

(2) ^{131}I-WBS missed two small bone metastasis (patient 11, see Fig. 1).

In CT alone, especially primary malignancies, lymph node metastasis and small metastases involving the bone were not detected, yielding in a lesion delectability of 35, 50 and 65%, respectively. On the other hand, CT showed iodine-negative pulmonary metastases in 4/12 (33%) patients [16].

Compared to the combination of separate ^{124}I-PET and CT readings, the combined assessment of fused PET and CT images in a fusion display did not reveal additional tumor manifestations. However, the accurate topographic localization of the tumor resulted in a change of staging in two patients and a change in management in one patient who underwent re-surgery due to a lymph node metastasis (patient 4). Table 3 summarizes the results of the different imaging procedures including ^{131}I-WBS and ultrasound (cervical and abdominal).

As can be seen from Tables 2, 3, the morphologic and metabolic imaging procedures showed considerable variation in results. The sensitivities of each modality for primary tumor, lymph node staging and organ metastases are shown Table 3. The overall lesion delectability in ^{124}I-PET, CT, ^{124}I-PET/CT and ^{131}I-WBS were 87, 56, 100 and 83%, respectively.

Discussion

In CT alone, especially primary malignancies, lymph node metastasis [17, 18] and small metastases involving the bone were not detected. On the other hand, CT showed iodine-negative pulmonary metastases in 4/12 (33%) patients [16] and thus was highly accurate in the diagnosis of organ metastases. These findings exclude curative ^{131}I therapy and convey important prognostic information. Therefore, the combination of ^{124}I-PET and CT appears to be synergistic.

Compared to the combination of separate ^{124}I-PET and CT readings, the combined assessment of fused PET and CT resulted in a change of staging in two patients

and a change in management in one patient. From these considerations, it is clear that ^{124}I-PET/CT may provide incremental diagnostic value over the individual imaging modalities.

To date, there have been no studies examining the impact of ^{124}I-PET on the management of DTC, although ^{124}I-PET has been shown to be a useful imaging technique for the diagnosis and management of thyroid diseases [12]. However, interpreting PET scans with highly specific tracers such as ^{124}I is challenged by the lack of identifiable anatomical structures in the PET imaging. This shortcoming of diagnostic procedures using radioactive iodine is subdued by PET/CT as we firstly could show in this study. This data confirms the promising results of first case studies from our group [16–18].

Moreover, several other aspects favor ^{124}I-PET and ^{124}I-PET/CT imaging. High-dose WBS is typically performed 3–8 days after the administration of ^{131}I. Our data indicate that ^{124}I-PET can be performed as early as 24 h after the administration of the radiotracer without sacrifice in diagnostic accuracy compared to high-dose WBS. As a consequence, faster treatment stratification is possible, e.g., initiation of surgery for the removal of easily accessible tumor manifestations or external beam radiation for metastases with insufficient uptake for radio-iodine therapy. Finally, a radiation exposure of 5–10 mSv from the administration of 50–100 MBq ^{124}I compares favorably with 60 mSv from 1,000 MBq ^{131}I [23]. Our data prove the superiority of ^{124}I-PET over planar ^{131}I-WBS even at lower ^{124}I activities and therefore at considerably lower radiation exposure. Thus, ^{124}I-PET is an alternative for high-dose diagnostic ^{131}I-WBS [24] in follow-up of DTC, which is less time-consuming and more convenient for the patient.

Limitations of the present study are the small number of patients, which results from the rarity of the disease, and also the fact that histological confirmation of the findings was possible in only some of the cases, since the other patients were treated by radio-iodine and in some cases by external radiotherapy or were classified as inoperable.

Conclusions

Using a combined PET/CT system, we were firstly able to show that ^{124}I is an efficient diagnostic tool in DTC. With an overall lesion delectability of 97%, ^{124}I-PET/CT is a promising approach in patients suffering from advanced DTC before radio-iodine therapy and patients with suspected recurrence and/or metastases. In addition to the synergistic effects of combining morphologic imaging with highly specific functional imaging, ^{124}I-PET/CT represents a innovative, suitable, low-dose alternative to the clinical standard of high-dose ^{131}I-WBS in follow-up of patients with DTC.

The diagnostic and logistic advantages of ^{124}I-PET and ^{124}I-PET/CT can only be utilized clinically if ^{124}I becomes more widely available. If a PET/CT scanner is available, it should be the preferred imaging technique for DTC patients.

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