CLINICAL STUDY

Is [18F]-2-fluoro-2-deoxy-D-glucose (FDG) scintigraphy with non-dedicated positron emission tomography useful in the diagnostic management of suspected metastatic thyroid carcinoma in patients with no detectable radioiodine uptake?

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Abstract

Objective: Dedifferentiation of thyroid cancer leads to an inability of thyroid cells to concentrate iodine. In these cases, imaging methods that allow an accurate detection of recurrence and/or metastases at an early stage are essential for an adequate management of patients. Positron emission tomography using [18F]-2-fluoro-2-deoxy-D-glucose and a dedicated (dPET-FDG) or non-dedicated (nPET-FDG) camera has been suggested as a potential tool for the detection of tumour foci.

Design and methods: This prospective study was undertaken to evaluate nPET-FDG in 51 consecutive patients (18 men, 33 women) with differentiated thyroid cancer (33 papillary, 11 follicular, four insular and three oncocyctic (Hürthle-cell) thyroid carcinomas). Selection criteria were high thyroglobulin (Tg) levels (> 10 ng/ml off-levothyroxine treatment) and no detectable radioiodine uptake, on a whole body scan performed with a high dose, in the absence of iodine contamination.

Results: Results were interpreted in terms of assumed presence of tumoral tissue. Sensitivity of nPET-FDG was similar to that of conventional imaging modalities (67%). False negative nPET-FDG ($n = 16$) were observed mostly in cases of micro-lesions (lymph nodes or lung metastases). Conversely, nPET-FDG identified new tumoral sites in 11 cases. Better sensitivity was found for nPET-FDG in patients with Tg levels higher than 15 µg/l ($P < 0.05$). On a patient basis, results of nPET-FDG were equivalent to that of dPET-FDG. Finally, nPET-FDG changed treatment strategy in seven patients.

Conclusions: nPET-FDG has a high sensitivity for the detection of tumour sites in patients when pathological iodine uptake cannot be demonstrated and appears to be a useful method in patients with elevated Tg levels, especially when dedicated PET is either unavailable or impractical.

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Introduction

The follow-up of patients with differentiated thyroid cancer, after total thyroidectomy and radioiodine ablation therapy, is based on the combination of human thyroglobulin (Tg) serum monitoring and radioiodine whole body scans (WBS) (1). When tumoral sites are able to concentrate radioiodine, ¹³¹I therapy is effective. However, in a third of patients with elevated Tg levels, which indicate persistent or recurrent disease, there is no identifiable focus on the WBS, even when performed after a therapeutic administration of ¹³¹I (2). It is generally considered that the

lack or the loss over time of the ability of tumoral cells to trap iodine (while still retaining the ability to secrete Tg) may be associated with poorly differentiated tumours and indicate aggressive behaviour and poor prognosis (3, 4). In such patients, who cannot benefit from iodine therapy, precise localisation of tumoral sites is essential to define the therapeutic strategy, namely, a surgical treatment whenever possible, or palliative measures.

Conventional imaging procedures (CIP), mostly ultrasound of neck and abdomen, computerised tomography (CT) and/or magnetic resonance imaging (MRI), and bone scintigraphy, are effective but poorly

specific since it is difficult to distinguish active disease from fibrotic tissue, particularly when normal anatomy is altered by previous treatments. The use of CT contrast enhancement imaging is restricted if planned less than 6 weeks before a further radioiodine administration.

Functional imaging modalities offer the possibility for a whole body evaluation. Several radiopharmaceuticals such as thallium-201 chloride, technetium-99m labelled isonitrile compounds (sestamibi or tetrafosmin) and [indium-111 DTPA D Phe]octreotide have been therefore proposed as a potential tool for the diagnosis of recurrences in thyroid carcinomas, but results have proved controversial with sensitivities depending on patient selection. In general, all these techniques are viable in the presence of a sizeable tumour but, having poor sensitivities, they are incapable of detecting micrometastases (2, 5–8).

Positron emission tomography (PET) using [18F]-2-fluoro-2-deoxy-D-glucose (FDG), an analogue of glucose, has been widely used in clinical oncology (9). In thyroid cancer, previous studies have pointed to the high sensitivity of the examination for the detection of recurrences, especially in patients whose tumours do not concentrate iodine. For instance, Grunwald *et al.* (10) reported in such patients a sensitivity of 85% and in the study conducted by Helal *et al.*, PET-FDG was significantly more sensitive than CIP in localising tumoral sites (11). These results may be explained by a higher glucose metabolism in these tumours, often poorly differentiated (12–15), and PET-FDG has been suggested as a prognostic indicator (16–18). Most of the above data have been obtained with dedicated cameras (dPET). An alternative method for FDG detection is the use of a gamma camera with coincidence detection capability, called non-dedicated PET (nPET) (19, 20). The sensitivity and clinical impact of this easily available and less expensive method have not yet been precisely evaluated in thyroid cancer.

The aim of this study, performed in a prospective series of 51 patients with elevated Tg and negative WBS without any iodine contamination, was to evaluate nPET by reference to CIP and clinical follow-up, and to compare the performances of nPET and dPET.

Materials and methods

Patients

Fifty-one patients with differentiated thyroid cancer (18 men, 33 women; age range: 14–80 years; mean age: 54 years) were studied prospectively. Total thyroidectomy had been performed 1–34 years previously in all cases. The histopathological analysis revealed 33 papillary, 11 follicular, four insular and three oncocyctic (Hürthle-cell) thyroid carcinomas. The disease stage at diagnosis was defined according to the National Thyroid Cancer

Treatment Cooperative Study staging system (21). Surgical treatment was followed by ^{131}I ablative therapy with 1.9–3.7 GBq (depending on the radioiodine uptake in the thyroid bed). Subsequently, the patients received one to nine therapeutic doses of ^{131}I (cumulative range: 1.9–48.5 GBq, average dose: 12.4 GBq) because of elevated serum thyroglobulin levels (mean $771 \pm 1618 \mu\text{g/l}$, range: 21–10 893 $\mu\text{g/l}$). In eight patients, the WBS, performed after the therapeutic dose of radioiodine, showed no uptake at all. In the other 43 patients, repeated ^{131}I treatments resulted in the disappearance of radioiodine uptake in tumour sites. However, the Tg level remained mostly elevated (mean $644 \pm 1966 \mu\text{g/l}$, range: 0.7–11 617 $\mu\text{g/l}$, during levothyroxine treatment), with no anti-Tg antibody. In 17 patients, the elevated Tg level was the only evidence of the presence of tumour at the time of FDG exploration. The other 34 patients had been treated for metastases visualized by CIP. The mean delay between the last radioiodine treatment and FDG scintigraphy was 21 ± 28 months (range: 1 week to 10 years).

The study was performed according to the Helsinki Guidelines and was approved by the local ethics committee. Each patient gave informed written consent.

Conventional imaging methods

A WBS was performed 3–4 days after the administration of ^{131}I (1.9–5.6 GBq), under endogenous thyrotrophin (TSH) stimulation (TSH level higher than 30 mU/l), using a dual-head large-field-of-view gamma camera equipped with high-energy collimators.

Serum Tg and anti-Tg antibody were measured by IRMA (PASTEUR) and recorded at the time of WBS and on the day of nPET-FDG scintigraphy.

CIP first included chest X-rays and neck ultrasound. Spiral CT with contrast enhancement and/or MRI of the neck and chest (and occasionally the abdomen) were performed by two experienced radiologists, mostly when the two first examinations were negative or doubtful, and always in the case of unexpected FDG findings. A technetium-99m diphosphonate scan was performed in cases of clinically suspected bone metastases.

PET-FDG acquisitions (Fig. 1)

Examinations were performed under levothyroxine suppression therapy ($\text{TSH} < 0.1 \text{ UI}$), except in six cases (Table 1). Images were generally obtained in fasting patients 60 min after intravenous administration of 2 (for nPET) or 4–5 (for dPET) MBq/kg of FDG. Dedicated PET-FDG was performed the same day in seven patients or shortly after nPET (less than 15 days) in 13 patients. When the two examinations were planned for the same day, nPET-FDG images were obtained 2–3 h after

Table 1 Patient characteristics and results.

Pt	G	A	H	Tg	nPET	CIP	Vf	Tm
1	M	48	I	12.5	0 cer (FN)	3 cer (TP)	B	Survey
2	F	45	P	9	1 cer (TP)	0 cer (FN)	H	<i>Surgery</i>
3	F	24	P	5.3	2 cer (TP)	2 cer (TP)	H	Surgery
4	F	23	P	3	1 cer (TP)	1 cer (TP)	H	Surgery
5	F	22	P	7.4	0 (FN)	0 (FN)	F	Survey
6	F	24	P	0.7	0 cer (FN)	4 cer (TP)	H	Surgery
7	M	29	P	6	0 (FN)	0 (FN)	F	Survey
8	F	31	P	13.4	0 cer (FN)	1 cer (TP)	B	Survey
9	M	45	P	13.6	1 cer (TP)	1 cer (TP)	H	Surgery
10	F	29	P	1.6	0 cer (FN)	2 cer (TP)	B	Survey
11	M	67	P	2.4	1 cer (TP)	1 cer (TP)	B, F	Survey
					1 pulm (TP) 1 med (TP)	0 pulm (FN) 1 med (TP)		
12	F	67	F	12	1 cer (TP)	0 cer (FN)	B, F	Redifferentiation
					3 pulm (TP)	2 pulm (TP)		
13	F	27	P	1.4	1 bone (TP?)	0 bone (FN?)	F	Survey
14	F	65	F pd	11.2	0 (FN)	0 (FN)	F	Survey
15	M	52	I	7	0 cer (FN)	1 cer (TP)	B, F	Radiotherapy
					1 med (TP)	1 med (TP)		
16	M	50	P	2.1	0 (FN)	0 (FN)	F	Survey
17	F	10	P	10	1 cer (TP)	1 cer (TP)	H	Surgery
18	M	21	P	2.1	4 cer (TP)	2 cer (TP)	H	Surgery
19	F	11	P	33	0 (FN)	0 (FN)	F	Survey
20	F	54	P	36	0 (FN)	0 (FN)	F	Survey
21	M	66	P	38	1 cer (TP)	1 cer (TP)	H	Surgery
22	F	54	P	19.1	0 (FN)	0 (FN)	F	Survey
23*	F	43	F pd	38	1 pulm (TP)	1 pulm (TP)	H	Surgery
24	F	67	O	23.1	1 cer (TP)	1 cer (TP)	H	Surgery
25	F	35	P	50	0 pulm (FN?)	1 pulm (TP?)	F	Survey
26	M	10	P	49	1 cer (TP)	1 cer (TP)	H	Surgery
27	F	51	F pd	17	1 cer (TP) 0 μ pulm (FN)	0 cer (FN) 1 μ pulm (TP)	H, F	<i>Surgery</i>
28	F	45	O	96	1 pulm (TP) 1 med (TP)	1 pulm (TP) 1 med (TP)	H	Surgery
29	M	50	P	29	0 μ pulm (FN)	3 μ pulm (TP)	F	Survey
30*	F	42	F	130	4 cer (TP)	4 cer (TP)	H	Surgery
31*	M	31	P	90	1 cer (TP)	1 cer (TP)	H	Surgery
32	F	63	I	59	1 med (TP)	0 med (FN)	H	<i>Surgery</i>
33	F	66	P	43.5	1 cer (TP)	0 cer (FN)	H, F	Redifferentiation
					0 pulm (FN) 0 med (FN)	1 pulm (TP) 1 med (TP)		
34	F	38	P	245	4 pulm (TP) 1 med (TP)	4 pulm (TP) 1 med (TP)	F	Redifferentiation
35*	F	18	P	35	1 cer (TP)	1 cer (TP)	H	Surgery
36	F	63	O	142	0 (FN)	0 (FN)	F	Survey
37	F	58	F pd	1755	M pulm (TP) 1 med (TP)	M pulm (TP) 1 med (TP)	F	Redifferentiation
					0 hep (FN)†	1 hep (TP)		
38*	F	50	P	168	M pulm (TP) 1 bone (TP)	0 pulm (FN) 0 bone (FN)	F	<i>Redifferentiation</i>
39*	M	72	P	579	2 cer (TP) 2 pulm (TP)	1 cer (TP) M pulm (TP)	H	Surgery
40	M	74	P	161	1 cer (TP) M axil (TP)	1 cer (TP) M axil (TP)	B, F	Radiotherapy
					1 bone (TP?)	0 bone (FN?)		
41	F	62	F	5250	1 med (TP)	1 med (TP)	H	Surgery/Radiotherapy
42*	F	69	P	11 617	4 cer (TP) 1 med (TP)	4 cer (TP) 0 med (FN)	F	Redifferentiation
					1 bone (TP) 1 abd (TP)	1 bone (TP) + 1 bone (FP)		
						0 abd (FN)		
43	M	60	F	850	0 (FN)	0 (FN)	F	Survey
44*	M	71	F pd	638	1 cer (TP)	0 cer (FN)	H	<i>Surgery</i>
45	F	29	F	187	M cer (TP) 1 med (TP)	2 cer (TP) 0 med (FN)	H	<i>Surgery</i>
46	M	70	F pd	1964	1 bone (TP)	0 bone (FN)	F	<i>Radiotherapy</i>
47	F	53	P	609	1 bone (TP)	1 bone (TP)	F	Radiotherapy
48	M	49	I	210	0 pulm (FN) 2 bone (TP)	M pulm (TP) 1 bone (TP)	F	Redifferentiation
49	F	53	P	5850	1 med (TP)	2 med (TP)	H	Surgery
50	M	62	P	278	M pulm (TP) 3 bone (TP?)	M pulm (TP) 0 bone (FN?)	F	Redifferentiation
51	F	41	P	171	1 abd (FP: bladder)	0 (FN)	F	Survey

Pt: Patient number; *patients with no evidence of disease on initial WBS.

G: Gender (male or female).

A: Age at diagnosis (in years).

H: Histology: P, papillary; F, follicular, I, insular; and O, oncocytic thyroid carcinomas. pd, poorly differentiated forms.

Tg: Tg the day of FDG examination (in μ g/l) (all patients had undetectable TSH levels except nos 35, 48, 49, 50 and 51).nPET: Non-dedicated PET using FDG results. TP, true positive; FN, false negative, FP, false positive. abd, abdominal; cer, cervical; hep, hepatic; M axil, Multiple axillary; med, mediastinal; pulm, pulmonary; M pulm, Multiple pulmonary; μ pulm, Micro-metastasis pulmonary. †One hepatic lesion seen only on dPET.

CIP: TP, true positive; FN, false negative; FP, false positive.

Vf: verification by cytology (B), histology (H) or follow-up (F).

Tm: Therapeutic management (in italics: nPET-FDG findings changed management).

the initial injection of FDG for dPET, in order to avoid tracer re-injection.

nPET-FDG images were acquired using a three-head large field-of-view gamma camera equipped with coincidence detection of 511 keV annihilation quanta (IRIX Philips Medical Systems, Cleveland, OH, USA) in all the patients. Three acquisitions of neck, chest and abdomen involved a 120° rotation of each detector, with 60 steps of 20–25 s and the total scanning time was approximately 1.5 h. The non-attenuated corrected images were reconstructed using the iterative reconstruction technique.

dPET-FDG images were acquired using a PET camera, with an axial field of view of 15.2 cm (ECAT EXACT HR + Siemens/CTI, Knoxville, TN, USA) in 20 patients, including all the cases showing no pathological uptake on nPET-FDG. All scannings were performed in a three-dimensional (septa-out) mode, from the cerebellum to the femur, and the total scanning time was approximately 1 h. Transmission images using a ⁶⁸Ge source were acquired for attenuation correction. Images were reconstructed using the OSEM technique (iterative reconstruction algorithm).

Image interpretations and evaluation

All scintigraphic images were analysed visually by at least two experienced nuclear physicians blinded to the clinical situation and the consensus was reported in the clinical record. All foci of increased abnormal uptake were interpreted as pathological sites (true or false positives). The regions of uptake were divided into five areas: neck, lung, mediastinum, bone and other (including the liver). Lesions were arbitrarily classified as multiple if more than four sites were detected. Overall, a positive examination in a patient was defined by at least one abnormal uptake in one site and results were expressed both in terms of positive patients and tumour sites. The scintigraphic results were compared retrospectively with conventional imaging studies, obtained within 6 months. If necessary, the CIP examinations were repeated with the radiologist aware of PET-FDG findings.

Since no single imaging modality is recognised as a gold standard to indicate the presence or absence of thyroid cancer, the evaluation criteria were defined in terms of assumed presence of tumoral tissue (because of persistent Tg levels) and not on the basis of CIP findings. Verification of a true positive finding was then achieved by positive cytology (performed by ultrasonography-guided fine-needle aspiration biopsy) or histology (performed after surgery) in 30 patients. In the other 21 patients, the final classification was based on the clinical outcome and biological follow-up, together with all imaging findings. Modifications of therapeutic management after FDG scintigraphy were recorded in all patients.

Statistical analysis

Lesion detectability in CIP, nPET and dPET-FDG are expressed as the percentage of patients with positive rates and compared using the χ^2 test. The threshold of significance was set at 0.05.

Results

Overall results (Table 1)

In nine patients, no tumour site could be detected with any of the available methods ('all negative patients'). Misleading findings occurred in patient no. 51, where nPET-FDG disclosed one false positive due to false interpretation of urinary activity in bladder. Two patients had equivocal findings: one patient had a bone lesion seen on nPET-FDG (patient no. 13) and one patient had a pulmonary metastasis seen on CIP (patient no. 25). In both cases, no confirmation of the presence of disease activity could be obtained.

The remaining 39 patients included in the study presented with unequivocal tumour sites (distant metastases, local recurrence or residual thyroid tumour), diagnosed by at least one imaging modality, and then confirmed either directly (histopathologically) or indirectly (by clinical follow-up).

Both CIP and nPET-FDG were unequivocally positive in 34 of 51 (67%) patients, and were concordant in 29 positive cases (85%). Thus, CIP in five patients and nPET in five other patients were the only diagnostic methods showing unequivocal pathological localisation. Dedicated PET was negative in the 16 patients showing no pathological uptake on nPET-FDG. In the remaining four patients who underwent both FDG scintigraphies, dPET results were similarly positive on nPET in three patients and more informative in only one (no. 37), with the identification of more lung metastases and of a liver site that were subsequently confirmed by CIP.

Sensitivity according to tumour site (Table 2)

In the 39 patients in whom a lesion was unequivocally detected, by combining the results of all the image modalities, the following tumour sites were detected: cervical (26 patients), mediastinal (11 patients), pulmonary (13 patients, including two diffuse micro-metastases), skeletal (five patients); and other (three patients).

In these patients, nPET-FDG and CIP findings were comparable for neck recurrences, nPET-FDG was superior to CIP for mediastinal and bone localisation, and CIP was superior for lung localisation, mainly for miliary forms.

Overall, nPET-FDG identified new tumoral sites in 13 sites (five cervical, three mediastinal, two pulmonary, two skeletal and one abdominal) in 11 patients.

Table 2 Site sensitivity.

Site	CIP				nPET			
	TP	FN	Se	Eq	TP	FN	Se	Eq
Cervical	22	4	85	—	21	5	81	—
Mediastinal	8	3	73	—	10	1	91	—
Pulmonary	11 (2 μ)	2	85	1 TP?	9	4 (2 μ)	69	1 FN?
Bone	3	2	60	3 FN?	5	0	100	3 TP?
Other	2	1	67	—	2	1*	100	—
Total	46	12	79	—	48	10	83	—
FP	1 (irradiated bone)				1 (bladder)			

nPET, Non-dedicated PET using FDG results; TP, true positive; FN, false negative; FP, false positive; Se, sensitivity (%); Eq: equivocal findings.

*One hepatic lesion seen only on PET. μ , lesion size < 1 cm.

For the five cervical sites, neck ultrasound was previously considered as non-informative. However, the examination found the lesions (subsequently confirmed by histopathology) when it was oriented by nPET-FDG results. Conversely, nPET-FDG was falsely negative in 11 tumoral sites (five cervical identified by neck ultrasound, one mediastinal, four pulmonary, and one skeletal) in 10 patients.

An irradiated bone was interpreted as a bone metastasis with bone scintigraphy and was negative with nPET-FDG (patient no. 42). The clinical follow-up confirmed nPET-FDG interpretation. The smallest lesion detected with nPET-FDG was a cervical metastasis of 8 mm diameter (patient no. 4).

Scintigraphic sensitivity according to Tg (Table 3)

To evaluate the influence of the Tg level on the sensitivity, the patients were divided into three groups, based on serum Tg levels obtained during levothyroxine therapy: less than 15 μ g/l (group I), between 15 and 150 μ g/l (group II), and higher than 150 μ g/l (group III). Considering only the 45 patients who underwent scintigraphic examinations while the TSH level was undetectable, in group I nPET-FDG was unequivocally positive in nine of 18 patients (50%), which is significantly lower than in the two other groups ($P < 0.05$ for group I vs II + III). The lowest Tg with positive nPET-FDG findings was 2.1 μ g/l (patient no. 18) and the highest Tg level with negative FDG scintigraphy was 3700 μ g/l (patient no. 43).

Table 3 Scintigraphic sensitivity according to Tg in patients with undetectable TSH levels.

mPET	Tg level (μ g/l)			
	Tg < 15	15 > Tg < 150	Tg > 150	Total
Positive	9	11	10	30
Total	18	16	11	45
Positive rate (%)	50	69	91	67
Equivocal and 'all negative' patients	6	4	1	11

Scintigraphic sensitivity according to histology and stage (Table 4)

In the 33 patients with papillary carcinoma, nPET findings were unequivocally positive in 20 patients (61%), equivocal in one and completely negative in 13. In the other 18 patients presenting mostly with aggressive or poorly differentiated tumours, FDG showed pathological localisation in 15 (78%). These results are strictly associated with Tg levels, 14 patients with papillary thyroid carcinoma being in group I, 11 in group II and only eight in group III.

Patient management

The nPET-FDG findings led to a change in the management in seven patients (surgical treatment was decided or modified in patients nos 2, 27, 32, 44 and 45, radiotherapy in patient no. 46 and redifferentiation therapy with retinoic acid analogues in patient no. 38).

The 12 patients with persistent elevated Tg levels (range 1.4–850 μ g/ml, mean 110.8 μ g/ml) and negative or equivocal imaging findings were carefully followed-up for 26 months (range 11–42) and at the time of writing remained without detectable metastases.

Discussion

The management of patients with recurrent differentiated thyroid cancer who cannot benefit from 131 I therapy is difficult. Possible therapeutic strategies include surgery, radiation therapy, chemotherapy and redifferentiation therapy with retinoic acid analogues, depending on the metastatic spread (22). Nowadays,

Table 4 Scintigraphic sensitivity according to histology and stage.

nPET	Histology				Stage				
	P	F	I	O	I	II	III	IV	X
Positive	20	9	3	2	6	17	7	2	2
Total	33	11	4	3	13	19	10	2	7
Positive rate (%)	61	78 (F+I+O)			55 (I+II)		75 (III+IV)		
Equivocal and 'all negative' patients	7	2	1	0	4	2	1	0	5

Histology: P, papillary; F, follicular; I, insular; and O, oncocytic thyroid carcinoma.

only surgery is curative and it is crucial to detect early and localise accurately the recurrence. Since the identification of the tumour masses is often questionable with conventional imaging procedures, several scintigraphic methods have been proposed.

Enhanced glucose metabolism is a non-specific feature of tumour proliferative activity and fast-growing tumours are detectable with a high sensitivity by PET using FDG. The high sensitivity of PET-FDG in the detection of thyroid cancer has been demonstrated in a number of prospective studies (10, 12–14, 16–18). Glucose metabolism is generally increased in poorly differentiated carcinomas and FDG uptake correlates with malignant grade. An over-expression of the glucose transporter GLUT 1 was found in thyroid cancer with the most aggressive behaviour (15). Therefore, the discordance between radioiodine and FDG tumour uptake may reflect differences in functional differentiation. The intensity of FDG uptake could reflect tumour dedifferentiation and PET-FDG has been suggested as a prognostic indicator in thyroid cancers (16–18).

In our study, all patients presented with elevated Tg levels and negative WBS. Apparently, in these patients, thyroid cancer tissue has lost the ability to take up iodine, but was still able to produce Tg. It is now well known that the mechanisms of iodine storage implies the sodium iodide symporter and that the synthesis of Tg is maintained longer in the process of dedifferentiation than is the ability to take up radioiodine (23). Thyroglobulin determination by a reference method (IRMA) is highly sensitive and specific (respectively 92% and 93%) when obtained after withdrawal of thyroid hormone therapy, and in the absence of anti-Tg antibody. Persistent or recurrent disease was consequently assumed in all our patients, despite the fact that no lesion could be detected with any of the available methods in 10 cases. Thus, no false negative patient was possible and we could only assess the sensitivity of the imaging methods.

CIP were performed within 3 months of scintigraphic examinations, allowing comparison of the techniques for the identifications of lesions. While histopathological investigations of lesions in the neck area were obtained in all patients, this was not feasible for lung masses. We therefore admitted that the clinical follow-up and a congruence of CIP and nPET-FDG findings should represent confirmed disease.

In these conditions, the ability of nPET-FDG seems to vary with anatomical location. Cervical and mediastinal metastases are well detected by nPET-FDG whose diagnostic accuracy was similar or superior to that of CIP. Even if neck ultrasound resolution is typically 2–3 mm, in some cases only the repetition of this exam with the awareness of nPET-FDG findings allowed the detection of a lesion. In five patients the lesion was surgically removed and histopathologically assumed as false negative for CIP and true positive for nPET-FDG. In

our series, in fact, no false positive focus was detected by nPET-FDG in the neck region due to physiological muscle uptake or inflammatory uptake.

Conversely, false negatives of nPET were mostly small lung metastases, demonstrated by spiral CT, in agreement with previous reports (14, 19). Bone lesions were detected by nPET-FDG with a higher sensitivity than bone scintigraphy. In three patients, however, bone FDG uptake could not be fully interpreted since no biopsy was performed. It is well known that the sensitivity of bone scintigraphy in patient with thyroid cancer varies from 65 to 85%, due to the presence of purely osteolytic lesions (24). The higher sensitivity of nPET may have been caused by differences in tracer uptake mechanism or different acquisition methods.

In the near future, fused images (simultaneous multi-modality display of images) will allow anatomical localisation of uptake foci, thus improving sensitivity of both modalities and anatomical details of FDG examination.

In the present study, the influence of various factors on the sensitivity of nPET-FDG could be evaluated. Firstly the fraction of positive nPET-FDG increased with increasing Tg level, and this in accordance with the correlation between Tg level and the tumour mass. We found a significantly higher sensitivity in patients with Tg levels $>15 \mu\text{g/l}$, in accordance with previous studies (25). The rate of positive nPET-FDG was markedly lower in patients with papillary thyroid cancer, who may benefit more from neck ultrasound for the detection of small lymph nodes metastases. Conversely, the effects of TSH levels on the FDG uptake could not be established in our patients since nearly all scintigraphic examinations were performed during thyroid hormone suppressive therapy.

It is important to note that in our study, examinations performed with a dedicated PET were negative in all the patients showing no pathological FDG uptake on nPET. Therefore, on a patient basis, both methods showed the same efficacy. However, PET detected more lesions in one FDG-positive patient, without change in the therapeutic management.

We can therefore conclude that, before planning neck surgery, PET-FDG is useful for exploring the mediastinal region, mainly when CIP is inconclusive. A spiral CT of the lung is more efficient than FDG examination to exclude small pulmonary metastases. When ultrasound of the neck is inconclusive, or in patients with poorly differentiated thyroid carcinoma, and especially when an aggressive treatment is planned (i.e. before extensive surgery or external radiation therapy) PET-FDG is indicated. A possible routine algorithm is indicated in Table 5.

Finally, the modification of patient staging may suggest or contraindicate a therapy. After nPET-FDG, the clinical management changed in seven of our 51 patients. In particular, the precise localisation of the Tg production site allowed it to be subsequently totally

Figure 1 nPET-FDG coronal views performed in patient no. 50, with inconclusive WBS and elevated Tg level (283 µg/ml at the time of the examination, with TSH at 72 mU/ml). Images (obtained 60 min after intravenous administration of 2 MBq/kg of FDG using a three-head large field-of-view gamma camera equipped with coincidence detection) showed multiple pathological increased uptakes in thoracic areas corresponding to unequivocal pulmonary (white arrows) and suspected bone (dark arrow) metastases. A CT scan confirmed the lung involvement while bone scan was normal.

Table 5 Routine diagnostic algorithm.

High Tg levels (> 10 ng/ml off-T ₄) and no detectable radioiodine uptake
1. No lesions on CIP
⇒ PET-FDG
– if positive: repetition of CIP and treatment when possible
– if negative: survey with CIP
2. Localised disease on CIP
⇒ PET-FDG
– to confirm CIP data (staging, specificity) and surgical treatment indication
3. Extensive disease on CIP
⇒ PET-FDG
– for prediction of survival and response to therapy

surgically removed in five patients. However, the clinical impact of the early recognition of a recurrent or metastatic thyroid cancer by means of PET-FDG in patients with persistent Tg levels and inconclusive WBS is still not demonstrated.

Conclusion

Our findings seem to support the diagnostic potential of nPET-FDG in patients with differentiated thyroid cancer who present with thyroglobulinaemia, mostly when

Tg levels are above 15 µg/l, and when WBS, performed with a high dose of ¹³¹I, is inconclusive.

Although the clinical consequences of these observations have not been precisely documented, we suggest that PET using FDG could be used with high efficacy for the follow-up of patients with inconclusive WBS and elevated Tg levels.

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