Increasing the yield of recombinant thyroid-stimulating hormone-stimulated 2-(18-fluoride)-flu-2-deoxy-D-glucose positron emission tomography-CT in patients with differentiated thyroid carcinoma

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Objective: The aim of this study was to assess the accuracy of recombinant thyroid-stimulating hormone (rTSH)-stimulated 2-(18-fluoride)-flu-2-deoxy-D-glucose (¹⁸F-FDG) positron emission tomography (PET)-CT in detecting recurrence in patients with differentiated thyroid cancer.

Methods: Consecutive ¹⁸F-FDG PET-CT scans performed with rTSH stimulation between 2007 and 2010 in patients with a history of papillary or follicular thyroid carcinoma were reviewed. PET-CT findings were correlated with thyroglobulin levels, and histological, clinical and radiological follow-up.

Results: 58 rTSH PET-CT scans were performed in 47 patients with a previous thyroidectomy and radioiodine ablation. The only indication for PET-CT was a raised thyroglobulin level in 46 of 58 scans, with the remainder for characterisation of equivocal radiology or staging. 25 (43%) of PET-CT scans were positive for recurrent disease. Histological correlation was available for 21 (36%) scans. The overall sensitivity, specificity, positive predictive value and negative predictive value were 69%, 76%, 72% and 73%, respectively. Median unstimulated thyroglobulin in true-positive scans was 33 µg l⁻¹ and 2.2 µg l⁻¹ in the remainder ($p=0.12$). 4 of 35 (11%) patients with unstimulated thyroglobulin levels <10 µg l⁻¹ had true-positive scans. Median stimulated thyroglobulin in true-positive scans was 320 µg l⁻¹, and 10 µg l⁻¹ in the remainder ($p=0.046$), with no positive scans with a stimulated thyroglobulin <8 µg l⁻¹. PET-CT directly influenced patient management in 17/58 (29%) scans.

Conclusion: rTSH PET-CT is a useful imaging technique for detecting disease recurrence in patients with iodine-resistant differentiated thyroid cancer. Low stimulated thyroglobulin levels are potentially useful in identifying patients unlikely to benefit from a PET-CT scan.

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Thyroid cancer is the most common malignant endocrine cancer, although it represents only 1% of all malignancies [1]. Differentiated thyroid cancer, which includes papillary and follicular carcinoma, usually has a favourable prognosis [2]. Treatment commonly involves a total thyroidectomy, radioiodine (¹³¹I) remnant ablation and thyroid hormone replacement suppressing thyroid-stimulating hormone (TSH) [3]. However, around 15% of cases may have recurrent or persistent disease [4]. Recurrent disease remains potentially curable, with available treatments including resection, further therapeutic radioiodine or external beam radiotherapy.

Long-term follow-up of patients who have received treatment for differentiated thyroid cancer is important to

detect local and distant recurrence. Radioiodine uptake scans and measurement of serum thyroglobulin are both sensitive methods to detect disease [5]. Radioiodine scintigraphy, either as a purely diagnostic procedure or following ablative doses, is commonly an effective method of localising the source of raised thyroglobulin. However, the clinical scenario of a raised thyroglobulin with negative radioiodine whole-body imaging is well recognised [5–7]. In this situation, localising non-iodine-avid recurrence is essential to allow potentially curative resection or external beam radiotherapy. Conventional imaging techniques are routinely employed in an attempt to detect the site of recurrence, including MRI or ultrasound scans of the neck, CT of the thorax and bone scintigraphy [3]. 2-(18-fluoride)-flu-2-deoxy-D-glucose (¹⁸F-FDG) positron emission tomography (PET)-CT scanning has emerged as a promising imaging technique for recurrence detection in selected patients with differentiated thyroid cancer and can help determine further management [8–17].

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FDG PET in combination with thyroid-stimulating hormone (TSH) stimulation has been proposed as a more sensitive technique [12, 18–20] based upon the assumption that TSH stimulation will increase the metabolic activity of any thyroid cancer. Prior studies have shown that the combination of PET with TSH stimulation can improve detection of FDG-avid disease and increase the total number of lesions detected [12, 18–20]. The use of recombinant TSH (rTSH) allows TSH stimulation without the symptom difficulties caused by thyroid hormone withdrawal.

PET-CT is a relatively expensive examination, particularly when combined with rTSH, and it remains unclear which patients are most likely to benefit from this technique. One retrospective series recommended that PET-CT be reserved for patients with unstimulated thyroglobulin levels higher than $10\mu\text{g ml}^{-1}$ [11]. Other studies have shown a greater specificity of PET in patients with higher thyroglobulin levels [15, 16]. However, the relationship with serum thyroglobulin levels has not been a consistent finding. TSH-stimulated PET-CT has been shown capable of detecting recurrence even in patients with low stimulated thyroglobulin levels [21]. In one series ($n=44$), rTSH-stimulated PET-CT scans were positive in nine patients with serum thyroglobulin levels less than $10\mu\text{g l}^{-1}$ [13]. Impact on patient management in addition to disease detection rate is an important factor in determining optimal patient selection for utilising PET-CT in the management of differentiated thyroid cancer.

The aim of this study was to review initial experience of using rTSH-stimulated PET-CT in a large tertiary referral centre to assess the accuracy of the technique and impact on patient management. Specifically, we wished to correlate unstimulated and stimulated thyroglobulin levels with scan positivity in an attempt to further define which patients are likely to benefit most from this expensive resource.

Methods and materials

Inclusion criteria

Following consultation with the chairman of our institutional ethics committee, full ethics review board submission and approval was waived for this retrospective study. Data were collected retrospectively over a 3-year period (from 1 November 2007 to 31 December 2010). All patients who had undergone an ^{18}F -FDG PET-CT scan for thyroid cancer were obtained from an institutional PET-CT database. Electronic case notes were used to identify patients who fulfilled eligibility criteria for the study.

Eligible patients fulfilled both of the following criteria:

- (1) Histologically confirmed differentiated thyroid cancer, including papillary, follicular and Hurtle cell carcinoma.
- (2) ^{18}F -FDG PET-CT performed with rTSH stimulation.

Baseline demographics, details of prior treatment and imaging were obtained from a review of electronic case notes (Patient Pathway Manager, Leeds, UK).

Thyroglobulin levels

Thyroglobulin levels were determined using an institutional pathology results server. The assay utilised was DPC Immulite® 2000 (Siemens Medical Solutions Diagnostics, Deerfield, IL). An unstimulated thyroglobulin was defined as a thyroglobulin result that was not preceded within the prior 2-month period by rTSH or thyroid hormone withdrawal, and preceded the rTSH-stimulated FDG PET-CT. A stimulated thyroglobulin was defined as a thyroglobulin result within 3 days of rTSH.

Definition of iodine-refractory disease

Patients were classified as being refractory to iodine if a prior I^{131} uptake scan or a post-therapeutic radioiodine scan had not demonstrated iodine-avid sites of disease in the presence of detectable thyroglobulin levels.

Positron emission tomography-CT protocol

A dose of 0.9 mg intramuscular rTSH (Thyrogen®; Genzyme Corporation, Cambridge, MA) was administered 48 and 24 h prior to the PET-CT examination. ^{18}F -FDG PET-CT examinations were performed prior to June 2010 on a 16-slice Discovery® STE PET-CT scanner (GE Healthcare, Amersham, UK), and subsequently on a 64-slice Philips Gemini® TF64 scanner (Philips Healthcare, Best, Netherlands), 60 min following a 400 mBq dose of intravenous ^{18}F -FDG. Images were acquired from skull vertex to upper thigh. The CT component of the PET-CT was performed according to a standardised protocol with the following settings: 140 kV; 80 mAs; tube rotation time 0.5 s per rotation; pitch 6; section thickness 3.75 mm (to match the PET section thickness). Patients maintained normal shallow respiration during the CT acquisition. No iodinated contrast material was administered.

Analysis of recombinant thyroid-stimulating hormone positron emission tomography-CT results and correlation with histology and/or clinical/radiological outcome

The sensitivity, specificity, and positive and negative predictive values of ^{18}F -FDG PET-CT were analysed. All ^{18}F -FDG PET-CT scans were reported at the time of imaging by at least one radiologist experienced in PET-CT or a dual-certified radiologist and nuclear medicine physician. Imaging was reviewed to determine whether scan appearances were benign (a negative scan) or suggestive of malignancy (a positive scan). Imaging findings were correlated with the results of pathological samples which were classified as either positive or negative for disease. If pathology investigations had not been performed, clinical and/or radiological data were reviewed to assign positive or negative status for disease. Positive clinical and/or radiological evidence of disease was defined as any of:

- (1) subsequent radiological disease progression
- (2) progressive rise in unstimulated thyroglobulin

- (3) response to treatment (radiotherapy or systemic treatment) as assessed by imaging or a fall in thyroglobulin.

Negative clinical and/or radiological evidence of disease was defined as all of:

- (1) absence of radiological evidence of disease on subsequent imaging
- (2) stable or falling thyroglobulin level in the absence of treatment
- (3) no clinical evidence of disease.

In order to classify a disease status as “negative”, a minimum of 12 months’ follow-up with thyroglobulin measurement was required with no rise in thyroglobulin and no clinical/imaging evidence of disease. If a disease status could not be obtained owing to inadequate follow-up, the patient was excluded from analysis of sensitivity, specificity, and positive and negative predictive values.

Impact of recombinant thyroid-stimulating hormone-stimulated flu-2-deoxy-D-glucose positron emission tomography-CT on patient management

Electronic case notes were reviewed to determine the impact of the rTSH-stimulated ^{18}F -FDG PET-CT on patient management. The PET-CT was classed as having a beneficial impact on management if PET-CT findings led to a surgical intervention with positive histological correlation, treatment with radioiodine, radiotherapy and/or systemic treatment, or avoidance of an unnecessary intervention. PET-CT was classed as having a detrimental effect if surgery was performed on the basis of the PET-CT finding, but with negative histology (*i.e.* false-positive PET-CT). The PET-CT was classed as having no effect upon management if no alterations to management/treatment plan were made on the basis of the PET-CT.

Statistical analysis

Descriptive statistics were used. An unpaired *t*-test was used to calculate a two-tailed *p*-value. Statistical significance was declared at $p < 0.05$.

Results

58 rTSH-stimulated ^{18}F -FDG PET-CT scans were performed in a total of 47 patients eligible for inclusion in the study. 39, 5 and 3 patients underwent 1, 2 and 3 PET-CT scans, respectively.

Patient and tumour characteristics

33 patients were female and 14 male. Median age was 50 years (range 17–81 years). All had a history of histologically confirmed differentiated thyroid cancer: 36 papillary and 11 follicular. All had previously

undergone a total thyroidectomy followed by radioiodine ablation. 16, 22, 6, 2 and 1 patient(s) had received a total of 1, 2, 3, 4 and 5 prior therapeutic ^{131}I -ablation treatments, respectively. Documentation of being refractory to radioiodine was present in the notes of 42 (89%) patients, on the basis of negative ^{131}I uptake or post-ablation scans at the time of a raised thyroglobulin. In the remaining five patients who had previously undergone ^{131}I therapy, post-ablation or uptake scans had not been performed in the presence of a raised thyroglobulin level.

Indication for performing a recombinant thyroid-stimulating hormone positron emission tomography-CT scan

The documented indication for requesting 46 of the PET-CT scans was a raised thyroglobulin level in the presence of negative prior imaging to search for a site of disease (an unstimulated thyroglobulin in 43 cases and a stimulated thyroglobulin in 3 cases). PET-CT was also performed to guide management in the presence of known metastases: three scans were performed for staging prior to a potential resection of a metastatic site and one scan was used to stage disease in the presence of known metastases prior to systemic therapy. PET-CT scans were also performed to clarify the nature of equivocal abnormalities on cross-sectional imaging: two for a lung nodule, one for an abnormality in the anterior mediastinum, two for neck lymph nodes and one for a pericardiac lymph node. The median unstimulated thyroglobulin in patients undergoing a PET-CT for investigation of a raised thyroglobulin level was $4.7\mu\text{g l}^{-1}$ (range $0.2\text{--}250\mu\text{g l}^{-1}$) compared with $1.2\mu\text{g l}^{-1}$ (range $0.2\text{--}30\,000\mu\text{g l}^{-1}$) for patients with another indication for the PET-CT, with no statistical difference between these groups ($p=0.35$). Of the five patients without a documented absence of radioiodine uptake in the presence of a raised thyroglobulin, PET-CT was performed in one case to determine management of a solitary metastasis and in three cases for equivocal radiological abnormalities; the remaining patient had been heavily pre-treated with radioiodine and was clinically thought likely to be radioiodine refractory.

Imaging investigations prior to recombinant thyroid-stimulating hormone positron emission tomography-CT scans

Patients had generally undergone extensive cross-sectional imaging during the course of their disease. Following institutional imaging guidelines, the majority of patients had undergone at least an MRI neck and CT thorax without contrast prior to the rTSH PET-CT scan. For patients who did not tolerate an MRI scan, a CT of the neck without contrast was routinely performed. A total of 43 MRI neck scans, 48 CT scans, 25 bone scans, 6 ultrasound scans and 1 octreotide scan had been performed within 12 months prior to the 58 PET-CT examinations.

Recombinant thyroid-stimulating hormone positron emission tomography-CT results and histological, clinical and radiology correlation

Of the 58 rTSH PET-CT scans, 25 (43%) were positive and 33 (57%) negative. Histological correlation was available for 15 (60%) of the 25 positive scans and 6 (18%) of the 33 negative scans. The method of obtaining histology varied: neck dissection in 10, fine needle aspiration in 7, and mediastinoscopy, video-assisted thoracotomy, lung resection and bone resection in a single patient each. In the six cases with a negative PET-CT, histology was obtained from abnormalities demonstrated on prior cross-sectional imaging. In cases for which there was no histological correlation, outcomes were assigned as "positive" or "negative" for disease on the basis of subsequent clinical follow-up and imaging investigations. Three patients had less than 12 months' follow-up after PET-CT and were not classified in this manner. Overall, 26 cases were classed by histology or clinical/radiology outcomes as positive for disease and 29 cases as negative. Correlation of the 25 positive PET-CT scans with histology or clinical/radiology follow-up is shown in Table 1.

During the follow-up period, nine patients demonstrated clinical or radiological response or progression as follows: a radiological response to radiotherapy in four cases, fall in thyroglobulin after radiotherapy in two, radiological progression of metastases in two and death from liver metastases in a single case.

Correlation of the 33 negative PET-CT scans with histology or clinical/radiology follow-up is shown in Table 2. The classification of all five cases of subsequent clinical/radiological progression was made on the basis of a progressive rise in thyroglobulin.

Overall in the cohort, the sensitivity of rTSH PET-CT for detecting disease not identified on prior imaging was 69%, with a specificity of 76%. The positive predictive value was 72% and the negative predictive value 73%. The false-positive and false-negative rates were 28% and 27%, respectively.

Unstimulated serum thyroglobulin levels and diagnostic accuracy of recombinant thyroid-stimulating hormone positron emission tomography-CT

An unstimulated thyroglobulin level was available prior to 56 PET-CT scans (97%). The presence of thyroglobulin antibodies precluded interpretation of the thyroglobulin level in the remaining two scans. The median unstimulated thyroglobulin was $4.5 \mu\text{g l}^{-1}$ (range

Table 1. Correlation of recombinant thyroid-stimulating hormone positron emission tomography-CT positive scans with histology or clinical/radiology follow-up ($n=25$)

Classification	Histological correlation	Clinical/radiological correlation	Overall
Disease positive	9	9	18 (72%)
Disease negative	6	1	7 (28%)

Table 2. Correlation of recombinant thyroid-stimulating hormone positron emission tomography-CT negative scans with histology or clinical/radiology follow-up ($n=30$; 3 not included owing to insufficient follow-up)

Classification	Histological correlation	Clinical/radiological correlation	Overall
Disease positive	3	5	8 (27%)
Disease negative	3	19	22 (73%)

$0.2\text{--}30\,000 \mu\text{g l}^{-1}$). Median unstimulated thyroglobulin in all PET-CT positive scans was $14.8 \mu\text{g l}^{-1}$ (range $0.2\text{--}30\,000 \mu\text{g l}^{-1}$) and in all PET-CT negative scans was $3.4 \mu\text{g l}^{-1}$ (range $0.2\text{--}26.7 \mu\text{g l}^{-1}$), with no significant difference between positive and negative PET-CT scans ($p=0.29$). The median unstimulated thyroglobulin from true-positive PET-CT scans was $33 \mu\text{g l}^{-1}$ (range $1.1\text{--}30\,000 \mu\text{g l}^{-1}$), and was $2.2 \mu\text{g l}^{-1}$ (range $0.2\text{--}26.7 \mu\text{g l}^{-1}$) from false-positive and -negative scans combined with no significant difference ($p=0.12$). These data are shown in Figure 1.

The diagnostic accuracy of PET-CT was compared between patients with an unstimulated thyroglobulin level of $<10 \mu\text{g l}^{-1}$ and $>10 \mu\text{g l}^{-1}$ as previously described [11]. The results of PET-CT scans with an unstimulated thyroglobulin level of $<10 \mu\text{g l}^{-1}$ are shown in Table 3 and those for $>10 \mu\text{g l}^{-1}$ in Table 4. In the presence of an unstimulated thyroglobulin level of $>10 \mu\text{g l}^{-1}$, PET-CT had a sensitivity of 87%, specificity of 100%, positive predictive value of 100% and negative predictive value of 60%. When the unstimulated thyroglobulin level was $<10 \mu\text{g l}^{-1}$, sensitivity fell to 44%, specificity 73%, positive predictive value 36% and negative predictive value 79%.

In five PET-CT scans performed in patients who did not have documented iodine-refractory disease, the

Figure 1. Recombinant thyroid-stimulating hormone positron emission tomography-CT findings and unstimulated serum thyroglobulin levels ($n=53$).

median unstimulated thyroglobulin was $6.4 \mu\text{g l}^{-1}$ (range $0.2\text{--}23 \mu\text{g l}^{-1}$). The PET-CT scan was positive in three of the five scans. The PET-CT was a histologically confirmed true positive in two patients, a true negative in one, a false positive in one and a false negative in one. There was no correlation between unstimulated thyroglobulin levels and the PET-CT result in this subgroup ($p=0.72$).

Stimulated thyroglobulin and the diagnostic accuracy of recombinant thyroid-stimulating hormone positron emission tomography-CT

A stimulated thyroglobulin was available prior to or at the time of 27 scans (10 of which were positive scans). The median stimulated thyroglobulin levels was $16 \mu\text{g l}^{-1}$ (range $0.2\text{--}30\,000 \mu\text{g l}^{-1}$). The median stimulated thyroglobulin level in PET-CT positive scans was $59 \mu\text{g l}^{-1}$ (range $8\text{--}30\,000 \mu\text{g l}^{-1}$) and in all PET-CT negative scans was $10 \mu\text{g l}^{-1}$ (range $0.2\text{--}90 \mu\text{g l}^{-1}$), with no significant difference between positive and negative PET-CT scans ($p=0.17$).

The median stimulated thyroglobulin level from true-positive PET-CT scans ($n=6$) was $320 \mu\text{g l}^{-1}$ (range $8\text{--}30\,000 \mu\text{g l}^{-1}$), and was $10 \mu\text{g l}^{-1}$ (range $0.2\text{--}90 \mu\text{g l}^{-1}$) from false-positive and -negative scans combined with a statistically significant difference between the two groups ($p=0.046$). These data are shown in Figure 2.

Impact of recombinant thyroid-stimulating hormone positron emission tomography-CT on clinical management

On review of electronic case notes, 19 (33%) of the 58 rTSH PET-CT scans had an impact upon clinical management. In 17 (29%) instances the PET-CT was judged to have made a beneficial impact. Beneficial alterations to management influenced by PET-CT included seven positive neck dissections (Figure 3), administration of radiotherapy in four cases (Figure 4), empirical radioiodine in one case, resection of solitary metastasis in the absence of other sites of disease in two cases, avoidance of mediastinoscopy for a PET-negative anterior mediastinal abnormality, avoidance of a liver resection in the presence of extensive liver metastasis and resection of an incidental lung carcinoid tumour. In 2 (3%) cases, a neck dissection was performed following a positive PET-CT scan, but histology was negative (Figure 5). PET-CT was judged to have had a detrimental impact upon management in these two patients.

Following PET-CT scans performed with an unstimulated thyroglobulin level of $<10 \mu\text{g l}^{-1}$ ($n=35$), a bene-

Table 4. Performance of recombinant thyroid-stimulating hormone positron emission tomography-CT (PET-CT) with an unstimulated serum thyroglobulin of $<10 \mu\text{g l}^{-1}$ ($n=35$)

Histological or clinical/radiology follow-up	PET-CT positive	PET-CT negative
Disease positive	4	5
Disease negative	7	19

ficial impact on management occurred in 6 (17%) cases, a detrimental impact in 2 and no impact in 27. For PET-CT scans performed with an unstimulated thyroglobulin level of $>10 \mu\text{g l}^{-1}$ ($n=18$), a beneficial alteration in management occurred in 11 (61%) cases, with no change in 7 cases.

Discussion

The detection of non-iodine-avid disease is an important issue in the management of differentiated thyroid cancer. This is commonly in the context of a raised thyroglobulin with negative radioiodine whole-body imaging. In some patients, the presence of thyroglobulin antibodies invalidates the serum thyroglobulin result [5]; additional methods are required to detect non-iodine-avid recurrence. In the context of known non-iodine-avid oligometastases, the detection of additional sites of disease is a pivotal issue in the decision-making process regarding resection.

^{18}F -FDG PET has been shown to be an effective tool for detecting thyroid cancer recurrence or metastases [8–17]. A recent meta-analysis of 17 studies between 1990 and 2008 including a total of 571 patients found an overall sensitivity for PET of 0.835 (95% CI 0.791–0.873) and specificity of 0.843 (95% CI 0.791–0.886) [22]. Within the pooled subgroup of patients with a raised thyroglobulin

Figure 2. Recombinant thyroid-stimulating hormone positron emission tomography-CT findings and stimulated serum thyroglobulin levels ($n=29$).

Figure 3. Example of a true-positive recombinant thyroid-stimulating hormone positron emission tomography (PET)-CT leading to a neck dissection. A 42-year-old female had a papillary thyroid cancer treated with thyroidectomy and three radioiodine ablation treatments for a persistent thyroglobulin level with no ^{131}I uptake following the final ablation. An unstimulated thyroglobulin level of $12\mu\text{g l}^{-1}$ was recorded, and a CT neck and thorax and a bone scan failed to identify a source. PET-CT demonstrated two 5-mm nodes in the right lower neck (specific uptake value 4.2). A right level VI neck dissection was performed, with 6 of 7 nodes containing metastatic papillary carcinoma. Thyroglobulin subsequently normalised. (a) CT, (b) fused PET-CT, (c) PET. Arrow indicates area of abnormal fludeoxyglucose avidity.

levels and negative imaging, ^{131}I imaging sensitivity was 0.885 (95% CI 0.828–0.929) and specificity 0.847 (95% CI 0.715–0.934).

Integrated ^{18}F -FDG PET-CT has been reported to have higher accuracy than ^{18}F -FDG PET or CT alone in head and neck cancer [23, 24]. Similarly, studies of the use of integrated PET-CT in thyroid cancer have suggested an improved diagnostic ability [22, 25]. In view of the potential for TSH stimulation to improve detection rates of sites of thyroid cancer [12, 18–20], a TSH-stimulated integrated PET-CT scan may offer the optimum diagnostic accuracy.

A key difficulty in interpreting this series, and others [8, 11, 13, 17, 25], is in interpreting the disease status of patients who have a raised thyroglobulin level with negative imaging, including radioiodine whole-body scintigraphy and PET-CT. In order to make an estimate of the accuracy of PET-CT we adopted a cut-off for defining a true-negative PET-CT scan as a negative scan and no rise in thyroglobulin over at least a 12-month period following the scan with no clinical or radiological evidence of disease. Although similar to the methodology of other series [8, 11, 13, 17, 25], this definition is limited by the often indolent nature of thyroid cancer, along with the ability of exogenous thyroid hormone-mediated TSH suppression to limit disease progression. It is a common clinical experience that a low level of thyroglobulin may persist for many years without any evidence of progression and negative imaging; in this situation it is not possible to be dogmatic regarding the source of the thyroglobulin. The presence of detectable thyroglobulin does not necessarily mean disease is present, thyroglobulin levels may also be raised owing to persistent residual thyroid tissue, resulting in a false-positive raised thyroglobulin level [26]. While it is important to recognise this limitation when interpreting the results, it is necessary to define a clinically relevant definition of a true-negative population in order to assess the usefulness of PET-CT.

The patients who underwent rTSH PET-CT in this series had all received at least one ^{131}I ablation dose. A high proportion (42 out of 47 patients; 89%) had clear

documentation of being refractory to radioiodine with negative scintigraphy following ^{131}I ablation or on a follow-up whole-body scan in the presence of a raised thyroglobulin level. The PET-CT was performed in four of the remaining five for reasons other than an isolated raised thyroglobulin level. The majority of the scans performed (46/58) were to investigate a raised thyroglobulin level. In the remainder, PET-CT was used to clarify the nature of equivocal anatomical abnormalities on other imaging, and in four cases to stage disease in the presence of known metastases. All patients within this latter group had a raised unstimulated thyroglobulin level. There was no significant difference between unstimulated thyroglobulin levels for PET-CT scans performed for investigation of a raised unstimulated thyroglobulin level and PET-CT scans performed for the other indications ($p=0.35$). Therefore, the overall cohort of patients has been included in the analysis to determine the accuracy of PET-CT.

Out of the 58 rTSH PET-CT scans performed, 25 (43%) were regarded as positive. This is broadly in line with other studies, although there has been some variation of reported positivity rates: Lebouilleux et al [12] reported positive PET scans in 30 out of 63 (48%) scans, Razfar et al [11] in 75 out of 121 scans (62%), Saab et al [21] in 9/15 (60%) scans, and Zoller et al [14] in 35/47 (74%) scans. These variations are likely to be accounted for by the heterogeneous nature of the patient population in all of these studies.

The overall sensitivity of 69% and specificity of 76% of rTSH PET-CT in our series is lower than that reported in the meta-analysis [22]. Reasons for this are likely to relate to methodological variations between studies, including rates of histological confirmation, definition of a true-negative group, as well as differences in the thyroglobulin levels of patients included. One previous large retrospective study demonstrated a fall in sensitivity and specificity of PET-CT at lower levels of unstimulated thyroglobulin of 93.8% and 93.9%, respectively, above $10\mu\text{g l}^{-1}$, and 74.6% and 0%, respectively, below $10\mu\text{g l}^{-1}$ [11]. Unstimulated thyroglobulin levels were below $10\mu\text{g l}^{-1}$ in 35 scans in our series, which may explain

Figure 4. Example of a true-positive recombinant thyroid-stimulating hormone positron emission tomography-CT (PET-CT) leading to radiotherapy. An 83-year-old female had a papillary thyroid cancer treated with a thyroidectomy and two radioiodine ablation treatments for a persistent thyroglobulin with no ^{131}I uptake following the final ablation. An unstimulated thyroglobulin was $53\text{ }\mu\text{g l}^{-1}$ and an MRI neck and CT thorax failed to identify a source. A PET-CT identified a small lytic deposit (specific uptake value 9) in the fourth lumbar vertebra. She was treated with radiotherapy (40 Gy in 15 fractions) with a subsequent fall in thyroglobulin levels. (a) CT, (b) fused PET-CT, (c) PET. Arrow indicates area of abnormal fludeoxyglucose avidity in vertebra.

the relatively low sensitivity and specificity compared with the meta-analysis results [22]. In a similar way to the series reported by Razfar et al [11], the sensitivity and specificity dropped in our series below the cut-off of $10\text{ }\mu\text{g l}^{-1}$: 87% and 100%, respectively, above $10\text{ }\mu\text{g l}^{-1}$, compared with 44% and 73% below $10\text{ }\mu\text{g l}^{-1}$. These results suggest that rTSH PET-CT has a greater accuracy at higher levels of unstimulated thyroglobulin. However, it is difficult to define a value of unstimulated thyroglobulin at which the investigation is no longer useful. There was no significant difference between unstimulated thyroglobulin levels when comparing positive and negative PET-CT scans ($p=0.29$), nor between true-positive PET-CT scans and all other scans ($p=0.12$). In addition, in 6 out of 35 scans performed with an unstimulated thyroglobulin of $<10\text{ }\mu\text{g l}^{-1}$, a beneficial change in management was judged to have occurred. Unstimulated thyroglobulin levels of $<10\text{ }\mu\text{g l}^{-1}$ were present in four cases of true-positive PET-CT. This is

similar to other studies that have found true-positive results at low thyroglobulin levels [13]. These findings, despite a fall in sensitivity and specificity, are important when considering that a localised recurrence/metastasis remains potentially curable.

The thyroglobulin level in patients with differentiated thyroid cancer is dependent upon the tumour being capable of producing and releasing thyroglobulin, tumour size, any remnant thyroid tissue and on response to TSH stimulation [26]. If a tumour is highly sensitive to TSH suppression, thyroglobulin levels may remain low or undetectable when adequate doses of thyroid hormones are administered. Therefore, an unstimulated thyroglobulin level is a very indirect indicator of tumour volume. The measurement of thyroglobulin under conditions of TSH stimulation may provide a more accurate reflection of tumour status. Levels of stimulated thyroglobulin were only obtainable for 27 PET-CT scans. However, there was a statistically significant difference

Figure 5. Example of a false-positive recombinant thyroid-stimulating hormone positron emission tomography (PET)-CT. A 33-year-old female had a papillary thyroid carcinoma treated with thyroidectomy followed by radioiodine ablation 10 years previously. An unstimulated thyroglobulin was elevated at $7\text{ }\mu\text{g l}^{-1}$ and an MRI neck, CT thorax and radioiodine uptake scan failed to identify a source. PET-CT identified bilateral fludeoxyglucose (FDG)-avid subcentimetre cervical lymph nodes (maximum specific uptake value 5). Bilateral neck dissections did not identify any thyroid cancer. (a) CT, (b) fused PET-CT, (c) PET. Arrows indicate FDG avidity in neck lymph nodes.

between stimulated thyroglobulin levels from true-positive scans and the remainder ($p=0.046$). There were no true-positive PET-CT scans with a stimulated thyroglobulin level below $8\mu\text{g l}^{-1}$. This suggests that the stimulated thyroglobulin level may provide a more accurate method of deciding which patients are likely to benefit from a PET-CT scan.

In this series PET-CT directly influenced patient management in 19 (33%) of 58 scans. In 17 (29%) cases this was judged to be beneficial. This is lower than the impact on management reported by others (40–48%) [11, 27]. This difference may again relate to a higher proportion of scans in our series being performed with a low unstimulated thyroglobulin level. Two patients underwent a histologically negative neck dissection following the PET-CT result. In view of this, histological confirmation is now obtained prior to proceeding to definitive intervention whenever possible.

The findings in our study are limited by the retrospective nature of the study and the consequent potential for selection bias, the limited availability of histological correlation, and the absence of a stimulated thyroglobulin level for 31 PET-CT scans. Further larger prospective studies are required to validate our findings. The cost-effectiveness of PET-CT in the management of differentiated thyroid cancer is uncertain. A cost-benefit analysis could be usefully incorporated into future studies.

Conclusion

rTSH stimulated ^{18}F -FDG PET-CT is a useful tool for detecting recurrence, defining disease extent and guiding management in patients with iodine-negative differentiated thyroid cancer. It is not possible to define an arbitrary unstimulated thyroglobulin cut-off value below which the investigation is no longer useful. However, the stimulated thyroglobulin level may be a more reliable method of identifying patients who may benefit from rTSH PET-CT. Validation and assessment of cost-effectiveness of the technique requires further investigation.

Conflict of interest

Dr Georgina Gerrard has previously had conference attendance funded by Genzyme.

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