The diagnosis of carcinoma of the thyroid is usually made in the process of investigating a thyroid nodule with clinical examination, Technetium-99m scan, ultrasonography and fine-needle aspiration (FNA) cytology. The follow-up is mainly based on 123-iodine and 131-iodine scans and serum thyroglobulin measurement. The aim of the present review was to establish the role of 18F-FDG PET in the differential diagnosis of doubtful thyroid nodules and in the follow-up of patients with increased serum thyroglobulin levels and negative iodine-scan. It remains to be defined if metabolic imaging with PET could be a useful routine procedure in the management of thyroid tumours since the majority of them are well-differentiated and therefore have less avidity to 18F-FDG. In the present work we collected the specific literature derived from MEDLINE over the last 10 years to clarify the potential clinical value of 18F-FDG PET in thyroid malignancies. An emerging role for 18F-FDG PET is in the assessment of incidental finding of a thyroid nodule which, when showing high FDG uptake should be regarded as a possible malignancy that needs further assessment. Another well-documented role for 18F-FDG PET is in the investigation of cases of established well-differentiated thyroid carcinomas presenting with high thyroglobulin and negative iodine imaging. An increase of the 18F-FDG uptake in these tumours indicates a shift towards lesser differentiation (with more aggression and poor prognosis) and may benefit from alternative management. 18F-FDG PET can be considered a routine functional imaging method in detecting iodine-negative recurrent disease in thyroid cancer patients with elevated serum thyroglobulin levels during follow-up. 18F-FDG PET seems to be useful also in differential diagnosis of suspected thyroid nodules, especially using the semi-quantitative SUV analysis.

Thyroid cancer is rare, accounting for less than 1% of all malignant diseases, but is the most common endocrine malignancy with 1,000 new cases and 250 deaths recorded each year in England and Wales (1). Differentiated thyroid cancer (DTC) is the most common form (85-90%) of thyroid cancer and is highly curable. The remainder comprise medullary carcinoma, anaplastic tumours, lymphomas and sarcomas. In the absence of widespread regional or distant metastasis, the overall 10-year survival rates for papillary, follicular and Hürthle cell carcinomas are 93%, 85% and 76%, respectively (2).

Most patients present with a painless thyroid nodule though only a small fraction of all thyroid nodules harbor malignant disease since they are common and are seen in up to 51% of the population on autopsy (3). High-resolution ultrasound (US) studies report a prevalence of thyroid nodules of 19% to 46% in the general population, with 1.5% to 10% risk of cancer (4). Fine needle aspiration (FNA) biopsy is routinely performed as part of the diagnostic procedure (5) and once a diagnosis of DTC is established, treatment is available with total thyroidectomy and radioiodine ablation. The patients are given life-long thyroxine replacement and followed-up with regular assays of thyroglobulin (Tg) and whole-body iodine-123 (123I) or iodine-131 (131I) imaging. For other forms of thyroid cancer, surgery with or without radiotherapy and chemotherapy are employed.

Despite the clear pathways in the diagnosis of thyroid nodules and the management of thyroid cancer, certain issues continue to be difficult to tackle. Thyroid nodules may be asymptomatic or impalpable and may come to light as an incidental finding during an imaging procedure performed for the investigation of a different complaint. An
issue may arise as to the nature and malignant potential of such incidental nodules. The ability of anatomical imaging in differentiating malignant from benign nodules is somewhat limited and an increasing number of reports of the value of 18F-FDG PET in the characterisation of such ‘incidentalomas’ are published.

The utility of 18F-FDG PET in the assessment of established DTC is currently limited to the diagnosis and follow-up of cases when standard imaging with 123I or 131I, and other DTC-avid radiopharmaceuticals, are negative in the face of rising Tg. This review is intended to explore the role of 18F-FDG PET in these two aspects of thyroid pathology.

FDG-PET in the Assessment of Incidentalomas

Thyroid incidentalomas are defined as newly diagnosed thyroid lesions encountered during an imaging study. Due to the increasingly extensive use of ultrasound (US), computed tomography (CT), magnetic resonance (MR) and 18F-FDG PET imaging, an incidental finding of a non-palpable thyroid nodule is a common problem. US, CT and MR imaging cannot accurately differentiate between benign and malignant thyroid nodules.

Most centres use fine needle-aspiration (FNA) cytology to evaluate thyroid nodules. However, FNA has several shortcomings, such as its inability to provide a diagnosis due to inadequate sampling or because it is impossible to clearly differentiate benign follicular adenomas from well-differentiated follicular carcinomas by FNA (5). The ability to better distinguish benign from malignant incidentalomas could be achieved with metabolic imaging and might spare patients undergoing unnecessary investigations and surgical resection.

The introduction of metabolic imaging with 18F-FDG PET into clinical practice and research was based on the demonstration of increased glucose consumption in malignant tissue, first noted by Warburg (6), which can be visualized by a suitably labelled sugar derivative. Fortunately, the major building blocks of the human body are made up of elements (oxygen, carbon, nitrogen and fluorine amongst others) for which there are isotopes that can be visualized by PET. These are positron emitters and their imaging utilizes the superior technique of positron emission tomography (PET) with its superb resolution. The most commonly used PET radiopharmaceutical in the management of a wide range of cancer types is 2-[18F]fluoro-2-deoxy-D-glucose (7).

18F-FDG PET is commonly used in primary staging, evaluation of treatment response, detection of recurrence and restaging of numerous malignancies. In addition, 18F-FDG PET is increasingly being used to assess non-neoplastic conditions such as infectious diseases. It is not uncommon to find a synchronous or metachronous cancer on these scans. FDG, as a glucose analogue, is transported into cells by glucose transporters and is subsequently phosphorylated but not further metabolized. The increased concentration of glucose transporters in most cancer cells, with increased glucose phosphorylation and low phosphatase enzymatic activity, result in relatively high concentrations of FDG in malignant tumours.

The normal thyroid gland shows low grade FDG uptake or is usually not visualized on the whole-body 18F-FDG PET scan (8, 9). Diffuse increased thyroid FDG uptake is usually an indicator of chronic thyroiditis (10) but has also been described in Grave’s disease (11). Several retrospective studies have assessed the incidence and causes of focal increased uptake within the thyroid gland on 18F-FDG PET. There is disagreement on the usefulness of quantifying the FDG uptake as standard uptake value (SUV) for characterisation of thyroid nodules.

A retrospective study by Bogsrud et al. (12) reviewed 18F-FDG PET-CT scans performed over a three-year period mainly in oncology patients and measured the maximum SUV (SUVmax) of thyroid incidentalomas. They found 79/7,347 patients (1.1%) demonstrating focal increased uptake within the thyroid gland. Of these, 48 patients had adequate follow up enabling correct diagnosis. A benign aetiology was determined in 31/48 (64.6%), while 17/48 patients (35.4%) had malignancy confirmed or had FNA highly suspicious of malignancy, with papillary carcinoma confirmed in 12/17 of those malignancies. There was no statistical difference between the SUVmax for the malignant vs. the benign group. Similarly, Are et al. (13) reviewed 18F-FDG PET scans of 8800 patients and found 101 patients (1.15%) with thyroid incidentalomas and 162 patients (1.84%) with diffuse increased thyroid uptake. In 24 (42%) of the 57 patients who had FNA, the results were suggestive of malignancy, while 20 (74%) of the 27 patients who had thyroid surgery were positive for malignancy. There was no correlation between the average SUV and the likelihood of malignancy (p=0.7). There have been other retrospective studies using 18F-FDG PET. In patients who had adequate follow-up, Cohen et al. (14), Kang et al. (15) and Kim et al. (16) found malignancy in 47% (7/15), 27% (4/15) and 50% (16/32), respectively.

Despite the non-discriminatory value of SUV mentioned earlier, a significant number of studies have found it to be useful in differentiating benign from malignant focal thyroid lesions. Bloom et al. (17) looked at 12 patients with focal thyroid uptake. Four malignant lesions (3 papillary and 1 follicular carcinoma) all had SUVmax >8.5. The 8 benign lesions (follicular adenomas) had SUVmax <7.6. Supportive data comes from Cohen et al. (14) who found that seven patients with malignant thyroid lesions had significantly higher SUV on average (6.92±1.54, range 4.1-14.5),
compared with seven patients with benign lesions (3.37±0.21, range 2.9-4.9) as calculated by a two-tailed t-test (p=0.04). The highest SUV in the benign group was 4.9 and the lowest in the malignant group was 4.1. One benign lesion overlapped the values for the malignant nodules. Kang et al. (15) reviewed 1,330 FDG-PET scans of cancer patients and healthy volunteers. The prevalence of thyroid incidentalomas was 2.2% with no significant difference in the prevalence between the patients with cancer and the healthy volunteers. In addition, they found that the average SUVmax of four malignant nodules (16.5±4.7, range 8.7-21.1) was significantly higher (p=0.001) than the average SUVmax for 11 benign lesions (6.5±3.8, range 2.2-12.4). Uematsu et al. (18) performed 18F-FDG PET on 11 patients with thyroid nodules awaiting surgery. They demonstrated a significantly higher FDG uptake for the malignant tumours than for the benign lesions. There was no overlap between the measured SUV values with the highest value of 4.34 in the benign group and 5.69 being the lowest value in the malignant group. Kresnik et al. (19) evaluated the usefulness of FDG-PET in the preoperative assessment of suspicious thyroid nodules in 43 patients. They found a significant difference in SUV between malignant lesions (3.7±1.9) and benign nodules as microfollicular adenomas (1.6±0.3), macrofollicular adenomas (0.9±0.1) and degenerative goitre (1.2±0.2). There was no overlap between the benign nodules and malignant lesions. The exception was Hürthle cell adenomas which demonstrated no difference in SUV between the malignant and benign lesions (4.4±2.2 vs. 3.7±1.9).

Better localisation and characterisation of lesions can be achieved with multi-modality imaging, particularly with the introduction of PET-CT. A retrospective study by Choi et al. (20) investigated whether the FDG uptake pattern and CT findings improved the accuracy over SUV alone for differentiating benign from malignant thyroid incidentalomas detected on 18F-FDG PET-CT scan. The prevalence of thyroid incidentalomas on 18F-FDG PET-CT was 4.0%. The maximum SUV of malignant thyroid lesions was significantly higher than that of benign lesions (6.7±5.5 vs.10.7±7.8, p<0.05). Most of the malignant thyroid lesions (16/18, 88.9%) had low attenuation on CT. All focal thyroid lesions with a diffuse increase in surrounding thyroid uptake, or very low attenuation on CT, were benign. Focally increased 18F-FDG uptake in the thyroid without a corresponding discernible focal anatomic lesion on CT also indicated a benign lesion with 100% certainty. When only maximum SUV was used to differentiate benign from malignant focal thyroid lesions for the receiver operating characteristics (ROC) curve analysis, the area under the curve of PET was 0.701±0.079. When a focal thyroid lesion with very low attenuation or non-localisation on CT, or with accompanying diffusely increased thyroid 18F-FDG uptake, was regarded as a benign lesion irrespective of maximum SUV, the area under the curve of PET/CT was significantly improved to 0.878±0.049 (p<0.01).

Another study using PET-CT was that by Mitchell et al. (21) who looked at 31 patients with 48 lesions who underwent FNA and 18F-FDG PET-CT before surgical resection of thyroid nodules. A total of 15/48 (31%) lesions were malignant and 33/48 (69%) were benign. One-way analysis of variance showed a significant difference in 18F-FDG uptake between benign and malignant lesions, with malignant lesions displaying consistently higher SUVs than benign nodules (6.5±1.2 vs. 2.4±0.4, p<0.001).

Most of these studies are limited by their retrospective design and many patients did not have follow-up. Patients undergoing 18F-FDG PET scans usually have a known malignancy and follow-up of thyroid incidentalomas to achieve a reliable diagnosis (FNA or histology) is often not feasible. Such follow-up, however, is desirable since early diagnosis of primary thyroid tumours can be effective in providing a cure. It is also possible that a number of patients with thyroid incidentalomas may have metastases in the thyroid, which may affect the prognosis and management, although this is rare. The incidental finding of a thyroid nodule with high FDG uptake should be reported as a possible malignancy regardless of SUV, with further imaging and investigation advised.

18F-FDG PET in the Follow-up of DTC

It is well-recognized that FDG uptake is a good marker of aggressiveness and grading of malignant lesions, their cell differentiation and proliferative potential. This has been demonstrated in a number of malignancies notably lung cancer, lymphoma, brain and soft tissue tumours (22-25). 18F-FDG PET is not ideal for the routine detection of well-differentiated thyroid cancer but can play a role in the detection of anaplastic cancer or when DTC becomes dedifferentiated.

The first report of such utility was published by Joensuu and Ahonen who investigated 18F-FDG uptake in three patients with multiple metastases of thyroid carcinoma (26). They found that some metastatic lesions were visualised only with 18F-FDG, others only with 131I and yet others with both. There was a tendency for 18F-FDG uptake to increase in parallel with the progressive nature of metastasis and to demonstrate lesion not visualised with 131I. Feine and colleagues coined the term ‘flip flop’ of alternating uptake in metastasis (those trapping 131I showing no 188F-FDG uptake and vice versa) in their larger series of 41 patients with DTC (12 papillary, 23 follicular, six Hürthle cell) (27). They found the flip-flop phenomenon in 30 patients and concluded that metastases with positive 131I and negative 18F-FDG uptake represent better differentiation and
tumour grade. Some of their patients who exhibited this pattern had long-standing ‘benign’ metastases for up to 31 years. On the other hand, metastases with negative $^{131}$I and positive $^{18}$F-FDG uptake were regarded as being of higher malignancy. These findings were confirmed by a number of other studies (28-30). Wang et al. (28) showed that high-dose $^{131}$I therapy appears to have little or no effect on the viability of $^{18}$F-FDG avid metastatic lesions. They showed clinical deterioration in 25 patients with $^{18}$F-FDG avid metastatic DTC after high-dose $^{131}$I therapy, with significant rise of total volume of $^{18}$F-FDG avid metastases from a mean of 159 ml to 235 ml, in association with a rise in SUV of 1.5 to 2.3, in high-grade tumours (80%) compared to low-grade tumours (47%).

The results of a multicentre study to establish the clinical significance of $^{18}$F-FDG PET in DTC in comparison with $^{131}$I, $^{99m}$Tc-MIBI and $^{201}$Tl was published by Grunwald et al. (29). They investigated a large cohort of 222 patients with DTC and found the sensitivity of $^{18}$F-FDG PET to be 85% and the specificity 90% for patients with negative $^{131}$I with better detection of mediastinal lymph nodes. The combination of $^{18}$F-FDG PET and $^{131}$I helped to detect 93% of lesions. This and other studies (26-38) have demonstrated the value of $^{18}$F-FDG PET in the management of DTC. There is a general agreement that this modality offers the value of $^{18}$F-FDG PET in DTC in comparison with $^{131}$I scan and $^{99m}$Tc-MIBI (29, 31-32, 43). It has been noted that sites of metastasis visualised better with $^{18}$F-FDG PET in comparison with $^{131}$I, $^{99m}$Tc-MIBI and $^{201}$Tl. $^{18}$F-FDG PET on 54 patients with papillary carcinoma of whom 33 were proven to have metastasis. The sensitivity of $^{18}$F-FDG PET was 94% whereas that of Tg was 54.5%. Specificity of Tg was also reduced at 76% compared to 95% for $^{18}$F-FDG PET. Low sensitivity and specificity of Tg assay were confirmed by others (2, 30) and should raise serious questions regarding the integrity of Tg as a true marker for DTC, and whether or not $^{18}$F-FDG PET should be offered more frequently to patients with falsely negative $^{131}$I WBS and/or falsely negative Tg assay.

Pitfalls of PET Imaging

It has been noted that sites of metastasis visualised better with $^{18}$F-FDG PET include cervical and mediastinal lymph nodes, whereas lung and bone lesions showed less uptake compared to $^{131}$I scan and $^{99m}$Tc-MIBI (29, 31-32, 43). False-negative results are encountered with very small lesions (<4 mm) or in well-differentiated lesions as mentioned above. False-positive results are due to uptake in normal brown fat and inflammatory lesions but these can easily be ruled out through careful review of the clinical history and other imaging. The increasing use of PET-CT scanners should make this less of a problem. Preparation for $^{18}$F-FDG PET scan is simple and requires a short period of fasting and proper glucose control for diabetic patients. Better visualisation of lesions has been reported when the $^{18}$F-FDG PET scan was performed under TSH stimulation induced by discontinuation of thyroxine (44), due to TSH induced increased expression of the GLUT transporter in malignant cells. Other studies have shown $^{18}$F-FDG PET scanning under TSH stimulation to have equal or superior detection (45), no clear advantage (27, 46) or inferior detection rate (29) compared to scanning under TSH suppression. Moog et al. (47) showed a significant improvement in $^{18}$F-FDG uptake under TSH stimulation in 10 patients with DTC who underwent two sets of $^{18}$F-FDG scanning with and without thyroxine discontinuation. Recombinant human TSH (rhTSH) has also been shown to provide similar results (48).

Conclusion

The introduction of molecular imaging with $^{18}$F-FDG PET imaging has revolutionised the way we evaluate malignant tissue starting from diagnosis, through follow-up and assessment of response to therapy. The use of $^{18}$F-FDG PET in the management of thyroid malignancy is not considered as a routine procedure since the majority of
these tumours are well-differentiated and therefore have less avidity to $^{18}$F-FDG which is taken up mostly by aggressive and undifferentiated tumours. However, there is a clear role for $^{18}$F-FDG PET in the assessment of incidental finding of a thyroid nodule which, when showing high FDG uptake should be regarded as a possible malignancy that needs further assessment. The discovery of a primary thyroid cancer (even in patients being investigated for another malignancy) should not deter the clinicians from offering the standard surgery and ablation employed, with success, in the treatment of thyroid cancer.

The other well-documented role for $^{18}$F-FDG PET is in the investigation of cases of DTC presenting with high Tg and negative iodine imaging. Uptake in these tumours indicates a shift towards lesser differentiation (with more aggression and poor prognosis) and may benefit from alternative management. Review of relevant literature suggests that $^{18}$F-FDG PET should be offered more frequently to patients with suspected falsely negative $^{131}$I WBS and/or falsely negative Tg assay.

References


