The Role of ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography in Thyroid Neoplasms

BRIAN HUNG-HIN LANG, TSZ TING LAW

Department of Surgery, The University of Hong Kong, Hong Kong SAR, China

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Evaluate and apply evidence regarding the use of FDG-PET scans in patients with thyroid nodules.
2. Identify differentiated thyroid carcinoma (DTC) patients who could benefit from FDG-PET scanning.

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ABSTRACT

¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has established itself as an important imaging modality in many oncological and nononcological specialties and, as a consequence, it is increasingly being used in clinical practice. Since the first report of FDG being taken up by metastatic differentiated thyroid carcinoma (DTC) cells >20 years ago, various groups of investigators have explored the potential role of FDG-PET scanning in patients with benign and malignant thyroid neoplasms. With the increasing demand for FDG-PET scanning, clinicians are faced with the

challenge of managing an increasing number of FDG-PET-detected thyroid incidentalomas because their significance remains unclear. The aims of this review are to address some of these issues, specifically, the clinical significance of FDG-PET-detected thyroid incidentalomas, the ability of FDG-PET to characterize thyroid nodules, especially those with indeterminate fine needle aspiration cytology results, and the role of FDG-PET in patients with confirmed primary DTC and with suspected recurrent DTC, by reviewing the current literature. *The Oncologist* 2011;16:458–466

Correspondence: Brian H.H. Lang, M.S., F.R.A.C.S., Division of Endocrine Surgery, Department of Surgery, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong SAR, China. Telephone: 852-22554773; Fax: 852-28172291; e-mail: blang@hkucc.hku.hk Received August 3, 2010; accepted for publication January 10, 2011; first published online in *The Oncologist Express* on March 4, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 doi: 10.1634/theoncologist.2010-0256

Table 1. Comparison of the prevalence of FDG-PET abnormalities and their associated risk for thyroid malignancy

Study	<i>n</i> of PET scans	<i>n</i> of PET abnormalities (%)	<i>n</i> of tissue diagnoses (%)	<i>n</i> of thyroid malignancies (%)
Cohen et al. (2001) [8]	4,525	102 (2.3)	15 (14.7)	7 (46.7)
Kang et al. (2003) [9]	1,330	29 (2.2)	15 (51.7)	4 (26.7)
Chen et al. (2005) [10]	4,803	60 (1.2)	50 (83.3)	7 (14.0)
Kim et al. (2005) [11]	4,136	94 (2.3)	32 (34.0)	16 (50.0)
Chu et al. (2006) [12]	6,241	76 (1.2)	14 (18.4)	4 (28.6)
Bogsrud et al. (2007) [13]	7,347	79 (1.1)	48 (60.8)	15 (31.3)
Are et al. (2007) [14]	17,250	377 (2.2)	32 (8.5)	22 (68.8)
Bae et al. (2009) [15]	3,379	285 (8.4)	99 (34.7)	22 (23.2)
Zhai et al. (2010) [16]	3,580	115 (3.2)	96 (83.5)	48 (50.0)
Ohba et al. (2010) [17]	1,501	20 (1.3)	20 (100.0)	12 (60.0)

Abbreviation: FDG-PET, fluorodeoxyglucose positron emission tomography.

INTRODUCTION

^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scanning is increasingly being used in oncology and other medical specialties such as neurology, cardiology, and infectious diseases. Despite the availability of many new PET nuclides, ^{18}F -FDG remains the most commonly used [1]. ^{18}F -FDG is comprised of two parts, namely, the vector part (i.e., 2-deoxy-D-glucose) and the positron-emitting nuclide part (i.e., ^{18}F). FDG works by acting as a false substrate for glucose metabolism and is preferentially taken up in malignant cells versus normal cells. Once inside a cell, FDG gets metabolized by hexokinase to become 2-fluoro-2-deoxyglucose-6-phosphate, but instead of undergoing further catabolization, it accumulates within the cell and emits positron radiation that is then detected by scintigraphy [2]. This is called metabolic trapping and it forms the principle of most radiopharmaceuticals in PET scanning. In oncology, FDG-PET has a well-established role in initial staging, monitoring response to therapy, and management of many cancers, including lung cancer, colon cancer, lymphoma, melanoma, esophageal cancer, head and neck cancer, and breast cancer [3]. In neurology and cardiology, FDG-PET is a useful tool for localization of epileptogenic zones inside the brain and is a “gold standard” tool for the detection of myocardial viability, respectively [4, 5].

Since the first observation of FDG uptake in metastatic differentiated thyroid carcinoma (DTC) >20 years ago [6], there has been increasing interest in evaluating the role of FDG-PET scanning in benign and malignant thyroid neoplasms. Also, with the greater use and greater demand for FDG-PET scans across most specialties, an increasing number of incidental thyroid lesions (so-called thyroid incidentalomas) has been found, and this poses a diagnostic

challenge to clinicians. Currently, there are still unresolved issues regarding the significance of these FDG-PET–detected thyroid incidentalomas, the ability of FDG-PET to characterize thyroid nodules, especially those with indeterminate fine needle aspiration cytology (FNAC) findings, and the role of FDG-PET in patients with confirmed DTC. The present review aimed to address these issues by reviewing the recent medical literature.

SIGNIFICANCE OF FDG-PET–DETECTED THYROID INCIDENTALOMAS AND ITS ABILITY TO DISCRIMINATE BENIGN FROM MALIGNANT THYROID LESIONS

With the increasing number of FDG-PET scans being performed for oncological and nononcological indications, there has been an increasing number of thyroid incidentalomas found. They can be defined as any abnormal FDG uptake found in the thyroid bed during investigation of a nonthyroid condition. Although the prevalence of thyroid nodules in the general population has been reported to be up to 50%–60%, the frequency of FDG-PET–detected thyroid incidentalomas is much lower [7]. As shown in Table 1, the reported frequency of these FDG-PET–detected incidentalomas in the thyroid gland only is in the range of 1.2%–4.3% [8–17]. However, one should be aware that this does not reflect the true incidence in the healthy general population because most of these series included patients with a known history of cancer or with abnormally elevated tumor markers detected during a health evaluation. Furthermore, the percentage of patients with these abnormal uptake values that had some form of tissue diagnosis (i.e., in the form of either FNAC or surgery) varied among series (8.5%–100%) because the decision to undertake tissue diagnosis often differed among institutions and was altered according

Table 2. Comparison of mean SUV_{max} between benign and malignant focal hypermetabolic uptake on FDG-PET or FDG-PET/CT scans

Study	<i>n</i> with focal uptake	Mean SUV _{max} in benign lesions	Mean SUV _{max} in malignant lesions	<i>p</i> -value
Cohen et al. (2001) [8]	71	3.8	6.9	<.05
Kang et al. (2003) [9]	21	6.5	14.2	<.05
Chen et al. (2005) [10]	60	2.6	6.7	<.05
Kim et al. (2005) [11]	45	3.6	3.4	.83
Choi et al. (2006) [23]	70	6.7	10.7	<.05
Bogsrud et al. (2007) [13]	79	5.6	6.4	.12
Nam et al. (2007) [24]	19	4.2	8.4	.40
Bae et al. (2009) [15]	99	3.4	6.6	<.05
Zhai et al. (2010) [16]	115	3.4	7.6	<.05
Traugott et al. (2010) [25]	51	1.9	12.7	<.05
D'Souza et al. (2010) [26]	200	4.5	16.2	<.05

Only includes studies that statistically compared mean SUV_{max} values between benign and malignant thyroid lesions. Abbreviations: CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; SUV, standardized uptake value.

to patient preference. Therefore, these reported malignancy rates are subject to a certain degree of selection bias. Nevertheless, a normal thyroid gland does not normally take up or trap FDG, and so the chance of FDG uptake in a healthy individual's thyroid gland is actually low [18]. For a clinician faced with the problem of a thyroid incidentaloma with abnormal FDG uptake, it is important to consider both the pattern (i.e., focal, diffuse, or other) and the intensity of uptake as measured by the mean or maximum standardized uptake value (SUV_{max}). For the FDG uptake pattern, numerous studies found that the malignancy rate for the focal FDG uptake pattern was in the range of 14.0%–68.8% (Table 1). A recent systematic review of >55,000 patients reported a malignancy risk of 33.2% for focal FDG uptake lesions [19]. Kang et al. [20] compared the malignancy rate between the focal and diffuse uptake patterns and found that the focal uptake group had a significantly higher rate than the diffuse uptake group (37.2% versus 4.7%). This means that the malignancy risk with the diffuse uptake pattern is not significantly higher than the risk with nodular goiters of 5%. In fact, some would even consider diffuse uptake, especially with a SUV_{max} <1.31, as a normal variant or normal physiological uptake [18]. Other common differential diagnoses for the diffuse uptake pattern include chronic thyroiditis and Graves' disease [11, 18]. In a series reported by Kurata et al. [21], they found that, of 1,626 patients undergoing an FDG-PET scan, all 25 (1.5%) patients with diffuse uptake turned out to have Hashimoto's thyroiditis. Kang et al. [20] showed that when both the focal and diffuse FDG uptake patterns were correlated with ultrasonography

(USG) findings, only 59.5% of those with a diffuse uptake pattern had a corresponding nodule in the lobe on USG, whereas >99% of those with a focal uptake pattern had a corresponding nodule on USG. Therefore, the diffuse FDG pattern might be regarded as nonspecific or benign in nature. However, the diffuse pattern should be considered separate from the multifocal and diffuse plus focal uptake patterns. These latter patterns were found to carry malignancy risks similar to that of focal uptake and should raise the possibility of thyroid malignancy. Kang et al. [20] examined 15 patients with multifocal uptake and found that all had thyroid malignancy on histology. Kurata et al. [21] reported that two of four patients (50%) with a diffuse plus focal FDG uptake pattern had papillary thyroid carcinoma (PTC) with a background of Hashimoto's thyroiditis. In other words, although the data remain limited, the multifocal and diffuse plus focal patterns warrant further investigation and should not be confused with the diffuse uptake pattern because they probably carry a similar, if not greater, malignancy risk as the focal pattern [22].

In addition to FDG pattern, the intensity of FDG uptake is an important consideration in thyroid incidentalomas. Table 2 shows a comparison of SUV_{max} between benign and malignant lesions [8–11, 13, 15, 16, 23–26]. In general, malignant lesions tend to have a higher intensity FDG uptake as measured by SUV_{max} than benign thyroid lesions [8–10, 15, 16, 23, 25, 26]. With the exception of a few studies [11, 13, 24], this finding supports the potential utility of FDG-PET and SUV_{max} in differentiating benign from malignant thyroid lesions. Certainly, several experimental

studies supported this clinical finding. These studies demonstrated that malignant tissues tended to take up glucose more quickly and efficiently than benign tissues, and one of the reasons is because greater expression of glucose transporters (GLUTs) has been found in the malignant group. Matsuzu et al. [27] examined the expression patterns and levels of *GLUT* genes in normal and malignant thyroid tissues and found greater expression of the *GLUT1*, *GLUT2*, *GLUT3*, *GLUT4*, and *GLUT10* genes as well as a higher *GLUT1* mRNA level in the malignant group, as measured by real-time polymerase chain reaction. GLUTs are now believed to be involved in thyroid carcinogenesis [27, 28].

Despite the evidence supporting the potential role of FDG-PET and SUV in characterizing thyroid nodules, there are still questions on the use of SUV as the criterion for malignancy because there is still a significant observed overlap between benign and malignant thyroid lesions. It should be noted that benign lesions, for example, Hürthle cell adenoma, might be associated with a high SUV_{max} . The mean SUV_{max} was 4.4 in 10 patients with Hürthle cell adenoma [29], whereas Are et al. [30] reported that the SUV_{max} was >5 in five of seven patients with Hürthle cell adenoma. The mechanism of the high SUV_{max} in Hürthle cell lesions is not well understood. The SUV_{max} in chronic thyroiditis was found to be higher than in normal variants. The SUV_{max} of chronic thyroiditis patients (2.76 ± 1.24) was significantly higher than that of normal variants (1.99 ± 0.63 ; $p = .002$) [31]. Kurata et al. [21] reported that the mean SUV_{max} was 3.5 (range, 1.6–7.8) in 25 patients with diffuse FDG uptake and a USG diagnosis of Hashimoto's thyroiditis. The mechanism of FDG uptake in Hashimoto's thyroiditis is not well understood. Greater cell death in chronic thyroiditis and chronic lymphocytic infiltration might play a role, whereas correlation between the SUV_{max} and serum thyroperoxidase level was poor [31, 32]. It is important to realize that statistical significance does not always translate into clinical significance. Table 2 shows a comparison of mean SUV_{max} between benign and malignant focal hypermetabolic uptake on FDG-PET or combined FDG-PET/computed tomography (CT). Despite achieving statistical significance when the mean of the benign and malignant uptake values were compared [8–10, 15, 16, 23, 25, 26], most studies revealed an overlap in SUVs. Bogsrud et al. [13] analyzed their data and used the receiver operator characteristic curve in an attempt to determine the best SUV cutoff level. They determined that the best SUV cutoff level was 6.0, but with this cutoff value the sensitivity and specificity were 69% and 61%, respectively. This means that the chance of discriminating benign from malignant lesions using SUVs is only slightly better than with random chance (e.g., flipping a coin). Another

group evaluated the diagnostic value of using FDG-PET/CT in thyroid nodule characterization in comparison with high-resolution USG but failed to demonstrate a significant advantage for FDG-PET/CT over high-resolution USG [26]. In summary, although, overall, malignant lesions have a higher SUV than benign lesions, the current evidence does not support the utility of FDG-PET and SUV in discriminating benign from malignant thyroid lesions or in characterizing thyroid nodules. Regardless of the SUV, all patients with focal, multifocal, and diffuse plus focal FDG uptake patterns should undergo further evaluation that includes high-resolution USG and/or USG-guided FNAC [33].

Regarding the question of whether these incidental carcinomas behave differently from those detected by other conventional imaging modalities such as USG or CT scan, Law et al. [34] recently compared the clinicopathological features of 22 patients with incidental DTC detected using FDG-PET with 11 patients with incidental DTC using USG and found that tumor bilaterality was significantly more frequent (45.0% versus 0.0%; $p = .040$) and the tumors in the PET group were more advanced according to tumor–node–metastasis staging ($p = .021$). Despite the apparent absence of tumors in the opposite lobe, the authors suggested that total thyroidectomy should be preferred over hemithyroidectomy in FDG-PET–detected incidental DTC. This is because of the higher incidence of tumor bilaterality and the inaccuracy of USG in detecting small bilateral tumors and more advanced tumors. This suggests that FDG-PET–detected incidental carcinoma tends to behave more aggressively and confer a worse prognosis. This concurs with an earlier study that found that FDG-PET–detected DTC tended to occur in older patients and was associated with more frequent extrathyroidal extension and more aggressive histological variants, such as the tall-cell variant [14].

ROLE OF FDG-PET IN INDETERMINATE THYROID LESIONS ON FNAC

Because FDG-PET has demonstrated potential in characterizing thyroid nodules through assessment of the FDG uptake pattern and intensity, it seems more logical, and possibly more cost-effective, if FDG-PET is performed not for all but for only a select group of patients with nodules carrying a greater risk for malignancy. One such group is patients with nodules with indeterminate FNAC findings. The definition of an indeterminate FNAC result usually includes follicular lesions, Hürthle cell (oncocytic) lesions, atypical cytology, abnormal cytology, or suspicious cytology. This group remains a diagnostic dilemma to clinicians because approximately 20%–30% of these are malignant whereas the rest are benign on pathological examination [35, 36]. However, nearly all patients with indeterminate

Table 3. Comparison of studies examining the utility of FDG-PET in detecting malignancy in cytologically indeterminate thyroid nodules

Study	<i>n</i> of patients	<i>n</i> of carcinomas (%)	Criterion for PET positivity	Sensitivity	Specificity
Kresnik et al. (2003) [29]	24	9 (37.5)	Focal uptake with SUV >2	100	100
Mitchell et al. (2005) [37]	24	11 (45.8)	Focal uptake	60	91
de Geus-Oei et al. (2006) [38]	44	6 (13.6)	Focal uptake	100	66
Sebastianes et al. (2007) [39]	42	11 (26.2)	Focal uptake	100	39
Hales et al. (2008) [40]	15	7 (46.7)	Focal uptake with SUV >2	57	50
Smith et al. (2008) [41]	23	5 (21.7)	Area under SUV curve >175.5	100	44
Traugott et al. (2010) [25]	51 ^a	8 (15.6)	Focal uptake	100	59

^aOngoing prospective trial.

Abbreviations: FDG-PET, fluorodeoxyglucose positron emission tomography; SUV, standardized uptake value.

FNAC are required to undergo thyroid lobectomy to establish a diagnosis. In other words, surgical resection will prove to be unnecessary in >60%–70% of cases. At present, there is no alternative algorithm for more conservative management of patients with indeterminate FNAC. Conventional USG, CT, and magnetic resonance imaging (MRI) have previously been shown to be of some value, but FDG-PET has yet to be assessed in a large prospective study [25]. Table 3 shows a comparison of series examining the utility of FDG-PET in detecting malignancy in a thyroid nodule with indeterminate FNAC findings [25, 29, 37–41]. Study size was in the range of 15–51 patients and the criterion for FDG-PET positivity varied among studies. One of the larger series was reported by De Geus-Oei et al. [38]. In that study, there were 44 patients with inconclusive FNAC findings (i.e., follicular neoplasm, Hürthle cell neoplasm, atypical cells, or inadequate), and of these six were malignant and the other 38 were benign. In their experience, FDG-PET did not lead to any false negatives, implying a negative predictive value (NPV) of 100%. All carcinomas demonstrated FDG uptake, but 13 of 38 benign nodules also had FDG uptake. They showed that using routine FDG-PET in their patient cohort could potentially reduce the number of unnecessary lobectomies by 66% (95% confidence interval, 49%–80%) if surgery was not advised for those with no uptake in the thyroid gland on FDG-PET imaging [38]. Importantly, no malignancies were missed (i.e., no false negatives) but 13 of 38 patients (34.2%) still underwent unnecessary lobectomies (i.e., false positives). It was interesting to note that, in their series, the mean SUV was similar between benign and malignant lesions and one of the PTCs actually had a SUV as low as 0.9. To improve the false-positive rate, some studies proposed using a focal SUV >2.0 as the criterion for FDG-PET positivity [33, 40]. However, regardless of the SUV cutoff, there is always go-

ing to be a trade-off between false positives and false negatives. Smith et al. [41] evaluated the association between SUV over time and malignancy in follicular neoplasms by performing serial FDG-PET scans over a 2-hour period and measuring the area under the SUV curve (AUC). They demonstrated no significant difference in AUC but found a difference in the dynamics of the SUV change over time between benign and malignant lesions [41]. Because of the significant overlap in AUC values, they concluded that FDG-PET was not able to predict malignancy in a follicular neoplasm [41]. However, because most of these reported series were retrospective in design and the patient selection was not formally standardized, there is a need for a large, well-designed prospective study. Recently, Traugott et al. [25] reported the results of 51 patients with indeterminate FNAC findings in an interim analysis of their prospective trial, which began in 2004. Their data suggested that FDG-PET was an accurate diagnostic modality for identifying malignancy in thyroid nodules ≥1 cm in diameter and with indeterminate FNAC results, with 100% sensitivity and NPV. They concluded that FDG-PET was of value in excluding malignancy in thyroid nodules with indeterminate FNAC. To overcome the spatial resolution limitation of FDG-PET, their study only included solitary or dominant nodules that measured ≥1 cm on USG. To achieve adequate power, the study aimed to recruit 125 patients and the results will be available within the next few years. However, there are some concerns in using FDG-PET in this group of patients. First, follicular thyroid carcinoma (FTC), a possible type of malignancy in the indeterminate group, is known to be associated with lower SUVs than other types of thyroid carcinoma [42]. It is also known that Hürthle cell adenoma, a benign lesion, tends to have a very high SUV [29]. Both entities could possibly lessen the usefulness of FDG-PET. Furthermore, a confirmatory diagnosis in this

group using FNAC is often difficult to make by experienced pathologists. Considerable interobserver and intraobserver variability in the histopathological diagnosis of follicular thyroid lesions have been reported [43, 44]. In one recent study, among 15 cases of suspected follicular variant of PTC, only two cases (13.3%) had unanimous agreement among six expert pathologists [44]. Given these concerns, the role of FDG-PET in evaluating thyroid nodules with indeterminate FNAC findings remains uncertain, but the interim results in one of the possibly largest prospective trials on FDG-PET in cytologically indeterminate nodules look promising [25]. Hopefully, this prospective trial, which is due to be completed in the next few years, will provide us with more information.

ROLE OF FDG-PET IN PATIENTS WITH PRIMARY DTC

Despite the fact that FDG-PET is involved with preoperative staging of many types of malignancy, the supporting evidence for its role as a preoperative staging tool in DTC remains weak. Currently, the staging of DTC relies on a combination of clinical, radiological, and pathological information. This is supplemented by findings on postradioiodine ablation whole-body ^{131}I scan. There have been surprisingly few studies evaluating the role of FDG-PET as a staging tool for DTC. Perhaps, this might be because there has not been any effective neoadjuvant therapy available for DTC and, regardless of tumor stage, all patients undergo surgical resection. In other words, accurate preoperative imaging and staging do not necessarily alter the choice of therapy. However, because routine prophylactic lateral neck dissection has not been advocated in DTC and it is now recognized that lymph node metastases do impact disease-free and specific survival times [44], accurate imaging of regional lymph nodes has now been recognized as very important. This is usually carried out by preoperative USG of the regional neck lymph nodes in the central and lateral neck compartments. Jeong et al. [45] compared the diagnostic accuracy of FDG-PET/CT as a novel staging alternative to USG for the preoperative evaluation of cervical lymph node status in patients with PTC. The final cervical lymph node status was confirmed by histopathology. However, for lateral neck lymph node metastases, FDG-PET/CT showed a sensitivity of only 50%, and this was not significantly better than the diagnostic sensitivity of 53.9% with USG. The study concluded that FDG-PET/CT did not provide additional benefits over conventional imaging modalities. Therefore, support for the routine use of FDG-PET as a preoperative staging tool in DTC is not justified, considering the extra cost and added risk from radiation.

ROLE OF FDG-PET IN PATIENTS WITH DTC RECURRENCE

The role of FDG-PET in patients with DTC recurrence is far better established than as a staging tool for primary DTC. Conventional imaging modalities for localizing tumor recurrence (as evidenced by raised thyroglobulin [Tg] or raised anti-Tg antibodies) consist of a combination of USG, noncontrast CT, MRI, and diagnostic whole-body ^{131}I scan (DxWBS). The first observation of FDG uptake in recurrent DTC lesions was made >20 years ago [6]. Although only three patients were reported on at the time, it was observed that some non-iodine avid lesions did concentrate FDG. In fact, there was a reciprocal pattern of iodine and FDG uptake. This simple observation is now known as the “flip-flop” relationship and has been confirmed in many subsequent large series [46, 47]. The reason why some DTC recurrences fail to concentrate iodine is probably related to progressive dedifferentiation of DTC cells, leading to false-negative DxWBS. These non-iodine avid lesions account for approximately 20% of all DTC metastases. It has been recognized that FDG-PET is able to localize residual or metastatic DTC lesions in patients with negative DxWBS and elevated Tg as well as in patients with negative DxWBS and undetectable Tg but elevated anti-Tg levels [47]. Wang et al. [48] reported their experience with 37 DTC patients with a negative DxWBS and elevated Tg level and found that FDG-PET was able to locate occult disease in 71% of cases, and they reported a positive predictive value (PPV) of 92%. More importantly, FDG-PET was able to change the clinical management in >50% of patients. In the presence of low Tg levels, FDG-PET had an NPV of 93% [48]. Similarly, Esteva et al. [49] reported FDG-PET findings in 50 patients with an elevated Tg level and a negative WBS and found that FDG-PET was positive in 32 of 39 (82.1%) patients with confirmed recurrence and negative in seven of 11 (63.6%) patients with no confirmed recurrence. The sensitivity and specificity were 82% and 64%, respectively. Tumor size and capsular tumor invasion were factors significantly associated with a positive FDG-PET study. They also concluded that FDG-PET is an extremely useful imaging tool in patients with a negative WBS and raised Tg level [49]. The SUV_{max} reported in patients with recurrent Hürthle cell carcinoma was remarkable. Hürthle cell carcinoma generally has a lower iodine avidity [50]. In one study of patients with a histological diagnosis of Hürthle cell carcinoma and biochemical or radiological findings suspicious for recurrence, 24 of 44 ^{18}F -FDG-PET scans were positive and the median SUV_{max} was 17.6 (range, 2.1–64.9). As a result, the authors suggested that ^{18}F -FDG-PET was useful in postoperative staging and detection of recurrence in these patients [51]. Few studies have directly evaluated the relationship between thyroid-stimulating hormone (TSH) level and

FDG uptake intensity [52–54]. To date, the evidence seems to suggest that a higher SUV_{max} can be obtained under TSH-stimulated conditions using recombinant human TSH stimulation; also, there were more positive FDG foci and patients identified [52–54].

Some authors evaluated the diagnostic accuracy of integrated FDG-PET/CT because it was believed that fusion of the two modalities may further enhance sensitivity, specificity, and tumor localization. For other types of head and neck tumors, combined FDG-PET/CT was shown to have better diagnostic accuracy than PET or CT alone [55]. Razfar et al. [56] evaluated the diagnostic accuracy of FDG-PET/CT in detecting recurrent or persistent DTC, and the sensitivity, specificity, PPV, and NPV were found to be 80.7%, 88.9%, 94.7%, and 65.3%, respectively. Again, they demonstrated that there was an alteration in the treatment strategy in 28.2% of patients as a result of adding the FDG-PET/CT information, and 21% required additional surgery [56]. However, the added value of FDG-PET/CT over good quality conventional imaging modalities such as USG, CT, MRI, and DxWBS in locating recurrent or persistent DTC was recently questioned because the extra cost of FDG-PET and its associated radiation can be concerning. Lal et al. [57] recently evaluated the added value of FDG-PET/CT in 20 DTC patients with an elevated Tg level and a negative DxWBS. They found that FDG-PET/CT provided additional information in only two of 20 (10.0%) patients, both of whom required no additional intervention, and it underestimated the extent of disease when compared with conventional imaging in three of 30 (15.0%) patients and led to unnecessary interventions (including surgery, radioiodine ablation, and antibiotics) in three of 30 (15.0%) additional patients. They concluded that FDG-PET/CT has good sensitivity in detecting recurrent or persistent DTC but the added value over good quality conventional imaging is very limited and could lead to unnecessary interventions [57].

Apart from providing additional information on the anatomical location of non-iodine avid metastases, FDG-PET has the ability to predict tumor behavior and prognosis. Similar to FDG-PET-detected thyroid carcinoma, FDG-PET may be used as a tool in defining the prognosis and guiding the timing and aggressiveness of therapeutic deci-

sions in patients with metastatic DTC [58]. When FDG-avid metastases were compared with non-FDG avid metastases, Robbins et al. [59] showed that patients with FDG-avid metastases had a 7.28-fold lower survival rate. This seems to be consistent with the molecular characteristics of these tumors and their metastases. In addition to being less differentiated on histology, the majority of these FDG-avid lesions do carry *BRAF* gene mutations, which make them behave more aggressively, less likely to take up ¹³¹I, and more likely to recur. Ricarte-Filho et al. [60] reported that 100% of FDG-PET⁺ but radioiodine ablation refractory PTC cases were *BRAF*⁺, which is significantly higher than the 45% rate of PTC in general. It is now believed that *BRAF* mutations tend to downregulate the promoter activity of the sodium/iodide symporter so that ¹³¹I is far less likely to be taken up by the tumor cell [28].

CONCLUSION

Thyroid incidentalomas with a focal FDG uptake pattern on FDG-PET are associated with a higher malignancy risk, in the range of 14.0%–68.8%. In contrast, those with diffuse FDG uptake are associated with a lower malignancy risk, in the region of 5%. In general, malignant thyroid lesions tend to have greater FDG uptake intensity (as indicated by a high SUV_{max}) than benign thyroid lesions. However, because there is significant overlap in the SUV_{max} between benign and malignant lesions, a clear cutoff SUV_{max} cannot be determined for discriminating benign from malignant lesions. FDG-PET has so far been shown to be useful in excluding malignancy in cytologically indeterminate thyroid nodules, especially nodules ≥ 1 cm in diameter. There is still little evidence to support the routine use of FDG-PET as a pre-operative staging tool for primary DTC. On the other hand, its routine use in patients with recurrent DTC with an elevated Tg level and a negative DxWBS is well established and accepted, and its sensitivity could be enhanced under stimulated TSH conditions.

AUTHOR CONTRIBUTIONS

Conception/Design: Brian Lang, Tsz Ting Law
Provision of study material or patients: Brian Lang, Tsz Ting Law
Collection and/or assembly of data: Brian Lang, Tsz Ting Law
Data analysis and interpretation: Brian Lang, Tsz Ting Law
Manuscript writing: Brian Lang, Tsz Ting Law
Final approval of manuscript: Brian Lang, Tsz Ting Law

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