The role of ^{18}F -fluorodeoxyglucose positron emission tomography in differentiated thyroid cancer before surgery

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Abstract

The incidence of thyroid cancer in both men and women is increasing faster than that of any other cancer. Although positron emission tomography (PET) using ^{18}F -fluorodeoxyglucose (FDG) has received much attention, the use of FDG PET for the management of thyroid cancer is limited primarily to postoperative follow-up. However, it might have a role in selected, more aggressive pathologies, and so patients at a high risk of distant metastasis may benefit from PET before surgery. As less FDG-avid thyroid cancers may lower the diagnostic accuracy of PET in preoperative assessment, an understanding of FDG avidity is important for the evaluation of thyroid cancer. FDG avidity has been shown to be associated with tumor size, lymph node metastasis, and glucose transporter expression and differentiation. As PET is commonly used in clinical practice, the detection of incidentalomas by PET is increasing. However, incidentalomas detected by PET have a high risk of malignancy. Clinicians handling cytologically indeterminate nodules face a dilemma regarding a procedure for a definitive diagnosis, usually lobectomy. With 'nondiagnostic (ND)' fine-needle biopsy (FNA), PET has shown a negative predictive value (NPV) of 100%, which indicates that negative uptake in a ND FNA procedure accurately excludes malignancy. With 'atypia of undetermined significance' or 'follicular neoplasm', the sensitivity and NPV of PET are 84 and 88%. PET does not provide additional information for the preoperative assessment of thyroid cancer. However, factors associated with FDG positivity are related to a poor prognosis; therefore, FDG PET scans before surgery may facilitate the prediction of the prognosis of differentiated thyroid cancer.

Key Words

- carcinoma
- thyroid

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Introduction

Thyroid nodules are common and can be detected incidentally in 27–67% of individuals (Brander *et al.* 1991, Ezzat *et al.* 1994). However, only 1 in 20 palpable nodules is malignant (Mazzaferri 1992). How can we

detect cancer among thyroid nodules? According to the revised American Thyroid Association (ATA) Management Guidelines, serum TSH level measurement and thyroid ultrasonography (US) are the initial workup of thyroid

nodules (American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer *et al.* 2009). If the serum TSH level is subnormal, radionuclide scanning should be utilized to identify whether a nodule is functioning (American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer *et al.* 2009). The most common and practical thyroid scintigraphy method is γ -camera planar imaging with ^{99m}Tc -pertechnetate. Nonfunctioning nodules, which constitute $\sim 90\%$ of the total, have a 5% risk of being malignant (Hegedus 2004). A more physiological approach to thyroid imaging would involve using a radioisotope of iodine (^{123}I or ^{131}I) (Hegedus 2004). In the absence of TSH suppression, fine-needle biopsy (FNA) is the procedure of choice and is the most accurate and cost-effective method of diagnosing thyroid carcinoma.

Globally, the incidence of thyroid cancer has been increasing sharply since the mid-1990s, and it is the cancer with the fastest increasing incidence in both men and women (Siegel *et al.* 2012). In the United States, 558 260 people have thyroid cancer, and an additional 56 460 have been diagnosed in 2012 (Siegel *et al.* 2012). The rising incidence of thyroid cancer is partly due to improved disease detection, although no other reasons for the substantial increases in both small and large tumors are known (Aschebrook-Kilfoy *et al.* 2011).

Fortunately, the survival rates of thyroid cancer are good. The 5-year survival rate for all thyroid cancer patients is 97.3% (Siegel *et al.* 2012). Differentiated thyroid cancers (DTCs), both papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), are slow growing and highly curable and generally have a good prognosis (Duntas & Grab-Duntas 2006). Prognostic factors for DTCs are well known. Age, gender, family history, tumor size, multifocality, extrathyroidal extension (EE), tumor subtype, vascular invasion, lymph node (LN) metastasis, distant metastasis, and low or no iodine uptake by the tumor are associated with metastasis, risk of recurrence, and death from DTCs (Duntas & Grab-Duntas 2006).

Recently, positron emission tomography (PET) using ^{18}F -fluorodeoxyglucose (FDG) in DTC patients has come into the spotlight; however, the use of FDG PET has been limited primarily to the postoperative surveillance of known DTCs. FDG PET has been known to show metastasis in ^{131}I scan-negative thyroid cancer patients with a high accuracy, which is thought to be related to increased glucose metabolism in poorly differentiated carcinoma (Chung *et al.* 1999). However, routine pre-operative use of PET was given an E rating in the ATA

guidelines, which means that PET does not improve important management or outcomes of thyroid cancer (American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer *et al.* 2009). Although controversy exists over the preoperative use of FDG PET, several studies have evaluated its use before surgery.

To address these issues, we evaluated i) factors associated with the FDG avidity of DTCs, ii) the role of FDG PET in the preoperative assessment of thyroid cancer, iii) incidentalomas detected by FDG PET, iv) the role of FDG PET in indeterminate thyroid nodules, and v) prediction of prognosis by FDG PET in patients with DTCs.

Review

Two independent reviewers performed an electronic PubMed search using the keywords PET and thyroid cancer. Only English-language full-text articles published between January 2000 and June 2012 were included. Studies on poorly DTC, recurrent thyroid cancer, and PET after surgery were excluded. A total of 45 articles were identified. The reference lists of related papers were also manually reviewed to identify further studies. No attempt was made to contact authors for additional information.

Factors associated with the FDG avidity of DTCs

An understanding of FDG avidity is important for the evaluation of thyroid cancer. Less FDG-avid thyroid cancers may yield false-negative findings, which lower the diagnostic accuracy of PET in preoperative assessment. In breast cancer, a high tumor grade, hormone receptor negativity, triple negativity, and metaplastic histology are factors associated with high FDG uptake. We reported previously that in thyroid cancer tumor size and cervical LN metastasis presence are associated with a greater likelihood of positive FDG uptake (Kim *et al.* 2012). None of the US features were significantly correlated with FDG uptake (Kim *et al.* 2012). Even though tumor size is known to be correlated with the standardized uptake value (SUV) in PTC (Kaida *et al.* 2011), it is not an independent factor predictive of positive FDG uptake (Choi *et al.* 2011a).

Since either none (Chandan *et al.* 2006) or only 50% (Yasuda *et al.* 2005) of DTCs express glucose transporter (GLUT) 1 (SLC2A1), its expression was not correlated with SUV (Kaida *et al.* 2011). However, the expression of GLUT3 (SLC2A3) can be observed in DTCs (Ciampi *et al.* 2008), and correlations between GLUT3, GLUT4 (SLC2A4), and

SUV were significant in thyroid cancer (Kaida *et al.* 2011). Therefore, FDG uptake may be determined by the expression of GLUT3 and GLUT4 (Kaida *et al.* 2011). However, in incidentally detected thyroid cancer, SUV was not correlated with either GLUT1 or GLUT3 (Kim *et al.* 2010a). As thyroid cells dedifferentiate, the capacity for iodine uptake is lost and cellular glucose metabolism is activated (Feine *et al.* 1996). This 'flip-flop' phenomenon has relevance to FDG avidity in thyroid cancer. FDG avidity may differ among thyroid cancer subtypes (Kim *et al.* 2007).

FDG avidity has been shown to be associated with tumor size, LN metastasis, and GLUT expression and differentiation. Identification of factors associated with the FDG avidity of thyroid cancer will likely reduce the number of false-negative findings and facilitate the prediction of prognosis.

Preoperative assessment of thyroid cancer with FDG PET

Preoperative evaluations of the extent of spread of the primary tumor and the presence of LN metastasis are crucial for optimal treatment intended to reduce the recurrence rate of thyroid cancer (Park *et al.* 2009). US is accepted as the technique of choice for staging of thyroid cancer by the ATA (American Thyroid Association) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer *et al.* 2009). However, there are limited data concerning the role of FDG PET in staging of thyroid cancer. Since there is no effective neoadjuvant therapy for thyroid cancer and there may be no alternative therapy, except for surgery, regardless of staging (Lang & Law 2011), preoperative use of PET has not been evaluated thoroughly.

To summarize the size and extent of spread of thyroid cancer, the TNM staging system proposed by the American Joint Committee on Cancer (AJCC; Compton *et al.* 2013) is commonly used. First, T staging of thyroid cancer is based on the size of the tumor and the extent of EE (Compton *et al.* 2013). Tumors are divided into four size categories: T1a (≤ 1 cm), T1b (> 1 cm and ≤ 2 cm), T2 (> 2 cm and ≤ 4 cm), and T3 (> 4 cm). Using US, 83.3% of the primary tumors have been measured accurately, as confirmed by comparison with diameters determined by pathology (Park *et al.* 2009). However, evaluation of the size of thyroid tumors by PET is limited by partial volume effects (Vriens *et al.* 2011).

Extent of EE is divided into T3 (minimal extension) and T4 (extension beyond the capsule). Jeong *et al.* (2006b) reported a strong correlation between SUV and EE of

papillary microcarcinoma in a univariate analysis; however, associations between SUV and EE or other aggressive tumor features were not significant in a multivariate analysis. Also, there was no significant difference in the SUV of papillary macrocarcinoma according to the presence or absence of EE (Choi *et al.* 2011b). However, US allows the detection of the tumor site attached to the thyroid capsule, which is associated with EE (Jeong *et al.* 2006b). Therefore, preoperative US may be the most appropriate tool for T staging of thyroid cancer.

Three previous studies have evaluated the diagnostic accuracy of FDG PET in N staging of thyroid cancer (Table 1; Jeong *et al.* 2006a, Morita *et al.* 2010, Choi *et al.* 2011b). LN metastases of thyroid cancer are found most commonly in the central neck compartment (Ferris *et al.* 2012). Although less frequent, metastasis to LNs in the lateral neck compartment is associated with a worse prognosis (American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer *et al.* 2009). Thus, imaging the neck before surgery for thyroid carcinoma is necessary to determine the appropriate extent of surgical resection (Langer & Mandel 2008). The sensitivity and specificity of PET for the evaluation of the central LNs were 5.0–22.7 and 93.6–98.8% respectively; those of US were 25–63.6 and 74.9–97.6% respectively; and those of contrast-enhanced computed tomography (CECT) were 15.1–25.0 and 93.8–98.8% respectively. The sensitivity and specificity of PET for the evaluation of lateral LNs were 30.6–50 and 90.4–97% respectively; those of US were 41.3–82.2 and 64.3–97.4% respectively; and those of CECT were 33.3–42.3 and 53.6–96.6% respectively. The specificities of PET, US, and CECT for the evaluation of both the central and the lateral neck were $> 90\%$, except in one study of US (Choi *et al.* 2011b). However, the sensitivities were $\leq 50\%$, except in two studies of US (Morita *et al.* 2010, Choi *et al.* 2011b). The overall diagnostic accuracy tended to be higher for lateral LNs than for central LNs. Jeong *et al.* (2006a) reported that 5% (1/20) of the metastatic LNs in the central compartment were detected by PET. PET did not prove to be superior to US or CT (Jeong *et al.* 2006a, Choi *et al.* 2011b). US imaging may thus be the best methodology for preoperative assessment since it yielded results superior to those of either PET or CT alone for the detection of LN metastasis (Morita *et al.* 2010).

FDG PET might be superior to anatomic imaging modalities in terms of detection of distant metastasis. The ability of PET to image the whole body in one session represents an advantage for the evaluation of M staging.

Table 1 Comparison of PET, ultrasonography, and contrast-enhanced computed tomography in the assessment of LN metastasis.

Ref.	No. of patients (M/F)	Age in years, mean (range)	No. of central LN metastases	No. of lateral LN metastases	Central LNs (sensitivity/specificity/accuracy)			Lateral LNs (sensitivity/specificity/accuracy)		
					PET	US	CECT	PET	US	CECT
Choi <i>et al.</i> (2011a,b)	65 (9/56)	48.8 (23–77)	113 (40)	134 (36)	17.3/93.6/70.3	28.0/74.9/60.6	–	30.6/90.8/74.6	52.8/64.3/61.2	–
Jeong <i>et al.</i> (2006a,b)	26 (7/19)	44 (17–73)	72 (20)	260 (26)	5.0/93.8/59.6	25.0/93.8/67.3	25/93.8/67.3	50.0/97.0/92.3	41.3/97.4/93.5	42.3/96.6/91.2
Morita <i>et al.</i> (2010)	74 (12/62)	65.6 (16–84)	148 (66)	201 (45)	22.7/98.8/64.9	63.6/97.6/82.0	15.1/98.8/61.5	40.0/90.4/79.1	82.2/96.8/94.0	33.3/53.6/78.6

Ref., reference; LN, lymph node; PET, positron emission tomography; US, ultrasonography; CECT, contrast-enhanced computed tomography.

However, because 4–7% of patients present initially with distant metastasis (Schlumberger *et al.* 1986, Shaha *et al.* 1997), and surgery is the only therapeutic option for thyroid cancer, advocating the routine use of PET to detect distant metastasis is inappropriate. In addition, because PET scanners have limited spatial resolution, nodules in the lung smaller than 5 mm may be missed (Jeong *et al.* 2006a).

Strict indications for the extent of surgical resection are necessary to optimize a benefit profile expected to outweigh the risks of the procedure (Ferris *et al.* 2012). Imaging, a cost-effective approach, is essential for the determination of the extent of surgical resection. Pre-operative US of the contralateral lobe and cervical LNs is recommended for all patients undergoing thyroidectomy for thyroid cancer (American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer *et al.* 2009). Although the effectiveness of US is dependent on the skill and experience of the operator (Mikosch *et al.* 2000), it is easily performed and provides accurate information regarding tumors (Hoang *et al.* 2007).

Because it does not provide information additional to that yielded by US, routine use of PET for preoperative assessment is inappropriate due to both the expense and radiation burden. However, it might have a role in selected, more aggressive pathologies, and so patients at a high risk of distant metastasis may benefit from PET before surgery (Pryma *et al.* 2006).

Incidentalomas detected by FDG PET

‘Incidentalomas’ are nonpalpable nodules detected by US or other anatomic imaging techniques including FDG PET (American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer *et al.* 2009). Nowadays, FDG PET is commonly being used in clinical practice, which has led to an increase in the detection of incidentalomas by FDG PET (Nishimori *et al.* 2011). Previous studies have documented the risk of malignancy in incidentalomas; however, it ranged between 10 and 63.6% (Are *et al.* 2007). The reason for this wide range might be variability of the population characteristics and background risk of thyroid disease related to geographic area (Bertagna *et al.* 2013). The high risk of malignancy in incidentalomas warrants further evaluation when detected (Shie *et al.* 2009), which might be explained in two ways. First, as increased FDG uptake indicates either accelerated production of GLUT or enhanced glycolysis related to malignancy,

incidentalomas detected by PET might have a higher risk of malignancy (Van den Bruel *et al.* 2002). Also, as most of the subjects on whom FDG PET imaging is performed are those with known malignancies, pretest probability for secondary cancers might be higher (Van den Bruel *et al.* 2002).

Soelberg *et al.* (2012) reviewed previous studies regarding SUV to differentiate malignant lesions from benign lesions and reported a significant difference between groups. However, there was a pronounced overlap, which makes it difficult to use it in any individual case (Kim *et al.* 2010b). In the study by Are *et al.* (2007), 22 among 32 patients with incidentalomas were diagnosed with thyroid cancer. Twelve patients (54%) were noted to have poor prognostic variants of thyroid carcinoma, which included the tall-cell variant PTCs (11 patients, 50%) and poorly DTC (1 patient, 4%). Also, incidentalomas detected by PET have been known to have higher incidence of tumor bilaterality than those detected by US (Lang & Law 2011).

Expressions of biological markers in incidental thyroid cancer were evaluated by Kim *et al.* (2013), and they found the expression of GLUT1 to be significantly lower in incidental thyroid cancer than in clinically primary thyroid carcinoma (Kim *et al.* 2013). In incidental thyroid cancer, lack or low levels of expression of HIF1 (HIF1A), GLUT3, and carbonic anhydrase (CA) IX (CA9) were found (Kim *et al.* 2013). Additionally, SUV was not correlated with hypoxia-induced upregulations of GLUT1, GLUT3, CA-IX, and hexokinase-II (Kim *et al.* 2013).

Given the higher rate of adverse prognostic features in incidental thyroid cancer detected by PET, different strategies may be proposed as therapeutic choices such as total thyroidectomy even for tumor size <10 mm (Are *et al.* 2007).

Role of FDG PET in thyroid nodules of nondiagnostic atypia of undetermined significance or follicular neoplasms

According to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) formulated in 2007, the terminology and criteria for reporting thyroid FNA are divided into six categories: nondiagnostic or unsatisfactory (ND), benign, atypia of undetermined significance or follicular lesions of undetermined significance (AUS), follicular neoplasm (FN) or suspicious for a FN, suspicious for malignancy, and malignant (Baloch *et al.* 2008). A parameter that consistently indicates the possibility of malignancy is needed to distinguish between benign and

malignant samples. This could be achieved by metabolic imaging, which might spare patients from undergoing unnecessary investigations and surgical resection (Al-Nahhas *et al.* 2008).

ND or unsatisfactory The ND category indicates that a specimen was processed and examined, but failed to meet the specified criteria due to limited cellularity, lack of follicular cells, or poor fixation and preservation (Baloch *et al.* 2008). At least six groups of benign follicular cells, each composed of at least ten cells, are required from at least two aspirates of a nodule (Goellner *et al.* 1987). However, there is no consensus regarding follow-up for ND FNA. The ATA guidelines strongly recommend the use of repeated FNA with US guidance for the ND category (American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer *et al.* 2009). Repeated FNA is usually performed at intervals of at least 3 months to avoid post-FNA reparative cellular atypia (Baloch *et al.* 2003), while a recent report has indicated that the timing of repeat FNA does not affect the diagnostic yield of samples (Lubitz *et al.* 2012). A repeat FNA leads to a definitive diagnosis in up to 90% of cases, reducing the ND rate from 15 to 3% (Danese *et al.* 1998). For persistent ND after repeated FNA, close clinical and US follow-up is recommended for partially cystic nodules, while surgery is considered for solid nodules (American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer *et al.* 2009). The risk of malignancy for the ND category is between 1 and 4% (Cibas and Ali 2009).

A Medline search for PET used for thyroid nodules of ND cytology yielded one study of 88 patients (Giovannella *et al.* 2011). Two ND cytologies were also found in two studies (Kresnik *et al.* 2003, de Geus-Oei *et al.* 2006). The prevalence of malignancy in the pooled population was 32% (29/92). Considering visually discernable FDG uptake within the nodules as positive, FDG PET showed 100% (29/29) sensitivity, 70% (44/63) specificity, a positive predictive value (PPV) of 60% (29/48), and a negative predictive value (NPV) of 100% (44/44) (Table 2).

False-positive findings related to the ND category in these studies included four follicular adenomas (Giovannella *et al.* 2011) and one Hürthle cell adenoma with a SUV of 4.7 (Kresnik *et al.* 2003). Four of seven follicular adenomas were FDG positive. Benign lesions, such as Hürthle cell adenoma or follicular adenoma, are known to be associated with a high SUV (Lang & Law 2011). Although positive FDG uptake needs a definitive diagnosis, the NPV of 100% indicates that negative uptake

Table 2 Test characteristics of positron emission tomography in thyroid nodules with nondiagnostic or unsatisfactory fine-needle aspiration.

Ref.	No. of patients	Sex (M/F)	Age in years, mean (range)	No. of repeat FNAs	Histology (no. of patients)			Size (mm)	SUV (range)	Visual assessment (no. of patients)				Sensitivity/ specificity/ PPV/NPV (%)
					Malignant	Benign								
							TP			FP	TN	FN		
Giovanella et al. (2011)	88	27/61	18–79	1	18 PTC 9 FTC 1 DLBCL 1 PDC	59	–	–	29	18	41	0	100/69/62/100	
de Geus-Oei et al. (2006)	2	1/1	38–41	2	0	2	–	–	0	0	2	0	NaN/100/NaN/100	
Kresnik et al. (2003)	2	1/1	41–57	–	0	2	26–40	1.6–4.7	0	1	1	0	NaN/50/0/100	
Total	92	29/64	18–79	–	29	63	–	–	29	19	44	0	100/70/60/100	

Ref., reference; FNA, fine-needle aspiration; SUV, standardized uptake value; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; DLBCL, diffuse large B-cell lymphoma; PDC, poorly differentiated carcinoma; NaN, not a number; TP, true positive; FP, false positive; TN, true negative; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.

in a ND FNA procedure accurately excludes malignancy in thyroid nodules (Giovanella *et al.* 2011).

Atypia of undetermined significance or follicular lesions of undetermined significance and FN or suspicious for a FN The AUS and FN categories correspond to the ‘All follicular lesions’ category of the British Association – Royal College of Physicians (Agarwal & Kocjan 2009) and the ‘Indeterminate (follicular proliferation)’ category of the Italian Society of Pathology and Cytopathology – Italian Section of the International Academy of Pathology (Fadda *et al.* 2010). The AUS category, neither convincingly benign nor sufficiently atypical to be in a different category, is a heterogeneous category with a risk of malignancy of 5–10% (Baloch *et al.* 2008). Abundant follicular epithelial cells are cytological features of FNs, which include follicular adenomas, follicular carcinomas, nodular goiters, and follicular variants of papillary carcinoma (Lowhagen & Sprenger 1974). Because a follicular carcinoma cannot be distinguished from a follicular adenoma based on cytological evaluation alone (McHenry & Phitayakorn 2011), clinicians handling these cytologically indeterminate nodules face a dilemma regarding a procedure for a definitive diagnosis, usually lobectomy. Therefore, prediction of the malignant potential of indeterminate thyroid nodules prior to surgery would be valuable.

Seven previous studies have evaluated the usefulness of FDG PET for the differentiation of indeterminate nodules of the thyroid, yielding conflicting results (Kresnik *et al.* 2003, de Geus-Oei *et al.* 2006, Kim *et al.* 2007, Sebastianes *et al.* 2007, Hales *et al.* 2008, Traugott *et al.* 2010, Deandreis *et al.* 2012). The sensitivity of FDG PET was 57–100%, depending on the characteristics of the patient population.

Table 3 summarizes data of 276 patients with AUS or FNs, 114 patients with AUS (de Geus-Oei *et al.* 2006, Hales *et al.* 2008, Traugott *et al.* 2010), 136 with FNs (Kresnik *et al.* 2003, Kim *et al.* 2007, Sebastianes *et al.* 2007), and 27 with AUS or FNs (Deandreis *et al.* 2012). Ten patients who refused surgery (Kim *et al.* 2007), four with ND specimens (Kresnik *et al.* 2003, de Geus-Oei *et al.* 2006), and six with malignancies were excluded from the analysis (Kresnik *et al.* 2003). Of the 277 nodules from 276 patients, 81 (29.4%) were confirmed to be malignant by final histopathology. Results of FDG PET were considered positive when uptake was higher than the normal thyroid background. In this analysis, there were 71 true positives, 93 false positives, 99 true negatives, and 14 false negatives.

Table 3 Test characteristics of positron emission tomography in thyroid nodules with atypia of undetermined significance or follicular lesions of undetermined significance, follicular neoplasms, and fine-needle aspirations suspicious for a follicular neoplasm.

Ref.	No. of patients	Sex (M/F)	Age (range)	FNA	Histology (no. of nodules)			SUV, median (range)			Visual assessment (no. of nodules)			Sensitivity/ specificity/ PPV/NPV (%)	
					Malignant	Benign	Size (cm)	Malignant	Benign	P	Positive		Negative		
											TP	FP			TN
de Geus-Oei et al. (2006)	42	2/40	24–77	42 FNs	2 PTCs 3 FTCs 1 PTC	36	–	3.8 (0.9–20.4)	–	–	6	13	23	0	100/64/32/100
Kresnik et al. (2003)	35	7/28	25–84	35 FNs	5 PTCs 3 FTCs 2 ATCs	25	0.7–6	2.9 (2.2–9.3)	1.9 (0.9–9.4)	0.0130	10	9	16	0	100/64/53/100
Deandreis et al. (2012)	55	13/42	18–83	27 AUS and FNs 6 AUS 23 FNs	7 PTCs	34	1–5.7	4.3 (1.3–55.3)	3.1 (1.3–11.2)	0.0011	17	13	21	5	77/62/57/81
Hales et al. (2008)	15	1/14	22–70	15 FNs	3 FTCs 12 TUMPs 4 PTCs	8	–	2.3 (1.5–7.4)	3.4 (1.5–7.4)	0.7282	4	4	4	3	57/50/50/43
Kim et al. (2007)	36	5/31	25–73	36 FNs	3 FVPTCs 11 FTCs 2 FVPTCs	21	1–9	2.6 (0.9–15.0)	2.5 (1.2–16.2)	0.8348	15	21	0	0	100/0/42/NE
Sebastianes et al. (2007)	42	4/38	18–80	42 AUS and FNs	2 HCCs 8 PTCs	31	0.4–8.5	7.4 (3.8–46.5)	4.1 (0–77.5)	0.069	11	19	12	0	100/39/37/100
Traugott et al. (2010)	51	10/41	22–69	51 AUS and FNs	2 FTCs 1 WDC 5 FVPTCs	41	0.5–5	–	–	–	8	14	23	6	57/62/36/79
Total	276	42/234	18–84	151 FNs 6 AUS 120 AUS and FNs	6 PTCs 2 FTCs 1 HCC 81	196					71	93	99	14	84/52/43/88

Ref., reference; FNA, fine-needle aspiration; SUV, standardized uptake value; PTC, papillary thyroid cancer; FVPTC, follicular variant papillary thyroid cancer; HCC, Hürthle cell carcinoma; ATC, anaplastic thyroid cancer; FTC, follicular thyroid cancer; WDC, well-differentiated carcinoma; TUMP, tumors of uncertain malignant potential; TP, true positive; FP, false positive; TN, true negative; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.

The sensitivity, specificity, PPV, and NPV of PET in the detection of malignancy were 84, 52, 43, and 88% respectively. Differences in SUV between malignant and benign nodules were statistically significant in only two studies ($P=0.0130$ and 0.0011) (Kresnik *et al.* 2003, Deandreis *et al.* 2012), while a significant overlap was observed in most of the studies.

Among 14 false negatives, 5 (0.3, 0.4, 0.7, 0.8, and 0.9 cm) of 6 (Traugott *et al.* 2010) and 1 (0.1 cm) of 3 (Hales *et al.* 2008) were smaller than 1 cm. Although Sebastianes *et al.* (2007) reported that nodule diameter was not related to SUV, Kim *et al.* (2007) found a significant correlation between SUV and maximum nodule diameter. Sensitivity and specificity were increased for nodules larger than 1 cm (Traugott *et al.* 2010). This may be due to partial volume effects related to the limited resolution of PET scanners (Vriens *et al.* 2011).

In this analysis, of the 164 positive findings, only 43.3% (71/164) were true positives. For the 93 patients with false-positive findings, surgery was unnecessary if the diagnosis was established preoperatively. Hürthle cell adenomas had SUVs in the malignant range and tended to accumulate more FDG than did carcinomas (Kresnik *et al.* 2003, de Geus-Oei *et al.* 2006, Kim *et al.* 2007). Although the numbers of patients were too small for statistical significance to be reached, the SUVs for follicular carcinomas were lower than those for other subtypes of thyroid carcinoma (Kim *et al.* 2007).

The NPV of 88% means that exclusion of malignancy is helpful for nodules without FDG uptake. Although the possibility of malignancy should be considered for thyroid nodules without FDG uptake, PET can help select patients who need surgery. However, given the 14 false negatives, 16.5% (14/85) of the cancers would have been missed if the decision regarding surgery had been based on FDG PET results.

Controversies over the routine clinical use of FDG PET in patients with indeterminate nodules are reflected in the ATA guidelines, which recommend neither its use nor nonuse (American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer *et al.* 2009). Based on visual assessment of FDG uptake, the sensitivity and specificity of PET were 100 and 70% respectively for the ND category and 84 and 52% respectively for the AUS or FN category. Although the role of FDG PET remains unclear, negative FDG uptake might be helpful to rule out surgery. Further studies of FDG PET according to the TBSRTC categories are needed.

Prediction of prognosis by FDG PET in patients with DTCs

The prognostic value of FDG PET in lung, esophageal, and gastric cancers has been demonstrated (Al-Sarraf *et al.* 2008, Hyun *et al.* 2010, Park *et al.* 2012). Jeong *et al.* (2006b) reported that the SUV of thyroid cancer alone is not predictive of the presence of EE, lymphatic metastasis, or the multiplicity of thyroid cancer. Although no studies have evaluated the association between prognosis and FDG uptake, several support the hypothesis that FDG PET before surgery has prognostic value in DTCs. FDG avidity in recurrent thyroid cancer is known to be a predictor of poor prognosis, while the value of FDG uptake in preoperative risk stratification remains controversial (Bogsrud *et al.* 2011).

Yun *et al.* (2010) reported that visual FDG positivity is a potential new risk factor that may be useful for preoperative risk stratification. Gender, age, and tumor size each showed a correlation with either EE or central LN involvement, while visually discernible FDG uptake was associated with a higher prevalence of EE and central LN involvement.

Thyroid cancers that are incidentally detected by FDG PET are histologically proven and exhibit positive FDG uptake. Are *et al.* (2007) reported that incidental thyroid cancer has a higher rate of EE and tends to have more aggressive histological features. Of 21 PTCs (52.4%), 11 were tall-cell variants in their study. Also, FDG-avid primary thyroid tumors are known to be not only larger, but also more aggressive, with a higher frequency of tumor bilaterality compared with non-FDG-avid tumors (Law & Lang 2011).

DTCs with negative FDG uptake are smaller and less frequently have EE and lymphovascular invasion and tend to have a better prognosis (Choi *et al.* 2011a). In other words, positive FDG uptake is associated with the presence of EE and lymphovascular invasion and a tendency to a poor prognosis.

A significant relationship between SUV and LN metastasis in PTC was reported (Kaida *et al.* 2011). The protein kinase B (AKT)/phosphatidylinositol-3-kinase (PI3K) signaling pathway is associated with angiogenesis mediated by vascular endothelial growth factor, which causes LN metastasis (Pandya *et al.* 2006). Therefore, the SUV in thyroid cancer may be related to the AKT/PI3K signaling pathway through the expression of GLUT4, which reflects tumor progression (Kaida *et al.* 2011).

DTCs with negative FDG uptake imply less aggressive characteristics and a better prognosis (Choi *et al.* 2011a). Therefore, FDG PET scans before surgery may be useful for the prediction of the prognosis of DTCs.

To date, the usefulness of PET in DTCs prior to surgery has been disappointing; however, the technique does show promise. If PET cannot be performed in all patients with thyroid cancer, further studies to select a group of patients who can get additional benefit from PET are required. PET using new radiopharmaceuticals has not yet been fully evaluated. The clinical advantage of PET using ^{124}I is the generation of information regarding lesional dosimetry for ^{131}I treatment (Lassmann *et al.* 2010). However, more research is needed to develop other radiopharmaceuticals that are complementary to FDG. Improved diagnostic performance has been reported under TSH stimulation induced by discontinuation of thyroxine treatment or injection of recombinant human TSH (Ma *et al.* 2010). Increased expression of GLUT in malignant cells is induced by TSH stimulation (Ma *et al.* 2010). However, the association of TSH level with FDG PET before surgery remains controversial. A study to evaluate the influence of TSH on FDG uptake is needed. Tyrosine kinase inhibitor (TKI) therapy has shown favorable responses in DTCs (Carr *et al.* 2010). PET may facilitate response monitoring in patients treated with TKIs. Due to the growing interest in combining functional imaging with the knowledge of cancer genetics, PET may provide further information regarding the biology of thyroid cancer, enabling personalized management of thyroid cancer based on its molecular characterization.

Conclusion

Routine use of FDG PET scans before DTC surgery has not been advocated in previous reports. However, controversies regarding the use of FDG PET remain. PET does not provide information additional to that yielded by US for the preoperative assessment of thyroid cancer and is associated with greater expense and radiation burden. Although FDG PET facilitates the selection of indeterminate nodules that require resection, these can be missed if the surgical decision is based on FDG PET results. The metabolic mechanisms of FDG uptake in thyroid cancer might be key information for the evaluation of the value of PET. Factors associated with FDG positivity are associated with a poor prognosis; therefore, FDG PET scans before surgery may be useful for the prediction of the prognosis of DTCs.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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