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Review

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Incidental thyroid uptake on PET scanning: epidemiology, clinical significance, and management challenge

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Abstract

Incidental lesions of the thyroid are increasingly discovered as the prevalence of medical imaging escalates. The likelihood of malignancy must be assessed for each of these incidentalomas. The utility of the metabolic data derived from the identification of these lesions on PET/CT imaging is unclear. The overall rate of detection of thyroid incidentalomas on PET/CT is estimated at 1.5%-4.2%. However, this rate varies by the pattern of uptake. Several studies have evaluated predictive measures such as maximal standardized uptake value (SUV_{max}) and radiomics. However, no definitive conclusion has been reached. Given that the majority of PET/CT scans are performed in the context of malignancy, we recommend first assessing the general condition and life expectancy of patients when PET-detected thyroid incidentalomas are unveiled. We also recommend considering observation versus diagnostic workup with further imaging and/or fine-needle aspiration and cytology.

Keywords: PEToma, PET-detected thyroid incidentaloma, PET-associated incidental neoplasm

INTRODUCTION

The relatively rapid development and diffusion of medical imaging technology have afforded tremendous benefits in the non-invasive evaluation of many benign and malignant lesions. Most forms of diagnostic imaging showed a growth rate of 2- to 6-fold between 2000 and 2016 in both the United States and Ontario, Canada[1], a trend expected worldwide. Imaging studies may be performed for a multitude of reasons, such as screening, staging, or surveillance of cancerous and noncancerous diagnoses. While studies may be undertaken for a specific and targeted purpose, the possibility of unveiling incidental lesions cannot be ignored. The likelihood of revealing an incidental finding varies substantially (< 5% to 22%) depending on the chosen imaging modality[2].

The primary concern of an incidentally discovered lesion, commonly termed an *incidentaloma*, relates to the associated risk of malignancy. While all imaging modalities may unveil incidentalomas, the metabolic data afforded by functional imaging such as ^{18}F-FDG PET/CT may provide further information to decipher the clinical relevance of such lesions. ^{18}F-FDG is a glucose analog that shows uptake levels corresponding to glycolysis rates and glucose consumption. It is frequently elevated in cancerous tissues due to inefficient aerobic glycolysis (termed the Warburg effect)[3]. Physiologic FDG uptake is reported in brown fat, skeletal muscle, lymphoid tissue, and the thymus[4]. Multiple benign etiologies, primarily inflammatory or infectious in origin, may also exhibit uptake due to increased rates of glucose metabolism[5,6]. Studies reveal a 1.2%-1.7% overall detection rate of unexpected malignancies or premalignant lesions in patients undergoing PET/CT evaluation[7,8].

Furthermore, second primary malignancies were described in 4.1%-8.5% of PET/CT scans completed for staging or surveillance purposes[8-10]. Interestingly, some studies describe a higher likelihood of incidentalomas in patients undergoing PET/CT for screening purposes (3.0%-3.1%) compared to the evaluation of known or suspected cancer (1.9%-2.3%)[11,12]. Given the estimated 2 million PET/CT scans performed annually in the United States, these small fractions add up to a significant number of lesions that must be addressed.

Incidentally discovered lesions in the thyroid are uncovered in 21%-34% of ultrasound examinations[13-15] and 16% of CT or MRI scans[16,17]. Among these lesions, the risk of malignancy is reported to range from 1.5%-11%[18,19]. On PET scans, the thyroid gland exhibits very low physiologic FDG avidity. However this is typically less than the background blood pool and is usually not clearly visualized on the whole-body fusion PET/CT images[5], which aligns with the observation that the primary energy substrate for the thyroid is free fatty acids[20,21]. In contrast, oncocytic/Hürthle cell lesions (both benign and malignant) are known to exhibit FDG-avidity due to an intrinsic mitochondrial defect that results in inefficient glycolytic metabolism[22,23]. In addition, thyroid malignancies, such as papillary, follicular, and anaplastic carcinomas and thyroid lymphoma, may also be expected to exhibit increased FDG uptake due to increased glucose metabolism.

Incidental FDG-avid uptake in the thyroid gland exists in two predominant patterns - focal and diffuse. The overall detection rate of thyroid incidentalomas on PET/CT, irrespective of uptake patterns, is estimated at 1.5%-4.2%[8,18,24-36]. Most reports attribute a risk of malignancy of 5.1%-22.0% of these PET-detected thyroid incidentalomas[8,28,31,33,35], notably higher than those detected by ultrasound or CT[37]. Similar rates of thyroid incidentaloma detection and associated malignancy are noted amongst those undergoing surveillance of a known cancer and the general population undergoing screening with PET/CT[38].

In this review, we will first discuss the abnormal patterns of FDG uptake in the thyroid gland and the associated risk of cancer, and the types of cancers diagnosed. Next, we will describe specific imaging features

and their ability to discriminate benign from malignant disease, together with related mutational analysis findings. Finally, we will provide recommendations for the evaluation and management of thyroid incidentalomas.

PATTERNS OF FDG UPTAKE IN THE THYROID GLAND

Lesions incidentally detected on PET/CT imaging may be referred to as PET-associated incidental neoplasms[39]. Within the thyroid, FDG uptake has been described in focal and diffuse patterns or combinations thereof. In general, lesions are designated as focal when the focus of uptake comprises less than one lobe of the thyroid, although such lesions may be multifocal and thus occur bilaterally. The term diffuse is applied when homogenous uptake is identified. Diffuse-plus-focal uptake has been described as focal lesions overlying a background of diffuse uptake. Table 1 describes the incidence of thyroid incidentalomas noted in selected references along with the absolute numbers of malignancies diagnosed. Unfortunately, it is impossible to determine the true rate of malignancy in this population as a significant proportion of patients do not undergo further investigation due to their underlying disease status.

Focal FDG uptake (see example, Figure 1)

Focal thyroid uptake is defined as FDG avidity occurring in less than one lobe of the thyroid gland[24], for which we suggested the term PEToma[18]. The prevalence of such lesions is reported in approximately 0.5%-2.5% of PET/CT imaging studies[18,24-27,29,30,32,33,35,36,46]. Most of these studies describe a slightly higher rate of detection of focal *vs*. diffuse patterns of uptake. The malignancy risk amongst the former lesions seems to be greater, with rates ranging from 8.6%-50%[18,24-27,29,33,35,46]. In Asian countries, the rate of focal uptake has been reported to be double that of American studies, yet the rate of cancer is unchanged[31].

A retrospective study of 4726 patients (6457 FDG PET/CT scans) at our institution[18] revealed a 3.4% rate of thyroid incidentalomas (160 of 6457 PET/CT scans). Focal uptake was noted in 2.2% (103 patients), and uptake was diffuse in 1.2% (57 patients). Fifty patients with focal uptake underwent further workup with imaging and/or fine-needle aspiration and cytology (FNAC), and thyroidectomy was completed in 10 patients. Nine of the ten surgical patients were ultimately diagnosed with papillary thyroid carcinoma on final histopathology: two micropapillary carcinomas, two extrathyroidal extensions, four multifocal involvement, and one had > 50% poorly differentiated papillary thyroid carcinoma. Thirty percent of the PETomas that received a tissue diagnosis (FNAC and/or histology) were cancerous, which relates to 8.7% of all focal thyroid lesions.

Amongst countries with known iodine deficiency, the frequency of focal thyroid uptake is unexpectedly reported to be at rates lower than the average, with incidences of 1.0%-1.8%[33,48-50]. The risk of malignancy seems similar, with cancers reported in 23%-59% of patients[51], and iodine supplementation programs have done little to change these rates[26].

Diffuse FDG uptake (see example, Figure 2)

Diffuse FDG uptake is reported in most studies at slightly lower rates than focal uptake. However, it was studied in Japan much earlier, more than two decades ago. Yasuda *et al.*[52] investigated 1102 healthy subjects using the ^{18}F-FDG PET scan, and they detected diffuse FDG thyroidal uptake in 36 (3.26%), only one of whom was found to have hypothyroidism. Furthermore, antithyroid antibodies were positive in 27 subjects, which led these authors to conclude that diffuse thyroidal FDG uptake may be an indicator of chronic thyroiditis.

Table 1. Incidence and malignancy in PET-detected thyroid incidentalomas

Authors	Country	#PET/CT scans	Incidence				Malignancy		
			Cumulative	Focal	Diffuse	Diffuse + focal	Focal	Diffuse	Diffuse + focal
Ceriani *et al.*[25]	Switzerland	12,652	333 (2.6%)	187 (1.5%)	146 (1.2%)	-	30	-	-
Beck *et al.*[40]	USA	35,124	-	227 (0.6%)	-	-	59	-	-
Kim *et al.*[41]	Korea	39,098*	-	-	635 (1.6%)	-	-	-	-
Gedberg *et al.*[26]	Denmark	2451	-	59 (2.4%)	-	-	10	-	-
Pattison *et al.*[32]	Australia	45,680	-	500 (1.1%)	-	-	-	-	-
Ozderya *et al.*[42]	Turkey	6873	138 (2.0%)	135 (2.0%)	3 (0.04%)	-	27	-	-
Makis *et al.*[43]	Canada	7252	-	157 (2.2%)	-	-	14	-	-
Sencan Eren *et al.*[35]†	Turkey	4204	178 (4.2%)	68 (1.6%)	35 (0.8%)	13 (0.3%)	11	-	4
Kim *et al.*[24]	Korea	18,172	-	358 (2.0%)	-	-	51	-	-
Chun *et al.*[29]	Korea	2584	-	52 (2.0%)	-	-	15	-	-
Jamsek *et al.*[36]	Slovenia	5911	230 (3.9%)	148 (2.5%)	82 (1.4%)	-	10	-	-
Brindle *et al.*[33]	UK	7221	156 (2.2%)	81 (1.1%)	75 (1.0%)	-	7	1	-
Lee *et al.*[30]	Korea	2368	-	64 (2.7%)	-	-	11	-	-
Nishimori *et al.*[18]	Canada	6457	160 (2.5%)	103 (1.6%)	57 (0.9%)	-	9	0	-
Kang *et al.*[44]	Korea	12,840*	1151 (9.0%)	612 (4.8%)	539 (4.2%)	-	55	2	-
Chen *et al.*[45]	USA	2594	99 (3.8%)	53 (2.0%)	46 (1.8%)	-	7	0	-
Karantanis *et al.*[34]	USA	4732	-	-	138 (2.9%)	-	-	0	-
Kurata *et al.*[46]	Japan	1626	-	-	25 (1.5%)	4 (0.24%)	-	1	2
Choi *et al.*[16]	Korea	1763	-	65 (3.7%)	-	5 (0.28%)	18	-	0
Nockel *et al.*[47]† DOTATATE	USA	237	26 (11.0%)	14 (5.9%)	12 (5.1%)	-	3	0	-

#Number of PET/CT scans. *Study population included PET/CT scans completed for screening/preventative measures. †Prospective study.

In a review of eight studies, the frequency of diffuse FDG uptake ranged from 0.1%-4.5%, with a mean of 1.9%[11,38,44,45,48,53-55]. Contemporary studies con similar to Yasuda *et al.*[52], namely that the diffuse uptake pattern is an indication of benign disease[34,37,46], predominantly attributed to inflammatory or autoimmune forms of thyroiditis such as Hashimoto's thyroiditis. Of note, only 10% of patients with these conditions exhibit diffuse FDG uptake on PET scan[56], and studies report chronic thyroiditis as the etiology of diffuse uptake in 47%-100% of patients[34,45,54]. Furthermore, there is no apparent relationship between serum TSH levels and diffuse FDG avidity in patients diagnosed with thyroiditis, and thyroid hormone replacement seems to have no effect on patterns of uptake[34,57]. The afore-mentioned studies were cross-sectional so that any impact of incidentally identified diffuse uptake on subsequent thyroid dysfunction was unclear. Kim *et al.*[41] did a cross-sectional and longitudinal study on 39,098 subjects undergoing comprehensive health examinations. At baseline, the prevalence of diffuse thyroidal FDG uptake was 1.6%. During 104,261.4 person-years of follow-up, 102 incident hypothyroid cases and 172 hyperthyroid cases were identified. The multivariable-adjusted HR for incident hypothyroidism and hyperthyroidism (comparing diffuse uptake to no uptake) were 15.72 and 7.38, respectively. Thus, euthyroid patients identified with diffuse thyroid uptake on PET scan should be regarded as being at risk for future development of thyroid

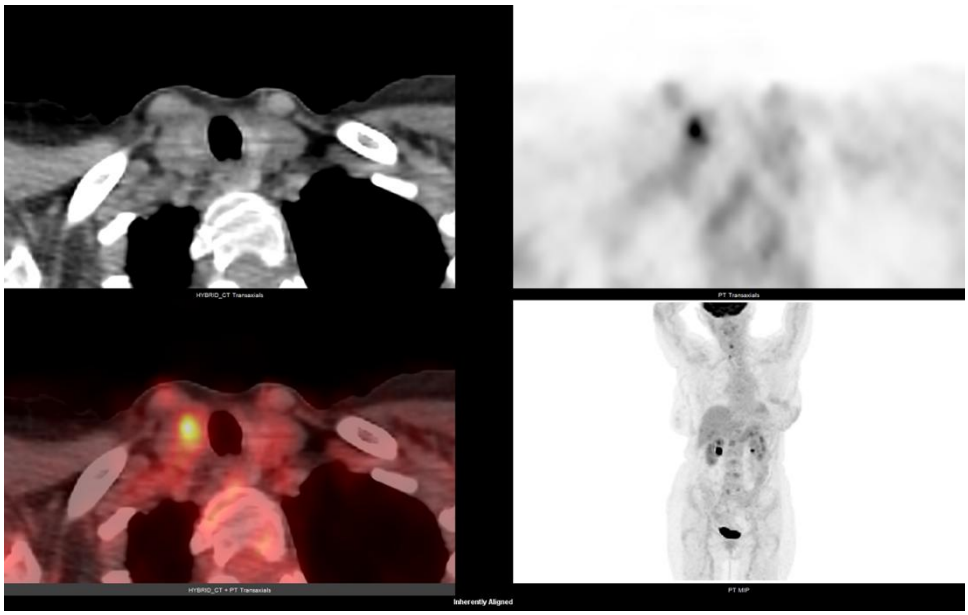

Figure 1. This is a case of focal thyroid FDG uptake in a 79-year-old female who underwent PET scanning for known laryngeal cancer. This revealed a 1.1 cm thyroid lesion in the right lower thyroid pole, SUV 6.0.

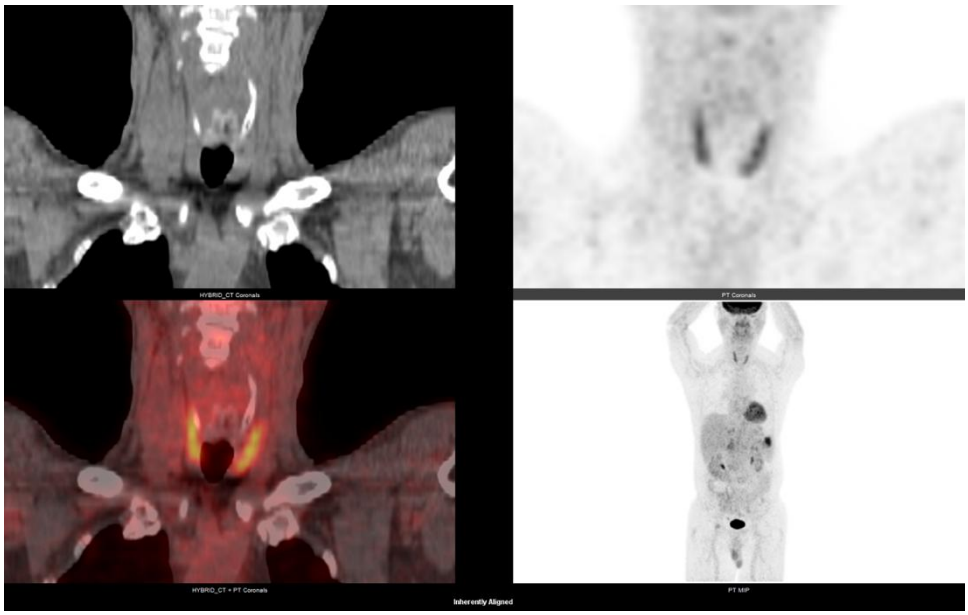

Figure 2. This is a case of mild diffuse FDG uptake throughout the thyroid with SUV 3.7 in a patient undergoing PET scanning for known metastatic sarcoma.

dysfunction and should be followed up. One of the major limitations of this paper is that 93.4% of the participants were male.

Of note, Kim *et al.*[58] selected for study 290 women with breast cancer who had undergone PET-CT scans before and after breast surgery and diffuse thyroidal uptake developed in 23 (9.3%) patients. Radiotherapy in breast cancer was found to be an independent predictive factor for the development of new diffuse thyroidal

uptake. Similar observations on the impact of radiotherapy on the emergence of the diffuse thyroidal uptake were made by Hassan *et al.*[27].

The risk of malignancy in patients found to have diffuse thyroidal uptake on PET scan is very low, with a quoted range of 0.6%-3.5% in the literature[5,57]. In a recent systematic analysis of 26 published articles encompassing 2255 cases, only one patient of differentiated thyroid cancer without thyroiditis displayed a diffuse thyroidal uptake. While in 4 other cases, differentiated thyroid cancer was present alongside thyroiditis. In addition, primary thyroid lymphoma was diagnosed in 10 cases[5].

Diffuse-plus-focal FDG uptake (see example, Figure 3)

Diffuse-plus-focal uptake describes the simultaneous occurrence of 1 or more focal FDG-avid thyroid lesions on a background of diffuse uptake, which was first described in 2006 by Choi *et al.*[16], who identified and reported this FDG thyroidal uptake variant in five patients among their 1763 subjects, yielding a prevalence of 0.28%. None of these 5 patients had malignancy, while three patients were judged to have chronic thyroiditis based on pathology (n = 2) and ultrasound imaging (n = 1). The preliminary conclusion was that a diffuse-plus-focal ^{18}FDG uptake pattern might have the same clinical significance as a diffuse pattern.

Kurata *et al.*[46] studied 1626 subjects who underwent PET scanning and unveiled 4 patients exhibiting the diffuse-plus-focal uptake (prevalence 0.24%). Two patients were confirmed to have papillary thyroid carcinoma associated with Hashimoto's thyroiditis, while the other two had adenomatous goiter associated with Hashimoto's thyroiditis. More recently, Sencan Eren *et al.*[35] published the results of their prospective study of 4202 patients, uncovering this diffuse-plus-focal pattern in 13 (prevalence 0.309%). Twelve of the latter group had adequate investigations allowing the recognition of malignancy in four (33.3%).

Thus, we presently have limited published data on this group of patients with simultaneous focal and diffuse uptake. However, it would appear that the diffuse component here is most often attributable to benign entities, especially chronic lymphocytic thyroiditis. The underlying pathology of the focal component would appear to be more heterogeneous, including benign Hashimoto's thyroiditis, adenomatous goiter and thyroid malignancy. It is well-established that the thyroid parenchyma is diffusely heterogenous in Hashimoto's thyroiditis, and formation of focal lymphocytic thyroiditis nodule may occur in some patients[59,60]. This schema may have been operative in the five patients of Choi *et al.*[16]. On the other hand, the findings of Kurata *et al.*[46] and Sencan Eren *et al.*[35] underscore the increased risk for malignancy in this subset of patients with diffuse-plus-focal uptake. Further data are needed for proper management guidance. But meanwhile, it is our view that patients with the diffuse-plus-focal uptake should be investigated in a manner similar to patients with focal uptake.

Progression of focal to diffuse thyroid uptake

This entity is extremely rare, having been described in a single case report, but is very challenging in need to differentiate malignant metastatic disease from benign thyroiditis. Thuillier *et al.*[61] reported the case of a 49-year-old man presenting with cerebral metastasis of unknown primary, and the ^{18}F-FDG PET/CT scan disclosed an incidental left focal thyroid uptake, while the thyroid ultrasound was considered consistent with thyroiditis. Upon the diagnosis of lung adenocarcinoma, pembrolizumab treatment was initiated. A follow-up PET/CT scan revealed the progression of focal thyroid uptake to an intense diffuse uptake (SUV_{max} 18.2). A fine-needle aspiration biopsy of the thyroid parenchyma indicated a diffuse involvement from lung adenocarcinoma.

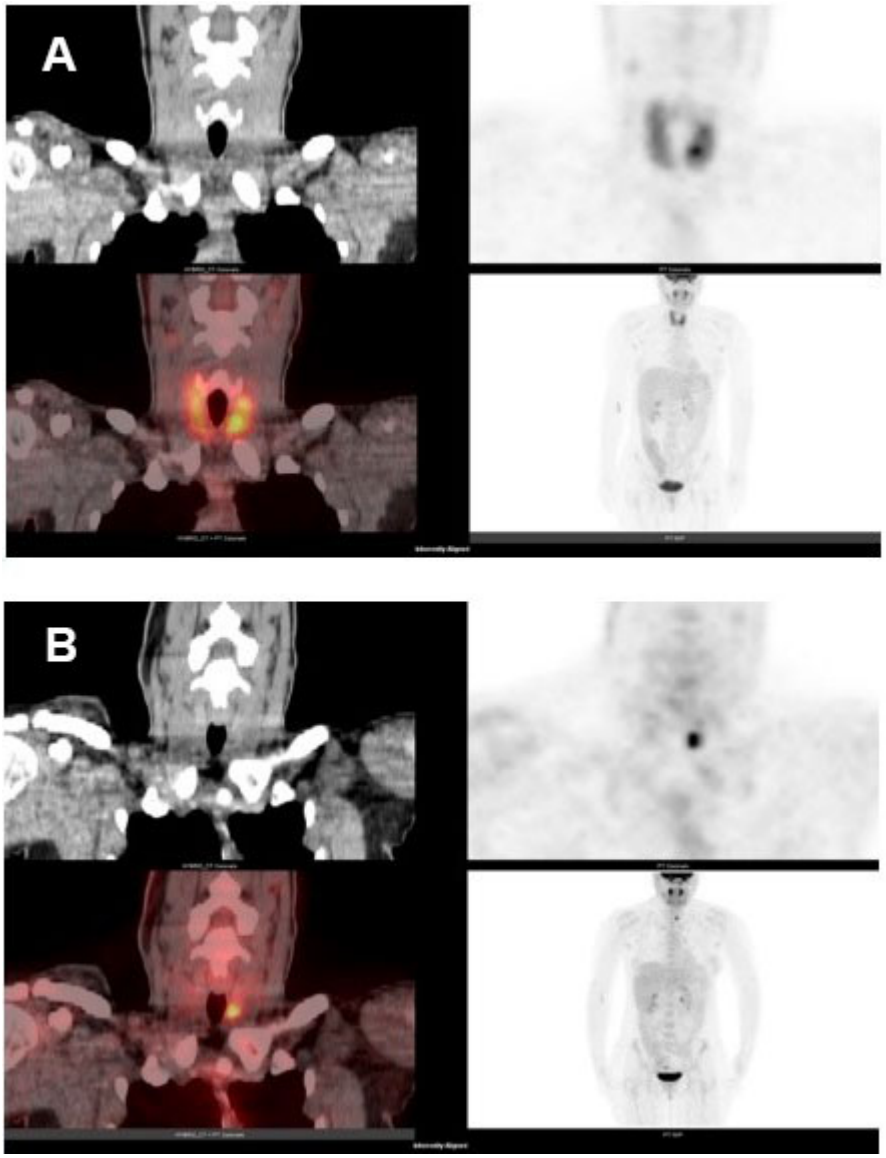

Figure 3. This is a case of diffuse-plus-focal FDG uptake transitioned to focal uptake in a patient with Stage III melanoma. (A) Diffuse-plus-focal FDG uptake (diffuse SUV 8.4, focal SUV 12.8) in the thyroid during treatment with interferon therapy resulting in induced primary hypothyroidism treated with I-T4. (B) FDG uptake regressed after treatment of thyroiditis to a focal area of increased uptake in the left thyroid lobe, SUV 9.8. Final pathology after total thyroidectomy showed multifocal papillary thyroid carcinoma.

Self-resolving variant

In our study of 6457 FDG-PET scans, we identified 103 patients with incidental focal thyroid uptake (PETomas), and unexpectedly 5 patients (4.9%) demonstrated self-resolution of the PETomas[18]. This phenomenon is probably overlooked, mainly because the published data on PETomas are invariably cross-sectional studies.

In a recent, detailed study of 47 patients with thyroid PETomas, Poller *et al.*[62] could not identify any specific cytological or histopathological cause in 14 (29.8%) of these lesions. The time frame between the discovery of the PEToma and the final diagnosis was not mentioned. But it is conceivable that some of the patients in this series manifested a natural history evolving towards self-resolution. The reasons underlying

this process are unknown.

Tumor types and uptake patterns

Papillary thyroid cancer accounts for nearly 90% of all cases of thyroid carcinomas[63]. Primary thyroid carcinomas would be expected to make up the majority of thyroid incidentalomas, however it is important to recognize that metastases and thyroid lymphomas have also been described. This is significant as it may prompt a change in prognosis and treatment. A meta-analysis identified 1.1% of PET-detected thyroid incidentalomas to represent metastatic disease and a 19.8% overall malignancy rate (with 15.4% representing papillary thyroid carcinoma)[64]. Metastases to the thyroid were described with solitary focal, multiple focal, and diffuse patterns of FDG avidity[65]. Table 2 includes tumor types diagnosed by either cytopathology or histopathology in studies reporting this information.

IMAGING CHARACTERISTICS

Although generally uncommon, focal thyroid incidentalomas are reported at higher frequencies than diffuse lesions, and the associated rate of malignancy is greater. Therefore, imaging characteristics, such as the magnitude of FDG uptake, have been postulated to adjust for malignancy risk.

Standardized uptake value

Standardized uptake values (SUV) are commonly reported to quantify the magnitude of FDG uptake on PET/CT. Several studies have evaluated the ability of SUV_{max} to discriminate malignant from benign thyroid incidentalomas with conflicting conclusions (see Table 3). Mitchell *et al.*[66] reported that using a SUV_{max} cutoff value of 5.0 resulted in 60% sensitivity and 91% specificity for detection of malignancy, while Boeckmann *et al.*[67] proposed a cutoff value of 4.2. Some reports noted a significant difference in SUV_{max} between malignant and benign lesions (albeit frequently with substantial overlap), while others showed no difference at all. Recall that benign and malignant oncocytic/Hürthle cell lesions are known to exhibit high FDG-avidity due to an intrinsic mitochondrial defect resulting in inefficient glucose metabolism[22,23].

Small tumors, including many thyroid incidentalomas, may not be accurately quantified on PET imaging due to the partial-volume effect[68]. It is generally thought that the limit of resolution for PET/CT uptake is 5-8 mm, although the partial volume effect may impact SUV values in lesions measuring 2 to 3 times the spatial resolution. Measures such as metabolic tumor volume (MTV) have attempted to correct for this limitation by accounting for volume, which may allow greater accuracy in the assessment of metabolic activity and thus the risk of malignancy. Unfortunately, data regarding these parameters remains inconclusive in their ability to discriminate benign from malignant thyroid incidentalomas. A study by Ceriani *et al.*[25] evaluated functional PET-derived measures and found that malignant lesions had significantly higher values of MTV, total lesion glycolysis (TLG = MTV × SUV_{mean}), SUV_{max}, SUV_{mean}, and SUV_{peak}. Of these, TLG was the most useful parameter as it correctly identified 79% of lesions (univariate logistic regression, $P < 0.0001$).

The study by Ceriani *et al.*[25] also employed radiomic analysis of these lesions, using quantitative data from medical imaging to glean additional information such as shape and texture analysis. A multivariate stepwise logistic regression analysis found that TLG, SUV_{max}, and shape sphericity remained significant ($P < 0.0001$). All triple-positive tumors were found to be malignant, while 93% of triple-negative lesions were benign. A recent study by Aksu *et al.*[69] supports these findings with the development of a predictive model combining SUV_{max} and a radionomic parameter noted as $GLRLM_{RLNU}$. GLRLM describes heterogeneity of the lesion and was found to have the highest AUC value on ROC analysis. The resulting model was found to have a sensitivity and specificity of 75% and 81.8%, respectively. Other studies support the utility of these measures

Table 2. Types of malignancies diagnosed in PET-detected thyroid incidentalomas by pattern of uptake

Authors	#PET/CT scans	FDG uptake pattern	Differentiated	Medullary	Anaplastic	Lymphoma	Metastasis
Ceriani *et al.*[25]	12,652	Focal	24	1	1	1	3 (sarcoma, renal, esophageal)
Beck *et al.*[40]	35,124	Focal	48	0	0	2	9
Gedberg *et al.*[26]	2451	Focal	9	1	0	0	0
Ozderya *et al.*[42]	6873	Focal	23	1	0	0	3 (lung 2, esophagus)
Makis *et al.*[43]	7252	Focal	12	0	0	1	1 (renal)
Kim *et al.*[24]	18,172	Focal	51	0	0	0	0
Chun *et al.*[29]	2584	Focal	14	0	0	0	1 (SCC esophagus)
Brindle *et al.*[33]	7221	Focal	6	0	0	1	0
Lee *et al.*[30]	2368	Focal	8	0	1	0	2 (melanoma, adenocarcinoma)
Nishimori *et al.*[18]	6457	Focal	9	0	0	0	0
Chen *et al.*[45]	2594	Focal	5	0	0	0	2 (H&N SCC, NHL)
Ishimori *et al.*[8]	1912	Diffuse	6	0	0	0	0
Kurata *et al.*[46]	1626	Diffuse Diffuse + focal	1 2	0 0	0 0	0 0	0 0
Choi *et al.*[16]	1763	Focal	16	0	0	1	1 (esophageal SCC)
Cumulative	101,797		234	3	2	6	22

#Number of PET/CT scans.

Table 3. SUV_{max} values in benign versus malignant PET-detected thyroid incidentalomas

Authors	Benign SUV_{max}	Malignant SUV_{max}	*P* value
Ceriani *et al.*[25]	6.71	10.81	0.0146[a]
Ozderya *et al.*[42]	6.1	11.3	0.01[a]
Sencan Eren *et al.*[35]	4.6	8.8	< 0.05
Chun *et al.*[29]	2.8	4.7	0.001
Brindle *et al.*[33]	5.4	9.9	< 0.05[a]
Lee *et al.*[30]	3.62	5.47	0.126
Nishimori *et al.*[18]	5.2	5.8	0.36
Kang *et al.*[44]	3.56	6.32	< 0.05
Chen *et al.*[45]	2.9	4.0	> 0.05
Choi *et al.*[16]	6.7	10.7	< 0.05

Due to heterogeneity of reported data (mean, median, range, SD), SUV_{max} values are expressed as mean or median alone with median indicated by [a].

to predict malignancy[31,70-72]. In opposition, other studies have shown no significant relationship between these indices and malignancy risk[73-76]. For now, the limited availability of these assessments may preclude the practical application of these parameters.

Alternative radiotracer imaging

FDG-PET/CT imaging accounts for most PET-identified thyroid incidentalomas, but this is increasingly recognized on other forms of functional imaging such as ^{68}Ga-DOTATATE, ^{68}Ga PSMA, and ^{18}F- or ^{11}C-choline PET/CT scans.

^{68}Ga-DOTA PET/CT imaging is evolving as a method to evaluate and monitor neuroendocrine tumors expressing somatostatin receptors with a sensitivity and specificity as high as 96% and 100%, respectively[77,78]. Multiple ^{68}Ga-DOTA peptides have been studied that have a variable affinity for somatostatin receptor subtypes[79]. ^{68}Ga- and ^{64}Cu-DOTATATE are currently the only peptides clinically approved by the FDA in the USA for PET imaging. Physiologic uptake has been noted in the pituitary, thyroid, spleen, liver, adrenal glands, head of the pancreas, and urinary tract[80]. Normal thyroid tissue expressed somatostatin transmembrane receptors (SSTR), typically resulting in very low, diffuse uptake[78]. High *SSTR2* expression has been noted in differentiated thyroid cancers and benign thyroid conditions[81], but it is unclear if this uptake pattern varies from baseline physiologic uptake. Furthermore, activated lymphocytes are known to express SSTR. Thus benign inflammatory conditions such as thyroiditis, trauma, or surgery may induce abnormal uptake[80]. Importantly, medullary thyroid cancers would be expected to be highlighted on ^{68}Ga-DOTATATE PET/CTs. However low or variable *SSTR* expression may give false-negative results[80]. These scans are also subject to spatial resolution limitations. Studies have shown a 4.1%-11% rate of detection of thyroid incidentalomas on this imaging[47,82], with an average of 2.6% (0.5%-2.9%) showing diffuse uptake. A study by Nockel *et al.*[47] evaluated 237 ^{68}Ga-DOTATATE scans to assess the uptake patterns in the thyroid gland. Abnormal thyroid uptake was noted in 11% (26 of 237), with 14 displaying focal uptake and 12 with a diffuse pattern. Three of the focal lesions were found to be differentiated thyroid cancers (21.4% of focal incidentalomas). No significant difference was noted in SUV_{max} values between benign and malignant lesions.

A recent study by Kohlenberg *et al.*[83] assessed thyroid lesions with focal ^{68}Ga-DOTATATE PET/CT uptake, which was detected in 4.9% of scans (94 of 1927). Notably, four patients were imaged for the staging of a known medullary thyroid cancer. Five patients (one multifocal) were diagnosed with medullary thyroid cancer, one of which was discovered incidentally due to this imaging. As expected, the baseline calcitonin levels were quite elevated in MTC patients (median 1156 pg/mL), while this data was limited in other patients. The 2015 American Thyroid Association guidelines do not recommend assessment of calcitonin in patients with thyroid nodules; however it certainly seems reasonable to consider it in patients with ^{68}Ga-DOTATATE avidity. In addition to commonly reported semiquantitative measures of PET avidity such as SUV_{max}, focal thyroid lesions were also graded relative to normal tissues as internal controls. Two-thirds of MTC nodules were found to have relative ^{68}Ga-DOTATATE avidity greater than that of the liver, which has previously been proposed as a favorable target for peptide receptor radionuclide therapy[84].

^{68}Ga-PSMA imaging is a promising tool increasingly used to stage and monitor prostate cancer by binding prostate-specific membrane antigen (PSMA)[48]. PSMA is expressed in normal prostate epithelium and highly expressed in prostate carcinoma. Expression of *PSMA* has been identified in the neovasculature of several other solid tumor types, including thyroid carcinomas, with strong staining noted in classical PTC, follicular thyroid carcinoma, and iodine-refractory cancers. All evaluated metastatic lesions exhibited *PSMA* expression compared to only 67% of lymph node metastases[85]. Furthermore, in a study of 10 patients with metastatic differentiated thyroid cancer, ^{68}Ga-PSMA PET/CT identified 30 of 32 metastatic lesions[86]. These findings may advocate for use of this imaging for evaluation of suspected metastatic disease, particularly in radioiodine-refractory tumors.

Incidental ^{68}Ga-PSMA thyroidal uptake is rare, the literature being punctuated mostly by single case reports. In a systematic review published in June 2019, Bertagna *et al.*[87] collected a total of 23 cases of PSMA thyroid incidentaloma from 12 papers. Among these 23 patients, malignancy was documented in 6:5 primary thyroid (4 papillary thyroid carcinoma, one follicular thyroid carcinoma) and one metastasis from renal cell carcinoma.

More recently, Gossili *et al.*[88] reported on their study of 341 patients with prostate cancer who had undergone ^{68}Ga-PSMA PET/CT scanning, identifying 13 patients (4%) with incidental increased thyroid uptake. The pattern of uptake was focal in seven, diffuse in five and diffuse-plus-focal in one. Malignancy was confirmed in 2 patients (2/13, 15%), and both displayed focal uptake. This paper was the subject of a commentary in *Clinical Thyroidology* by Santhanam and Cooper[89] who noted the lack of sensitivity and specificity of PSMA-based thyroid imaging but enunciated on some of the potential benefits of detecting neovasculature in advanced metastatic radioiodine refractory thyroid cancer. They also recommended further investigations in patients found to have focal thyroidal uptake on PSMA-based PET imaging, namely thyroid ultrasound and biopsy. It is very likely that the true prevalence of PSMA-PETomas is higher since the present application of this imaging modality is for prostate cancer, thereby excluding female patients who are known to have an incidence of thyroid disorders[87].

Radiolabeled choline (^{18}F or ^{11}C) is another radiopharmaceutical with utility in imaging several solid tumors[90,91], including potential for imaging parathyroid adenomas and hyperplasia[92]. Choline is a precursor to the phosphatidylcholine that comprises much of the cellular membrane and is internalized into the cell by choline kinase enzymes[93]. Increased uptake is noted in conditions with high proliferative rates. There are now reports of incidental thyroid uptake on radiolabelled choline PET/CT scans, mostly as case reports. In a retrospective analysis by Ruiz-Esponda *et al.*[94], only 30 thyroid incidentalomas were identified in a pool of 1197 radiolabelled choline PET/CT scans (2.5%). Of the 15 patients that underwent diagnostic FNAC only one malignancy was identified, indicating that incidental thyroid lesions detected by this method may have a lower likelihood of malignancy than those detected by FDG-PET/CT.

MUTATION ANALYSIS

Mutation analysis has garnered significant traction in recent years across various cancers as a method to improve the characterization of tumors and associated prognosis. *BRAF*^{V600E} is the commonest mutation encountered in adults with thyroid cancer, occurring in close to 50% of patients with papillary thyroid carcinoma[95]. Studies have shown that a *BRAF* mutation in papillary thyroid cancer is associated with worse outcomes[96,97], commonly reported as a higher stage at diagnosis and more frequent distant metastases[98]. A higher risk of death has also been described with *BRAF*-mutated thyroid cancers, on the order of 2.66-fold higher[99]. It has been reported that male gender is a robust independent risk factor for PTC-specific mortality in BRAF^{V600E} patients but not in wild-type BRAF patients[100]. Moreover, these same authors identified age-associated mortality risk in PTC as dependent on BRAF status[101]. In a study comparing PET-detected papillary thyroid cancers to conventionally detected controls, Beck *et al.*[40] described a higher rate of *BRAF* mutations in the PET-detected cohort (78% *vs.* 41%, $P = 0.05$). In this report, the PET-detected cancers were more commonly found in males (54% *vs.* 26%, $P = 0.003$) and higher stages (stage III 24% *vs.* 12%, stage IV 7% *vs.* 0%, $P = 0.05$). *BRAF*^{V600E} mutation is associated with increased expression of glucose transporters (GLUT-1) in papillary thyroid cancers[102], which may be responsible for the higher proportion of *BRAF* mutations in PET-detected cancers. In agreement with this, several studies have shown significantly higher SUV_{max} values in *BRAF*-mutated papillary thyroid cancers versus their BRAF-wild type counterparts[42,103,104].

GLUT transporter expression was also noted to be elevated in thyroid incidentalomas exhibiting loss of the oncosuppressor gene *PTEN*[105]. It was later confirmed by the same group that lack of *PTEN* expression in thyroid cancer cells was responsible for GLUT-1 upregulation and glucose uptake[106]. Aggressive, poorly differentiated thyroid cancers have higher levels of *GLUT-1* expression[20,107,108], which is the predominant isoform noted to be over-expressed with loss of *PTEN* expression[105]. Increased expression of GLUT proteins would be expected to correlate with increased cellular glucose, and thus FDG, uptake cancers

cells[108,109]. This increased expression of *GLUT* transporters in both *BRAF* and *PTEN* mutated phenotypes may give credence to the observation of PET-detected thyroid incidentalomas exhibiting more aggressive behavior. Notably, in a study of malignant PET-detected thyroid lesions not selected for PTEN loss by Kim *et al.*[110], there was overall a low degree of *GLUT-1* and *GLUT-3* expression but a high level of *VEGF* expression. Consistent results were reported by Ohba *et al.*[111] in a study of benign PET-detected thyroid incidentalomas that were found to have a higher degree of vascularity than benign thyroid nodules not exhibiting FDG uptake.

Mutations in the *p53* tumor suppressor gene are exhibited in nearly 50% of all cancers yet are identified in only 10% of thyroid cancers[112]. In a retrospective study of patients with PET-detected thyroid cancers, 86% of those that underwent operation were found to express *p53* mutations, and this was not related to SUV_{max}[42]. The significance of this finding is not yet known.

Fine needle aspiration yields indeterminate results in 15%-30% of patients[113], which may persist after repeat FNAC. Molecular diagnostic tests such as Afirma[114], ThyroSeq[115,116], and ThyGeNEXT/ThyraMIR[117] have been developed to differentiate this indeterminate category, yet the utility of these tests is unclear in a population selected for FDG avidity. In a study utilizing Afirma Gene Expression Classifier (GEC) or Genome Sequence Classifier (GSC) profiling in thyroid PETomas with indeterminate cytology, Endo *et al.*[118] found that 28.6% of these nodules were predicted malignant per Afirma GEC/GSC compared to a 36.4% rate of malignancy in histologically proven nodules. The benign call rate (BCR) was significantly higher in patients with low-risk ultrasound features (83.3%) *vs.* 29% in intermediate- or high-risk ultrasound features ($P = 0.026$). The higher BCR with Afirma GSC (64%) may indicate that surgical intervention can be safely avoided or delayed in these patients.

MANAGEMENT RECOMMENDATIONS

Clinical guidelines for the management of thyroid nodules in the general population are well established[119,120]. Given that most PET/CT imaging is pursued to evaluate another malignancy that may limit life expectancy, it is difficult to determine if these guidelines should apply to this population. Thyroid cancer is associated with an excellent prognosis, with overall 10-year survival rates of differentiated thyroid cancers exceeding 90%-95%[121]. For example, in patients that underwent cytologic diagnosis of an incidental thyroid cancer, the risk of death from thyroid cancer was < 1%[32]. Studies of active surveillance of low-risk papillary microcarcinomas (cytologically confirmed PTC with nodule diameter ≤ 1 cm without high-risk features) have shown safety with this approach. In this review, only 7%-8% of observed nodules increased in size, and there were no instances of recurrence or death following salvage surgery[122]. Contrary to this, Are *et al.*[55] suggested that incidentalomas are associated with a poorer prognosis due to a higher rate of unfavorable pathologic features such as tall cell variant, poor differentiation, and extrathyroidal extension. Data from our institution identified a 30% rate of poor prognostic features in these patients[18].

Although most thyroid carcinomas are associated with an excellent prognosis, it does seem prudent that each incidentally discovered thyroid lesion be carefully evaluated for risk factors that may elucidate the relevance of such lesions. Review of prior images should be conducted to evaluate the evolution of the noted lesion over time[123]. In addition to the previously mentioned features, PET scans may reveal signs of lateral lymph node metastases[24], which is associated with a poorer prognosis[124-126] and is key for developing adequate surgical plans should this route be pursued[127]. Other features contributing to malignancy risk include younger age[19,128], male gender[128,129], childhood radiation exposure[130,131], and family history of thyroid cancer[132].

Current clinical guidelines recommend further investigation, including FNAC, to evaluate all PET-identified thyroid incidentalomas greater than 1 cm in diameter[119]. However, a study utilizing SEER data found that only tumor size > 2.5 cm was associated with an increased mortality[133]. Another population-based study found size > 2 cm, microcalcifications, and solid composition related to increased malignancy risk[134]. The risk of cancer in solid lesions has been reported at 13% compared to 4% for mixed solid/cystic lesions[135].

Ultrasound has been the mainstay of imaging thyroid nodules. Several risk stratification systems (ACR-, EU-, and K-TIRADS) have been developed, however, it is open for debate if these systems are applicable to PET-detected thyroid incidentalomas. Previous investigators have proposed that these lesions have a greater likelihood of high-risk features[18,55], which may make these stratifications schemes unreliable. However, a reliable stratification schema is essential as it is impractical to require FNAC of all PET-detected thyroid incidentalomas. Trimboli *et al.*[136] examined the ability of EU-TIRADS to appropriately stratify focal PET-detected thyroid incidentalomas with histologic diagnoses or scintigraphic confirmation of an autonomously functioning thyroid nodule. Of the 13 confirmed malignancies included in this study, 11 were categorized as EU-TIRADS 5, 1 as EU-TIRADS 4, and 1 as EU-TIRADS 3. SUV_{max} and SUV_{max} ratio were also found to be significantly higher in the cancer population, with the most accurate cut-off values determined as > 7.1 and > 3.65, respectively. The presence of one of these risk factors (SUV_{max} > 7.1, SUV_{max} ratio > 3.65, or EU-TIRADS 5) detected 12 of 13 cancers (92% sensitivity) while the absence of these features detected 34 or 35 benign lesions (97% specificity). This data was recently expanded to evaluate ACR-TIRADS and K-TIRADS systems in addition to EU-TIRADS[137]. EU-TIRADS and K-TIRADS both showed 100% specificity and NPV, while the sensitivity of ACR-TIRADS was 81%. This resulted in recommendations to obtain FNAC in 48% of patients according to ACR-TIRADS, 61% per EU-TIRADS, and 75% per K-TIRADS. Given the higher likelihood of cancer in this population, EU-TIRADS and K-TIRADS were advocated as the preferred stratification tools due to the greater number of FNAC recommended.

In debating the issues of appropriate management, those with a known or suspected underlying cancer or life-limiting comorbidity must be considered separately from an asymptomatic, healthy patient. An otherwise healthy patient should receive the full measure of workup and treatment as indicated by current guidelines. In patients with life-limiting malignancies or comorbidities should be approached with further judiciousness. Thoughtful consideration of patient factors (age, comorbidities, quality of life), underlying malignancy (prognosis, required treatment), and local radiologic features are mandatory[32]. The risk of intervention must be weighed against the potential benefits. Further evaluation with dedicated ultrasound imaging incites little risk, and FNAC should be considered if appropriate per TIRADS recommendations. Given the diversity of cancers diagnosed in these patients (see Table 2), it does seem prudent to biopsy these lesions where possible. Confirmation of metastasis or thyroid lymphoma would be expected to drive a change in treatment approach. Diagnosis of a papillary thyroid cancer may prompt consideration of active surveillance due to the generally indolent nature of this condition, or surgical management if the patient's condition permits. Patient status should be continually assessed with re-evaluation of the management plan, and it is certainly plausible to consider surveillance of a thyroid nodule during treatment of the index cancer with conversion to active management as the status improves.

Summary of recommendations

1. Assess the patient's clinical condition, considering the index cancer, comorbidities, and frailty.

a. If unacceptable for further intervention, reassess for possible intervention as status changes.

2. For those with focal PET/CT thyroid avidity that is amenable to further intervention, neck ultrasound should be obtained, with FNAC pursued based on TIRADS guidelines.

3. In thyroid incidentalomas discovered on ^{68}Ga-DOTATATE PET/CT, consider obtaining a baseline calcitonin level.

4. Active surveillance of a well-differentiated thyroid carcinoma can be considered during active management of the index malignancy; however, it should be acknowledged that some PET-detected thyroid incidentalomas may represent more aggressive malignancies.

CONCLUSION

In conclusion, the incidence of PET-detected thyroid incidentalomas can only be expected to increase as further technological advancements are made. In the current state, no imaging features or patterns of uptake can definitively discern benign from malignant lesions. Clinicians must employ the art of medicine and carefully balance the risks and benefits of pursuing further workup and management while taking into account the underlying condition and expectations of the patient. As more developments are attained in research and technology, we will further refine this paradigm and enhance our ability to provide the best care for life.

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Authors' contributions

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