PET-Associated Incidental Neoplasms of the Thyroid

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2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG)-PET is an increasingly important imaging tool in oncology.[1] PET and PET/CT are currently used for detection and staging of malignancies, in addition to response to treatment.[2,3] The radiopharmaceutical isotope 2-[^{18}F] fluoro-2-deoxy-D-glucose is trapped in hypermetabolic cells and allows for detection of neoplastic tissue. As with any imaging procedure, incidental findings on a PET scan can create a dilemma for both patients and physicians. In patients undergoing PET for cancer staging, a second malignancy is discovered as a hypermetabolic focus in 4% to 6% of patients.[4,5] We have termed such findings *PET-associated incidental neoplasms* (PAINs).

Among PAINs from all sites, 27% to 44% of confirmed malignancies arise within the thyroid.[5,6] Thyroid PAINs have been reported by numerous authors[6-12] and represent an increasingly common clinical problem. The prevalence of malignancy in patients with thyroid PAINs ranges from 14% to 47%.[6-12] Given the frequency with which cancer patients undergo PET imaging, it is important to understand the implications of newly discovered hypermetabolic foci involving the thyroid gland.

The likelihood of malignancy in an individual with a thyroid PET abnormality depends in part on the pattern of FDG uptake.[7,8,11] Importantly, when a thyroid PAIN is confirmed to be malignant, an aggressive histologic subtype is likely.[8] When a thyroid PAIN is discovered, the considerable potential for a malignancy with unfavorable biologic characteristics warrants a comprehensive evaluation.

This article will review the diagnosis and management of incidentally detected thyroid PET abnormalities. We offer insight into the biologic implications of thyroid PAINs. We will review the patterns of thyroid FDG uptake and other clinicopathologic factors that allow for proper selection of patients for additional evaluation and treatment. In managing patient with thyroid PAINs, one should maximize the yield of invasive diagnostic and therapeutic interventions and avoid treating patients in whom the implications of a thyroid neoplasm are inconsequential in the context of a preexisting malignancy. Those patients at high risk for thyroid malignancy in whom thyroidectomy would be appropriate should be identified and treated.

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THYROID NEOPLASMS AND PET

PET imaging is playing an increasingly important role in management of established thyroid neoplasms. PET imaging is an important component in detection of metastatic well-differentiated thyroid cancer and can detect lesions that do not take up radioactive iodine.[13] Some authors have advocated preoperative PET imaging in patients with thyroid nodules to reduce the number of thyroidectomies for benign disease.[14,15] Others have suggested PET imaging may play a role in limiting operations in patients with thyroid nodules and indeterminate cytology.[16] PET can lead to detection of neoplastic thyroid tissue in numerous clinical settings.

Unlike sonography and CT imaging, PET provides information about tumor location, biologic activity, and potential for aggressive behavior in patients with thyroid PAINs.[7,8,11,12,17] A hypermetabolic thyroid lesion detected by PET is both a biologic and anatomic abnormality, although incidentalomas detected by CT or ultrasonography are purely physical or radiographic findings. As mentioned here, up to 47% of thyroid PAINs are proven to be malignant.[6,7,9,12] In contrast, an incidental thyroid nodule detected by sonography, CT, or MRI is far more likely to be benign.

Among 253 patients who underwent thyroid sonography, Brander and colleagues found that none of 30 patients with sonographically detected thyroid nodules had definitive evidence of malignancy on cytologic examination.[18] Likewise, Youserm and colleagues reported that although 14.5% of patients who underwent CT or MRI had incidental thyroid lesions, none were proved to be carcinoma.[19] The combination of metabolic and anatomic information makes a thyroid PAIN more likely to be malignant than an incidentaloma detected by CT or sonography. Thyroid PAINs warrant a higher degree of suspicion than lesions detected by sonogram or CT.

Not only are thyroid PAINs more likely to be malignant when compared with incidentalomas detected by other modalities, the biologic information provided by PET imaging can provide insight into tumor biology. Increased FDG uptake is associated with upregulation of glycolytic

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Abbreviations and Acronyms
FDG = 2-[^{18}F] fluoro-2-deoxy-D-glucose
PAIN = PET-associated incidental neoplasm
SUV = standardized uptake value

pathways. Overexpression of hexokinase II and glucose transporter proteins leads to increased FDG accumulation, which has been correlated with more aggressive disease.[20,21] It is not surprising that thyroid cancer detected incidentally by a PET scan is more likely to be an unfavorable variant, such as tall-cell papillary carcinoma.[7]

INCIDENCE OF PAINS

Although incidental abnormal FDG uptake in the thyroid is an infrequent occurrence in patients undergoing PET imaging, PAINs can be malignant in a substantial proportion of patients. Thyroid abnormalities were detected in 377 of 11,500 (2.9%) patients who underwent FDG-PET scanning at Memorial Sloan-Kettering Cancer Center.[7,8] Among 28,717 FDG-PET scans from several reports, 562 (2.0%) of patients were found to have a thyroid PAIN (Table 1).[6-11] In 148 patients with a tissue diagnosis, 32% were found to have definitive evidence of a thyroid malignancy.[6-11] As will be discussed below, this relatively high likelihood of malignancy among thyroid PAINs is in part a result of the nature of patient selection for additional evaluation.

As mentioned, the incidence of malignancy in thyroid PAINs subjected to fine-needle aspiration or operation varies from 14% to 47%. Chen and colleagues reported that only 14% of patients with a thyroid PAIN and a tissue diagnosis had a malignancy.[9] Of note, 83% of patients reported by Chen and colleagues with thyroid PAINs underwent biopsy. In contrast, at Memorial Sloan-Kettering Cancer Center, <1% of patients with thyroid FDG uptake on a PET scan underwent an invasive diagnostic procedure and 42% of those subjected to biopsy or operation were diagnosed with thyroid carcinoma.[8] The likelihood of diagnosing carcinoma in a thyroid PAIN can be enhanced through stringent criteria in choosing patients for additional evaluation. Overall status of the patient with reference to the underlying disease for which the PET is being performed must be taken into account. For example, there is rarely a benefit to pursuing a thyroid lesion in a patient with a disseminated malignancy.

DETERMINING RISK OF MALIGNANCY IN PATIENTS WITH ABNORMAL THYROID FDG UPTAKE

The normal thyroid is not visualized on PET and abnormal FDG uptake in the thyroid can be a result of benign or malignant conditions. The thyroid can accumulate FDG in numerous infectious or inflammatory processes. Benign conditions leading to abnormal thyroid FDG uptake include Grave's disease, multinodular goiter, thyroiditis, and Hürthle cell adenomas.[22-24] Presence of FDG uptake by the thyroid does not necessarily indicate presence of thyroid carcinoma. Fortunately, the diagnostic and therapeutic yield when managing patients with thyroid PAINs can be optimized through consideration of factors discussed here.

Several clinicopathologic factors have been analyzed for their ability to predict malignancy in patients with thyroid PAINs. Indication for PET scan does not seem to be predictive of thyroid PAIN malignancy. PET scans are performed primarily for evaluation of a patient with a known malignancy, but are occasionally performed for screening purposes as well. The purpose of the PET scan does not correlate with the incidence of thyroid PAINs.[11] In other words, presence of an earlier extrathyroidal malignancy in a patient with a newly detected PET abnormality in the thyroid does not correlate with risk of thyroid cancer. Yet, one should consider that treatment for other cancers, such as head and neck irradiation, does predispose to thyroid carcinoma.[25]

Presence of a finding on physical examination increases the likelihood that a thyroid PAIN will ultimately prove to be malignant. Incidence of malignancy may be much

Table 1. Incidence of PET-Associated Incidental Neoplasms

		PET abnormalities			Malignancies	
First author	n	n	%	Tissue diagnosis*	n	%
Cohen[10]	4,525	102	2.3	15	7	47
Kang[11]	1,330	29	2.2	15	4	27
Chen[9]	4,803	60	1.2	50	7	14
Ishimori[6]	1,912	29	1.5	11	6	24
Are[8]	8,800	263	2.9	57	24	42
Bogsrud[31]	7,347	79†	1.1	48	15	35

*Fine needle aspiration or operation.
†Focal uptake only.