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# PET



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## LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Recognize that the main challenge is to localize disease when a radioiodine scan is negative with elevated serum thyroglobulin levels.
- Describe the whole-body radioiodine scan's very high specificity but limited sensitivity for detection of recurrence and metastases of differentiated thyroid cancer.
- Discuss FDG-PET's high sensitivity and specificity for tumor recurrence and metastases in patients with a negative diagnostic radioiodine scan.
- Summarize the inverse relationship between iodine and FDG uptake and the coexistence of iodine-positive and FDG-positive tumors.

## PET and Thyroid Cancer

By Haluk Alibazoglu, M.D.

Clinically recognized thyroid carcinomas constitute less than 1% of malignant tumors, and the annual incidence rate in different parts of the world varies from 0.5 to 10 per 100,000 population. Despite this infrequency, thyroid carcinoma is as prevalent as multiple myeloma, twice as common as Hodgkin's disease, and comparable in frequency to cancers of the esophagus, larynx, mouth, and cervix uteri. Furthermore, it is the most common endocrine malignant condition and is responsible for more deaths than all other endocrine cancers combined.<sup>1</sup>

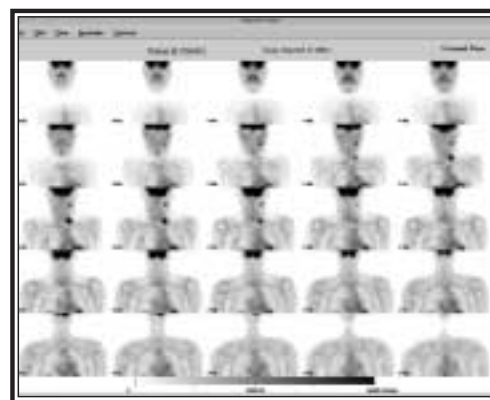
The American Cancer Society estimates that about 22,000 new cases of thyroid cancer (90% of all endocrine cancers) will have been diagnosed in 2003 in the U.S. population, with females more frequently affected than males at a ratio of 3.2:1. An estimated 1400 patients will have died of thyroid cancer during this period, and the number of new cases is increasing.<sup>2</sup> With appropriate treatment, the survival rate is very high. An estimated 190,000 patients are thyroid cancer survivors, some for more than 40 years after diagnosis.<sup>1</sup>

Carcinoma of the thyroid is usually derived from follicular cells, but the uncommon medullary carcinoma arises from the parafollicular or C cells. Four distinct histologic types of follicular cell-derived cancers (FCDC) are recognized.<sup>1</sup> Most are papillary (80%). Follicular cancer accounts for about 10% of cases, and rare Hürthle cell and anaplastic cancers about 5% each.

Papillary and follicular carcinomas are often referred to as differentiated thyroid cancers

(DTC). Papillary carcinoma typically presents as a unilateral thyroid mass. Regional lymph node spread is relatively common, and presence of initial nodal spread increases the risk of subsequent recurrence.

Follicular carcinoma, the next most common type, usually remains in the thyroid gland, does not often spread to lymph nodes, but most commonly metastasizes hematogenously to the lungs and bone. Hürthle cell carcinoma is thought to be a subtype of follicular cancer and follows a similar course. Anaplastic carcinoma, sometimes called undifferentiated thyroid cancer, is a rare form believed to develop from an existing papil-



**Figure 1.** Recurrence and metastasis to left cervical nodes in FDG-PET of 28-year-old woman with elevated serum Tg level and negative DxWBS. Patient had a history of surgical removal and radioiodine ablation of thyroid papillary cancer three years previously. (Images provided by Dr. Amjad Ali, Rush PET Center)

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lary or follicular cancer. It follows a very aggressive and rapid course with distant metastasis and is usually fatal.

Medullary thyroid carcinoma (MTC), unlike papillary and follicular thyroid cancers, does not produce thyroid hormones but is associated with production of calcitonin and carcinoembryonic antigen (CEA).<sup>2</sup> For DTC in general, patients with small tumors ( $\leq 2$  cm), women, and those

invasion of surgical material. This approach is particularly relevant to the diagnosis of follicular carcinoma (including the Hürthle cell variant), which requires demonstration of invasion of either the thyroid capsule or the adjacent blood vessels (angioinvasion).<sup>1</sup>

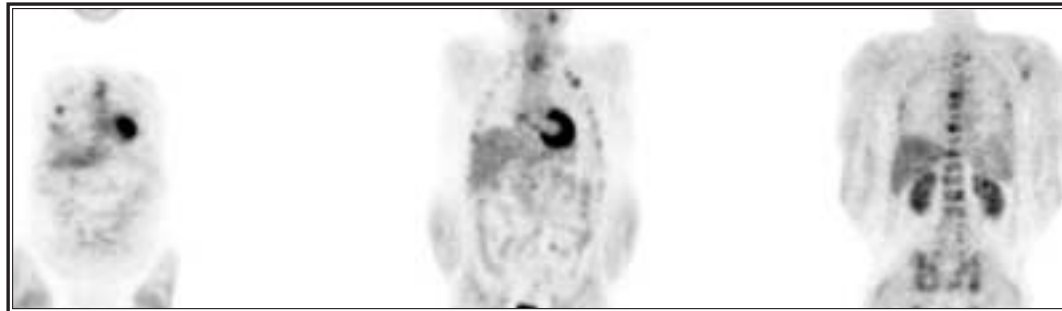
DTC is known to be one of the most curable of all cancers, through effective surgical resection of the primary tumor followed by radioiodine ablation therapy and serum

- destroy remaining normal thyroid tissue, particularly in the neck, so that any iodine uptake in a later follow-up scan can represent persistent or recurrent disease; and
- increase the value of serum Tg measurements during follow-up as its level should be under 10 ng/mL if radioiodine ablation destroyed almost all of the remaining thyroid tissue.

In all of these circumstances, the serum

TSH level should be at least 30 mIU/L, which can be achieved either by withdrawing thyroid hormone replacement therapy or by parenteral administration of recombinant human TSH (rh-TSH).

Preparing patients by rh-TSH is diagnostically equivalent to preparing them by thyroid hormone withdrawal for both serum Tg measurement and for diagnostic radioiodine whole-body scan.<sup>3,4,5</sup> High TSH level stimulates both normal thyroid tissue



**Figure 2.** Multiple distant metastases on FDG-PET, mostly to bone, in 48-year-old woman with thyroid follicular cancer and elevated serum Tg level. Bone metastasis is usually associated with worse prognosis and deserves higher radioiodine therapy dose if FDG-avid lesions accumulate iodine on D<sub>x</sub>WBS. Alternatively, due to the lower sensitivity of D<sub>x</sub>WBS, high-dose radioiodine therapy can be given, followed by T<sub>x</sub>WBS.

with neither local invasiveness nor distant metastases have a good prognosis, with low risk for recurrence or death. Cervical nodal disease as an independent variable may be associated with higher recurrence rates, and bilateral cervical nodal or mediastinal involvement may impart a poorer overall prognosis.<sup>1</sup>

Most patients with thyroid cancer present with a palpable neck mass, which may represent either the primary intrathyroidal tumor or metastatic regional lymphadenopathy. In some patients, however, the tumor may be clinically occult, and the impalpable lesion may first be recognized either on high-resolution neck imaging or during the course of a neck operation for presumed benign thyroid disease. A family history of MTC or multiple endocrine neoplasia type II syndromes, the finding of a RET oncogene mutation or abnormal calcitonin levels, or both, may necessitate an elective prophylactic thyroidectomy in patients who may prove to have early MTC, which can only be demonstrated by histologic examination.<sup>1</sup>

The diagnosis of thyroid cancer necessitates pathologic confirmation from both cytologic and histologic material. Fine-needle aspiration biopsy (FNAB) is the most effective method available to preoperatively distinguish between benign and malignant thyroid nodules. All cancer diagnoses, however, should be verified by histologic exam-

thyroglobulin (Tg) level, a very sensitive screening method for recurrence. Although little doubt exists about the primary role of FNAB in the preoperative diagnosis of thyroid cancer, each step in the subsequent management gives rise to controversy.

Most patients who have thyroid cancer are initially treated surgically. The goal of initial treatment is adequate excision of the primary tumor and any locoregional extension. Because of the increased risk of recurrence after unilateral thyroidectomy and the heightened risk of hypoparathyroidism after total thyroidectomy, near-total thyroidectomy usually is the procedure of choice for the initial treatment. Almost all patients will then be given daily thyroid hormone replacement. For FCDC, this mode of therapy is based on administration of supraphysiologic oral doses of levothyroxine for complete suppression of pituitary thyroid-stimulating hormone down to a basal serum level of  $<0.1$  mIU/L. It is assumed that suppression of pituitary secretion of TSH deprives differentiated FCDC cells of TSH-dependent growth.<sup>1</sup>

The second most frequently used postoperative therapy for patients with FCDC is radioiodine ablation therapy. This form of therapy typically has three main objectives:

- destroy occult microscopic carcinoma cells within the thyroid remnant and distant metastatic lesions;

and DTC to increase its uptake of radioiodine and stimulates secretion of Tg as well.<sup>6</sup> For radioiodine-negative tumors, retinoic acid therapy is reported to be an option that induces radioiodine uptake by redifferentiation.<sup>7</sup> External irradiation is also used in the postoperative period for tumors that do not concentrate radioiodine, such as anaplastic thyroid carcinoma, lymphoma, and secondary malignant tumors.

Serum Tg level measurement has been the most sensitive method for detection of recurrent or metastatic DTC. Most DTCs secrete Tg even if they do not accumulate radioiodine. Tg production rises with an increasing number of differentiated tumor cells. A Tg level above 10 ng/mL is associated with metastases in more than 85% of patients in whom most of the thyroid tissue was removed at surgery and destroyed with subsequent radioiodine ablation.<sup>8</sup> Tg autoantibodies remain a significant obstacle to the clinical use of Tg measurement.<sup>6</sup> In patients with undetectable Tg levels, persistently elevated antithyroglobulin antibody (TgAb) levels appear to serve as a useful marker for recurrent or persistent DTC.<sup>9</sup> Moreover, Tg levels measurable by enzyme-linked immunosorbent assay (ELISA) (0.03 ng/mL or greater) are more sensitive than Tg levels measurable by immunoradiometric assay (IRMA) (0.6 ng/mL or greater).<sup>10</sup>

## RADIOLOGICAL EVALUATION

Since DTCs account for the majority of thyroid malignant tumors and they frequently concentrate radioiodine, whole-body radioiodine scanning (WBS) has been the primary initial imaging modality for thyroid cancer recurrence and metastases. WBS has a very high specificity of 99% with a relatively low sensitivity in the 50% to 70% range.<sup>11</sup> In the absence of normal thyroid gland and elevated TSH levels (above 30 mIU/L), only about three-quarters of DTC recurrences and metastases accumulate radioiodine on WBS.<sup>12</sup> This relatively low sensitivity also depends on the administered dose: A diagnostic WBS (DxWBS) (up to 5 mCi) has sensitivity below 60%, whereas post-therapy WBS (TxWBS) (after 100 to 200 mCi) has sensitivity below 75%. About 10% to 15% of the metastatic lesions that can be seen on TxWBS will have been missed on DxWBS.<sup>13</sup> DxWBS is performed in cases of elevated Tg levels and if positive, high-dose radioiodine treatment can cure most DTC patients with metastases.

The well-known diagnostic and therapeutic dilemma arises in the case of elevated Tg levels and negative DxWBS. Patients with radioiodine-negative metastases are usually not treated with high-dose radioiodine. Instead, these lesions need to be surgically removed or given local radiotherapy, if they can be localized. Therefore, there is a need for alternative methods for tumor localization. Conventional imaging modalities used for this purpose include ultrasonography, CT, MR, and bone scan.

On the other hand, the lower sensitivity of DxWBS has also led to reports of empirical high-dose radioiodine treatment given even if DxWBS is negative with elevated Tg levels. This is followed by TxWBS seven to 12 days later. The diagnostic and therapeutic benefit of this approach is evidenced by demonstration of iodine uptake in lesions and by subsequent reduction of Tg level, respectively.<sup>14,15</sup> It is also useful in patients with lung metastases.<sup>16</sup>

The clinical utility of FDG-PET in localizing iodine-negative tumors has been demonstrated in a number of studies, with reported sensitivity of 71% to 94%,<sup>17</sup> positive predictive value of 83% to 92%,<sup>11,18-20</sup> specificity of 25% to 90%,<sup>21</sup> and negative predictive value of 93%.<sup>18</sup> Sensitivity is lower for minimal residual disease in cervical nodes<sup>18</sup> and in miliary pulmonary metastases.<sup>22,23</sup> Follicular adenoma in the thyroid,<sup>24</sup> sarcoidosis, and granulomas in the chest<sup>11</sup>

are also known causes of false-positive FDG-PET. Probability of thyroid malignancy is high, however, in patients with incidental focal FDG uptake in the thyroid region in whom PET was performed for nonthyroidal reasons.<sup>24</sup> Most of the iodine-negative metastases demonstrate fluorine-18 FDG uptake, which is explained by poor differentiation with lost ability to accumulate iodine while maintaining Tg production and to accumulate FDG due to higher growth rate.<sup>11</sup> High-dose radioiodine therapy appears to have little or no effect on the viability of these iodine-negative metastatic FDG-avid lesions.<sup>25</sup> Conversely, FDG-PET can fail to localize the tumor sites in some patients with well-differentiated thyroid cancer that retains good iodine ability.<sup>11,21</sup>

In a number of studies in patients with elevated Tg levels and negative DxWBS, FDG-PET changed patient management in more than half of the cases.<sup>18,26,27</sup> However, in patients with elevated Tg levels and negative TxWBS, available data are controversial.<sup>12,28</sup> Since these studies involved small numbers, 11 patients each, the clinical utility of FDG-PET in this subgroup with negative TxWBS needs to be further identified. As coexistence of iodine-positive and FDG-positive lesions was also described, particularly in poorly differentiated tumors, FDG-PET can be used in patients with known iodine-positive tumor sites to localize coexisting additional iodine-negative tumor tissue that is FDG-positive.<sup>11</sup> If iodine-negative tumor sites exist in addition to iodine-positive sites, the benefit of further radioiodine therapy is questionable.<sup>11,25</sup> By coregistering PET and CT data in a single session and allowing correlation of functional and morphologic imaging, combined PET/CT scanners may improve tumor localization,<sup>29</sup> especially in early tumor stages<sup>30</sup> and in relationship to critical organs and structures.<sup>31</sup>

Other agents used to localize metastatic lesions include thallium-201, technetium-99m furifosmin, and Tc-99m sestamibi, which all have lower sensitivity and resolution than FDG-PET.<sup>11,18</sup> Because some metastases of differentiated thyroid cancers and the majority of metastases of Hürthle cell carcinoma express somatostatin receptors, indium-111 pentetreotide imaging in combination with FDG-PET is used in monitoring tumor response after octreotide therapy.<sup>32</sup> Hürthle cell carcinoma is an exception among differentiated tumors in that it has low avidity for iodine, while FDG-PET showed disease not identified by other imag-

ing methods in 50% of cases,<sup>33</sup> with sensitivity of 92% and specificity of 80%.<sup>34</sup> For medullary thyroid carcinoma, the reported sensitivity of FDG-PET is 76% to 78%<sup>35</sup> with a specificity of 79%,<sup>35</sup> far superior to CT, MR, and iodine-131 meta-iodobenzylguanidine (MIBG) for detecting metastases.<sup>35</sup>

FDG-PET may also provide prognostic information.<sup>36,37</sup> The higher the total volume of FDG-avid disease, the shorter the survival in a series of 125 patients.<sup>37</sup> Treatment with isotretinoin is a recent additional option in advanced, otherwise intractable differentiated thyroid cancers.<sup>18</sup> FDG-PET used three months into the treatment can differentiate those patients who will eventually benefit from isotretinoin from patients who will not.<sup>38</sup>

## DISCUSSION

Although most patients survive thyroid cancer, because DTC is slow growing and a tumor recurrence may take many years to become clinically apparent, sound judgment is essential in decision-making regarding tumor surveillance and imaging. FDG-PET is a useful modality for localization of thyroid cancer metastases and recurrence. Since serum Tg level and WBS are the initial principal methods for detection and localization of disease, respectively, the current role of FDG-PET would mainly be in localizing disease in patients with a negative WBS and elevated serum Tg levels.

FDG-PET has a very high positive predictive value, which correlates with serum Tg levels. In one study involving 64 patients, FDG-PET was true positive in 11%, 50%, and 93% of patients with Tg levels of <10, 10 to 20, and >100 mcg/L, respectively.<sup>20</sup> More definitive data suggest that FDG-PET should be performed under TSH stimulation. The sensitivity of FDG-PET can be increased by intramuscular injection of rh-TSH,<sup>4,21,27,39,40</sup> by increasing metabolism of thyroid tissue similar to rh-TSH stimulation of Tg secretion and uptake of radioiodine.<sup>4-6</sup>

It has been demonstrated in a number of studies that the sensitivity of PET is higher when DxWBS is negative, which supports the theory of progressive dedifferentiation of thyroid tumor associated with cessation of iodine uptake capability and enhanced glycolytic rate. However, most of the available data are based on studies performed after negative DxWBS, and there are very limited and conflicting data available for studies performed after negative TxWBSs.

The possibility of coexistence of iodine-negative/iodine-positive lesions and the discordance in localization of iodine-positive and FDG-positive lesions are clinical challenges that may further increase the clinical utility of FDG-PET even in presence of iodine-positive disease.

While diagnostic and therapeutic effect can be observed by administration of empirical high-dose radioiodine after a negative DxWBS in patients with elevated Tg, which most likely represents cases with differentiated thyroid cancers, administration of high-dose radioiodine had little or no effect on metastatic FDG-positive lesions<sup>25</sup> that most likely represent cases with poorly differentiated tumors. With availability of I-124, a positron emitter, PET imaging of differentiated thyroid

cancer will also become possible.

The lower sensitivity of other tumor seeking agents, including Th-201, Tc-99m furifosmin, and Tc-99m sestamibi, can be partly explained by the inferior spatial resolution of SPECT imaging compared with PET and differences in the mechanisms of tracer uptake. If there is a need to differentiate inflammatory enlarged lymph nodes from metastatic disease, Tc-99m sestamibi appears to be the agent of choice. However, the sensitivity of Tc-99m sestamibi is even lower than FDG-PET for minimal residual disease in cervical nodes and in miliary pulmonary metastases.<sup>22</sup> Although anatomical imaging modalities, including ultrasound, MR, and CT, are frequently performed in cases with negative DxWBS, their inferior specificity, particularly in

patients with altered anatomy, limits the information that can be obtained.

**CONCLUSION**

Surgical removal and radioiodine ablation are the primary modes of therapy for most thyroid cancers. Serum Tg level and DxWBS are established surveillance and imaging methods, respectively, during the lifelong follow-up period. In cases with negative DxWBS and elevated serum Tg levels, FDG-PET, with superior sensitivity and higher specificity than other functional and anatomical imaging methods, is the imaging method of choice for recurrence and metastases. Combined PET/CT either with FDG or I-124 is a newly emerging method for tumor localization in thyroid cancer.

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