INVITED COMMENTARY

FDG PET in Thyroid Cancer: Thyroxine or Not?

For decades, highly specific functional imaging in thyroid cancer was associated with several disadvantages of hypothyroidism. To achieve an optimal radioiodine uptake in remnant tissue and in malignant thyroid cells, it was necessary to withdraw thyroid hormone medication to increase thyroid-stimulating hormone (TSH) secretion to values >30 mIU/L, if possible (*1*). This kind of functional imaging uses the Na^+/I^- symporter in cells originating from the thyroid gland to detect cancer cells scintigraphically. The Na^+/I^- symporter gene expression in thyroid cancer cells depends on several characteristics of the malignant cells, particularly on the degree of differentiation of the thyroid carcinoma. In most carcinomas, the Na^+/I^- symporter gene expression is decreased (*2*), and a correlation of tumor stage and degree of decrease has been observed (*3*). An increased expression in papillary thyroid carcinomas has also been described (*4*). In cases of poorly differentiated carcinoma and in Hürthle cell carcinoma, radioiodine scintigraphy is frequently negative in individuals with recurrence or metastatic disease. Patients with radioiodine-negative tumor tissue have a significantly poorer prognosis because of the higher malignancy potential of the tumor cells and the lack of radioiodine therapy options. Initial reports on the use of 13-*cis*-retinoic acid to induce radioiodine uptake in thyroid cancer gave encouraging results (*5–7*), but it is still too early to recommend this treatment for routine use.

In addition to radioiodine, several malignancy-specific and organ-nonspecific radiopharmaceuticals can be used for functional imaging in thyroid cancer. Thallium chloride was used initially (*8*) and subsequently was replaced by ^{99m}Tc-labeled myocardial tracers (*9,10*). PET imaging with FDG is now accepted as the method of choice with the highest sensitivity and is currently used, if available, in clinical routine. For all clinicians who plan and perform PET scanning, the question arises: Should the thyroid hormones be withdrawn before FDG PET to increase the chance of detecting tumor sites with this technique?

Various parameters with possible influence on FDG uptake in thyroid cancer cells and also in other organs must be considered. The organ-specific influence of TSH on thyroid cells through the TSH receptor comes first to the mind of physicians who are experienced with thyroid cancer. In normal thyroid cells, the TSH adenylate cyclase system is most important for the control of growth and function. The receptor belongs to the family of G protein–coupled receptors. It is preferentially coupled to the α subunit of the stimulatory guanyl-nucleotide–binding protein $G_s\alpha$ (*11*). The metabolic demand can be expected to increase during hypothyroidism. In contrast to benign adenomas, which show a high intensity in immunohistochemical detection of the TSH receptor, Tanaka et al. (*12*) and Lazar et al. (*3*) have observed a weak intensity in most thyroid carcinomas. Thyroid carcinomas with $G_s\alpha$ mutations do not concentrate iodine (*13*). The TSH-receptor expression was correlated with the prognosis (*12*). But in most malignant cells, other mechanisms of growth control must also be considered. Ohta et al. (*14*) observed a growth inhibition of some human thyroid carcinoma cells by the activation of adenylate cyclase through the β-adrenergic receptor. In addition to glucose consumption, the expression of several glucose transporter genes and hexokinase activity must be considered as parameters that influence FDG uptake. In a small group of cases, Lazar et al. (*3*) found an increased expression of GLUT-1 to be associated with a loss of radioiodine uptake in metastases. Their observation agrees with the fact that most tumors take up either FDG or radioiodine (*15–18*). Matthaei et al. (*19*) observed in isolated rat adipocytes an increased activity of glucose transporters (primarily GLUT-4) but a decreased total number of transporters in hypothyroidism. Börner et al. (*20*) found an increased FDG uptake in toxic adenomas. Whether this phenomenon is caused by direct alteration of the TSH receptor, which is associated with an increased iodine uptake, or secondarily by a suppression of TSH release remains to be determined. Which of these mechanisms has more influence on FDG uptake also must be examined. In general, the degree of differentiation affects the TSH dependency because very poorly differentiated thyroid carcinoma cells are less dependent on TSH (because of a loss of intact TSH receptors). The thyroglobulin response to TSH is significantly greater (>10-fold) in thyroid remnant and well-differentiated thyroid tumors than in poorly differentiated tumors (<3-fold) (*21*).

In addition to TSH, the influence of thyroid hormones on several mechanisms that have a role in FDG distribution must be considered. The metabolic activity is decreased in several organs during hypothyroidism because of decreased organ functions. In most cases, this can be expected to hold true for tumor cells. Therefore, the tumor-to-background ratio can be changed in both directions because FDG uptake in the tumor and in the background can be altered. An increased FDG uptake in a pituitary adenoma after therapy of hypothyroidism has been observed in spite of a size reduction of the tumor (*22*).

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What should the clinician do? To our knowledge, Sisson et al. (*23*) were the first to report sequential FDG PET studies that were performed during hypothyroidism and under hormone medication. They found decreased FDG uptake after administration of thyroxine. Although they suggest the use of FDG PET to estimate the optimal thyroxine dose, this technique seems to be expensive compared with other methods, particularly because TSH measurement is sufficient in most cases (because a careful suppressive titration is tolerated and without side effects in almost all patients). In the German multicenter study (*24*), which included 222 patients with differentiated thyroid cancer, a significantly higher sensitivity was found in patients with low TSH values (91%) compared with the sensitivity of FDG PET studies performed under TSH stimulation (67%). In contrast, the specificity was 74% under TSH suppression and 94% under TSH stimulation. The overall sensitivity was 75% in this patient group, 85% in radioiodine-negative cases, and 65% in radioiodine-positive cases (*24*). Sensitivity was higher in poorly differentiated tumors (higher than grade G2). Wang et al. (*25*) reported a positive predictive value of 92% and a negative predictive value of 93% for FDG PET and observed that TSH values had no influence on the capability of FDG PET to detect lesions in 37 patients with negative diagnostic whole-body radioiodine scans.

In this issue of *The Journal of Nuclear Medicine*, Moog et al. (*26*) present an intraindividual comparison of FDG PET results during TSH stimulation and during TSH suppression in a well-defined patient group. They found higher tumor-to-background ratios during TSH increase (5.84 versus 3.85). In 3 of 10 patients, new lesions were detected or known lesions were clearly classified as malignant only after withdrawal of thyroid hormone medication. Although evaluation of the influence of TSH on FDG PET by sequential PET studies is a very good idea, some modifications would improve the impact of such studies. Counting rates can be expected to be insufficient for measuring glucose consumption because of several obstacles that make a highly sophisticated acquisition protocol necessary for reliable measurement of glucose uptake. A crossover study would strengthen the conclusions of a study dealing with TSH's influence on FDG uptake to exclude a bias caused by a natural progression of the disease, which can lead to an increased FDG uptake. Moog et al. reported no changes in the volume of the known tumor sites evaluated by PET. A study with morphologic data would reinforce these conclusions. Taking all of these reports together, a clear recommendation concerning thyroid hormone medication before FDG PET is not yet possible (*23–26*). In contrast to radioiodine scintigraphy, the withdrawal of thyroxine before imaging does not seem to be essentially necessary.

What can the scientist do? A lot of work in this field is necessary because a prospective, randomized study dealing with the sensitivity and specificity of clinical FDG PET in thyroid cancer is still missing. Some specific aspects of associated questions are interesting: How does TSH influence FDG uptake in benign thyroid cells? Yasuda et al. (*27*) observed an increased FDG uptake in 36 of 1102 screening PET examinations with clinical parameters suggesting chronic thyroiditis in 27 of these 36 subjects. Six patients presented with an increased TSH level (subclinical hypothyroidism). In these patients it remains to be determined whether the increased FDG uptake is caused by the TSH stimulation or by other mechanisms—for example, inflammatory processes or changes of the glucose transporter gene expression. To answer the question of whether the different sensitivity and specificity values of FDG PET after thyroid hormone withdrawal (reported in the literature) are caused by differences mediated through the TSH receptor or by lower thyroid hormone values, the use of recombinant TSH is necessary. This would allow the exclusion of hypometabolic effects as factors of altered glucose uptake.

In conclusion, experiments in cell cultures and in animals seem to be most important to answer some basic questions. Subsequently, prospective studies with well-defined variables are necessary to evaluate the influence of TSH and thyroid hormones on FDG uptake in tumor cells in general, in malignant and benign thyroid cells, and in nonmalignant tissue besides the thyroid gland.

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