EDITORIAL

Role of FDG PET in Metastatic Thyroid Cancer

A report from the National Cancer Data Base revealed that the 10-y overall relative survival rates for U.S. patients with papillary, follicular, Hürthle cell, medullary and undifferentiated-anaplastic carcinoma were 93%, 85%, 76%, 75% and 14%, respectively (*1*). The predominant method for treatment of papillary and follicular (differentiated) neoplasms is surgery (total thyroidectomy ± lymph node sampling-dissection) with 38% of the patients receiving additional adjuvant ^{131}I ablation therapy (*1*). Long-term management of differentiated thyroid cancer (DTC) involves thyroxine suppressive therapy, serum thyroglobulin monitoring and radioactive iodine scintigraphy (RIS). However, the sensitivity of RIS in detecting metastatic disease due to DTC is relatively low, ranging from 42% to 62%, even though the specificity is high at 99%–100% (*2–5*). The sensitivity and specificity of serum thyroglobulin is also less, 55%–78% and 76%–78%, respectively, depending on the presence or absence of antithyroglobulin antibody (*6*), and serum thyroglobulin per se has no localizing value. Rising thyroglobulin or presence of antithyroglobulin antibody with negative RIS pose both a diagnostic and a therapeutic dilemma in management of differentiated thyroid cancer.

Previous studies have shown that the sensitivity of [^{18}F]fluorodeoxyglucose (FDG) PET ranges from 50% to 78% with a relatively high specificity of 90%–100% (*2–5*). These studies also address the complementary role of RIS and FDG PET in detection of recurrent or metastatic thyroid cancer with a higher combined sensitivity (86%–100%) than either tracer alone, whereas the specificity remains high (95%–100%) (*2–5*). The FDG PET studies were performed with both suppressed (*2,3*) and elevated (*2,4*) thyroid-stimulating hormone (TSH) and PET imaging was successful in various cell types: papillary (*2–4*), follicular (*2–4*) or Hürthle cell (*2*) thyroid cancers. The current hypothesis is that persistent iodine metabolism is present mostly in well-differentiated cells, whereas FDG uptake is associated with dedifferentiation and poor prognosis (*5*). Previous studies have briefly discussed the role of FDG PET in a few patients with rising thyroglobulin and negative RIS with a sensitivity from 82%–94% (*2–4*).

Many alternative nuclear medicine imaging techniques other than FDG PET have been investigated. Planar ^{201}Tl scintigraphic imaging had been compared with RIS about 10 y ago with conflicting sensitivities (^{201}Tl versus ^{131}I: 94% versus 48% [*7*] and 45% versus 84% [*8*]). This controversy persists in recent studies that may be related to different patient populations recruited for these studies (*9,10*). FDG PET appears to be superior to ^{201}Tl in differentiating malignant from benign thyroid tumors (*11*). FDG is also superior to ^{201}Tl in thyroid cancer patients with negative RIS (sensitivity 84% versus 49%) (*12*). ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) scintigraphy has a sensitivity varying from 50% to 88% and a specificity ranging from 92% to 96% for detecting recurrent or metastatic disease (*5,13*). Because ^{99m}Tc-MIBI "washes out" from tumors, the time chosen after injection for imaging affects the sensitivity (*13*). In addition, FDG PET has been reported to be more sensitive than ^{99m}Tc-MIBI because of better tomographic spatial resolution and differences in mechanism of tracer uptake (*14*). ^{99m}Tc-tetrofosmin scintigraphy has recently been reported to have a sensitivity of 86% in detecting distant metastasis with suppressed TSH (*15*) and a sensitivity of 89% with stimulated TSH compared with a 43% sensitivity of RIS (*16*). However, direct comparison with FDG PET was not available. Most of the studies using ^{201}Tl, ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin were designed primarily for comparison with ^{131}I whole-body scanning, and discrepant cases between these nonspecific tumor-seeking tracers and ^{131}I were reported, which also suggested the complementary role of these imaging modalities. However, these studies did not address specifically the situation of differentiated thyroid cancer with negative RIS on a patient-by-patient basis. Recent FDG PET multicenter studies have focused the application on thyroid cancer patients with negative RIS (*12*). In this issue of *The Journal of Nuclear Medicine,* Chung et al. (*6*) reported the value of PET in 54 athyrotic patients with pure papillary thyroid cancer in the TSH-suppressed state and negative RIS in the TSH-stimulated state. The reported sensitivity of 94% for PET in those with rising thyroglobulin is in line with previous studies (*2–4*). It is important to note that the study also addresses the sensitivity of PET in patients with a negative thyroglobulin. The sensitivity is similarly high at 93%. Not all patients with negative thyroglobulin had positive antithyroglobulin antibody in the study by Chung et al.; one third of the patients with metastatic thyroid cancer and negative RIS had normal thyroglobulin and negative antithyroglobulin antibody. This is lower than the reported rate by Seabold et al. (*12*). In their study, the true-positive rate of

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For correspondence or reprints contact: Chingyee Oliver Wong, MD, PhD, Positron Diagnostic Center, William Beaumont Hospital, 3601 West Thirteen Mile Rd., Royal Oak, MI 48073.

FDG PET in patients with metastatic thyroid cancer and negative RIS who have normal thyroglobulin and negative antithyroglobulin antibody is as high as 70%. Chung et al. (*6*) also reported that the patients with a truly false-negative serum thyroglobulin and a truly false-negative RIS are more likely to have regional lymph node metastasis. Those with distant metastatic disease were shown to be less likely to have false-negative serum thyroglobulin. In the same study, the pattern of regional metastasis revealed by FDG PET in 33 RIS negative patients was compared with that revealed by RIS in 117 RIS-positive patients. The positive rate of PET was higher than RIS in regional lymph node (even with normal size by anatomic criteria) metastasis and lower than RIS in lung metastasis. This concurs with a similar observation by Seabold et al. (*12*).

Because there is evidence to suggest that patients with distant metastatic disease can be diagnosed more easily by thyroglobulin and RIS than by FDG, these patients should be managed conventionally. When distant disease occurs, the high treatment dose of ^{131}I will adequately treat regional lymph node disease, if there is any that may or may not be detected initially by diagnostic RIS. Therefore, the role of FDG PET in metastatic thyroid detection would be mainly in patients with suspected regional lymph node metastasis revealed by high or rising serum thyroglobulin, clinical palpation, radiogram, CT, MRI or ultrasound but not revealed by RIS. A positive serum antithyroglobulin level serves as an additional guideline in patients with a falsely negative serum thyroglobulin, and imaging with FDG PET may be of value in that situation. The most difficult situation is in those thyroid cancer patients with truly negative RIS, serum thyroglobulin and antithyroglobulin antibodies. If the metastasis is detected by clinical palpation or incidental findings from anatomic imaging, then FDG would be beneficial for further evaluation. Otherwise, one may be guided by information revealed at the time of surgery (metastasis and local invasion), poor prognosis suggested by histological examination (tall cell, insular, diffuse sclerosing and Hürthle cell) and other factors as summarized by Dworkin et al. (*17*). Because FDG PET reveals sites of high-grade cancer cells that are not readily detected by anatomic imaging and serum thyroglobulin, the information from PET images would be useful for subsequent clinical decisions about surgical management, localized external radiation or radioactive ^{131}I therapy. Because the data so far suggest that FDG PET is superior to other nuclear medicine imaging methods such as ^{201}Tl (*12*) and ^{99m}Tc-sestamibi (*14*) scintigraphy, we propose PET as the first choice in managing thyroid patients with negative RIS. We and other investigators (*18*) have observed a subgroup of patients with initial negative RIS using a diagnostic dose but positive PET scan who become positive on subsequent post-treatment RIS. Thus, positive PET may support to some extent the long-debated therapeutic ^{131}I dose in those patients with high or rising thyroglobulin (*19*) but negative RIS and the recently reported redifferentiation therapy with 13-cis-retinoic acid (*20*).

Ching-yee Oliver Wong
Howard J. Dworkin
William Beaumont Hospital
Royal Oak, Michigan

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