

PET/CT in the Management of Thyroid Cancers

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OBJECTIVE. Thyroid cancer is the most common endocrine cancer. This review evaluates the established use of ¹⁸F-FDG PET/CT in papillary, follicular, Hürthle cell, anaplastic, and medullary thyroid cancers. The significance of incidental diffuse and focal thyroid FDG uptake is discussed. The evolving value of non-FDG radiotracers, including ¹²⁴I, ¹⁸F-dihydroxyphenylalanine, and ⁶⁸Ga somatostatin analogs, is summarized.

CONCLUSION. PET/CT is a valuable imaging test, in the appropriate clinical context, for the management of thyroid cancers.

Thyroid cancer is the most common endocrine cancer, accounting for approximately 1.0–1.5% of all new cancers diagnosed each year in the United States [1]. Primary thyroid cancers are typically classified according to their histologic subtype. The most common types include papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), Hürthle cell thyroid carcinoma, medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma (ATC). Each of these histologically classified diseases is biologically and clinically distinct. PTC and FTC are classified as differentiated thyroid cancers (DTCs) [2], whereas ATC is also referred to as undifferentiated thyroid cancer [3]. Risk factors associated with the development of thyroid cancer include exposure to radiation to the head and neck region, especially in childhood, exposure to radioactive fallout due to nuclear power plant accidents or nuclear weapons testing, family history of thyroid malignancy, and a diet low in iodine. Low iodine intake has been associated with FTC and ATC, whereas PTC is seen in populations in which there is adequate dietary iodine intake [4].

Survival outcomes of patients who have DTC are favorable, with 97% and 94% 10-year disease-specific survival rates for PTC and FTC, respectively [5, 6]. However, recurrence and survival rates of patients with MTC or Hürthle cell thyroid carcinoma are significantly worse; each has a disease-specific 10-year survival rate of 73% [7]. ATC has very poor cure and long-term survival

rates [8], with a median survival duration of 5 months and a 1-year survival rate of less than 20% [9]. Fluorine-18 FDG PET/CT is valuable in the management of many human solid tumors [10–19]. The objective of this review is to synthesize the value of FDG PET/CT and to summarize the evolving role of non-FDG PET/CT in the management of various thyroid cancers.

Anatomic Imaging in Thyroid Cancer

Conventional imaging methods used in the workup of thyroid cancer include ultrasound, CT, and MRI, which can provide important anatomic information about the thyroid and surrounding structures [20]. Ultrasound is easy to perform, widely available, does not involve ionizing radiation, and is readily combined with fine-needle aspiration biopsy, and its diagnostic accuracy for thyroid lesions is as high as 85% to determine whether the nodule is suspicious [21]. It is therefore often the first diagnostic choice for evaluating thyroid nodules [22]. However, well-known disadvantages of ultrasound include operator dependence, limited localization of cervical metastatic lesions, especially in the central compartment when the thyroid gland remains in situ, and restricted evaluation of the posterior mediastinal and the retrosternal spaces [23]. According to the American Thyroid Association, ultrasound is recommended for preoperative evaluation of the contralateral lobe and cervical lymph nodes [24].

CT and MRI are useful in the workup for locally advanced thyroid cancers to assess tu-

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mor extension into surrounding structures and cervical lymph node metastases, which can assist with surgical planning [25]. CT has a sensitivity of 80–90.6% for detecting cervical metastases, although it may fail to detect diffuse interstitial lung metastases that may be visualized on radioiodine scintigraphy [26]. Choi et al. [27] evaluated the diagnostic accuracies of ultrasound, CT, and the combination of the two in primary tumor and cervical lymph-node metastases in PTC by comparing their results to pathologic specimens ($n = 299$). They found that ultrasound had higher sensitivity than CT for predicting bilateral thyroid involvement (87.0% vs 49.3%; $p < 0.001$) and greater accuracy than CT in assigning staging T category ($p < 0.01$). Ultrasound combined with CT had higher sensitivity than did CT alone for detecting nodal metastases in levels II–V (95.9% vs 81.7%; $n = 53$; $p = 0.025$); however, CT had greater sensitivity than ultrasound for level VI nodal metastasis (66.7% vs 53.2%; $p = 0.04$) [27] because of the limitations of ultrasound in evaluating this compartment with the thyroid gland in place.

However, CT scans have limitations in the setting of managing patients with thyroid cancer because the administration of iodine

contrast medium can delay the administration of postoperative radioactive iodine therapy. Therefore, before obtaining a CT scan in patients with thyroid cancer, a discussion among the treating team, which includes both surgeons and endocrinologists, should be performed to determine the benefit-to-risk ratio. Other options for imaging the thyroid include MRI because gadolinium-based contrast agents can be used without interfering with radioiodine administration. The advantages of MRI over CT include excellent tissue contrast and lack of radiation exposure. However, MRI times are longer and signal characteristics are often nonspecific [28]. MRI would be useful in characterizing the invasion of trachea and adjacent organs for surgical planning.

Incidental Diffuse and Focal FDG Thyroid Uptake

Incidental FDG uptake within the thyroid gland has been reported in 1–4% of patients undergoing FDG PET or PET/CT for other reasons and can be characterized as focal or diffuse uptake [29, 30]. Diffusely increased uptake (Fig. 1) in the thyroid has been reported in 0.6–3.3% of patients undergoing

FDG PET or PET/CT and commonly represents benign disease such as thyroiditis [31–33]. Karantanis et al. [32] evaluated 4732 patients without a diagnosis of thyroid cancer who underwent FDG PET/CT for other reasons. The authors found that 19 of 32 patients (59.4%) who were further evaluated for incidental diffuse thyroid uptake had a diagnosis of chronic lymphocytic thyroiditis. Chen et al. [33] found that 1.8% (46/2594) of patients with diffuse thyroid uptake on FDG PET/CT had chronic lymphocytic thyroiditis on the basis of thyroid function tests or ultrasound. Immune lymphocytic infiltration is the pathognomonic feature of chronic thyroiditis. Diffuse thyroid uptake in chronic thyroiditis can be attributed to increased FDG uptake in activated lymphoid tissue [34]. Focal FDG uptake (Fig. 2) within the thyroid gland can be associated with malignancy, most commonly PTC [35, 36]. The risk of malignancy in incidental focal thyroid uptake has been reported to be 24–36% [37–39]. Because of this considerable risk of malignancy in patients with incidental focal thyroid uptake, further workup with an ultrasound and biopsy is necessary. Treglia et al. [37] performed a meta-analysis of 34 stud-

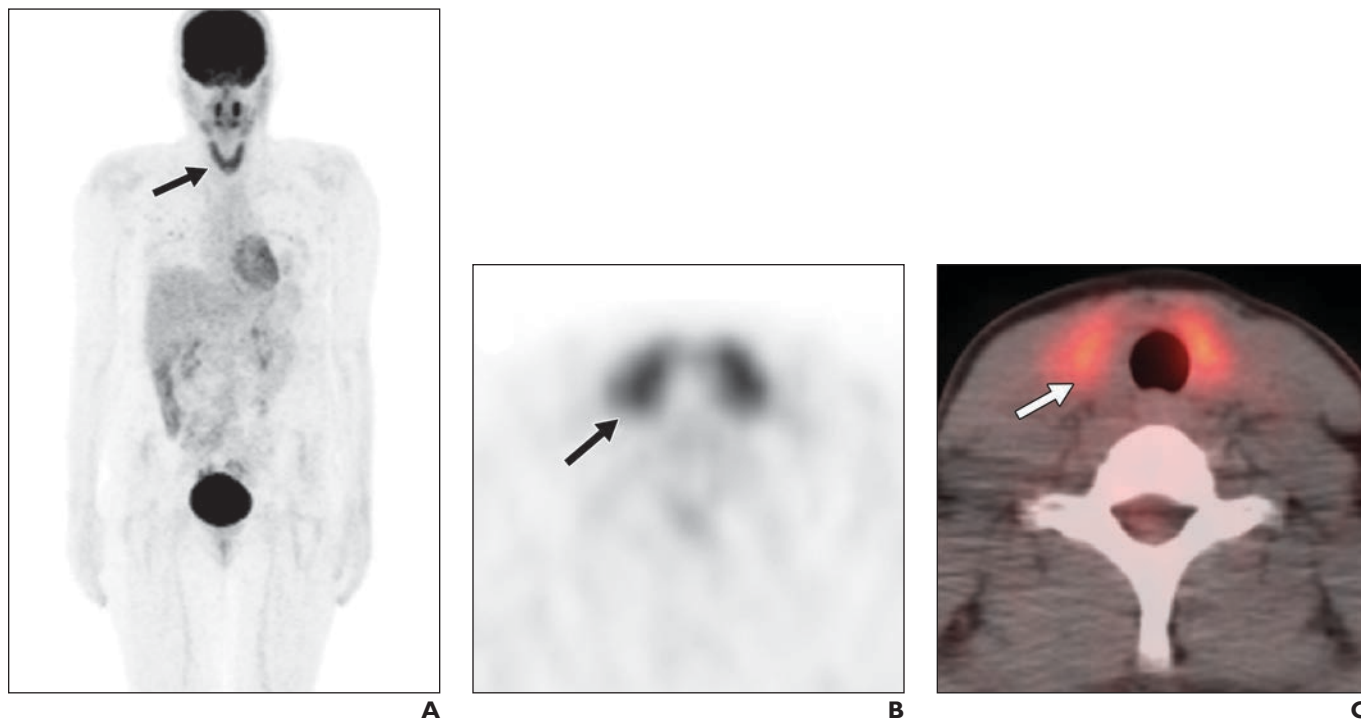


Fig. 1—23-year-old woman with melanoma of right shoulder who underwent restaging FDG PET/CT study after resection and adjuvant chemotherapy. **A–C**, Anterior maximum intensity projection (**A**), axial PET (**B**), and axial fused PET/CT (**C**) images show diffusely increased FDG uptake (maximum standardized uptake value, 5.58) in thyroid gland (arrows), which was incidentally noticed. Radioactive iodine uptake and scan of thyroid showed increased radiotracer uptake in normal-sized thyroid gland. Uptake of ^{123}I in thyroid was 8.1% at 4 hours and 9.6% at 25 hours (normal range, 12–34% at 24 hours). Antibody testing showed significantly elevated anti-thyroid peroxidase antibody level of 1633 ng/mL and antithyroglobulin level of 1740 ng/mL. Features are consistent with subacute thyroiditis.

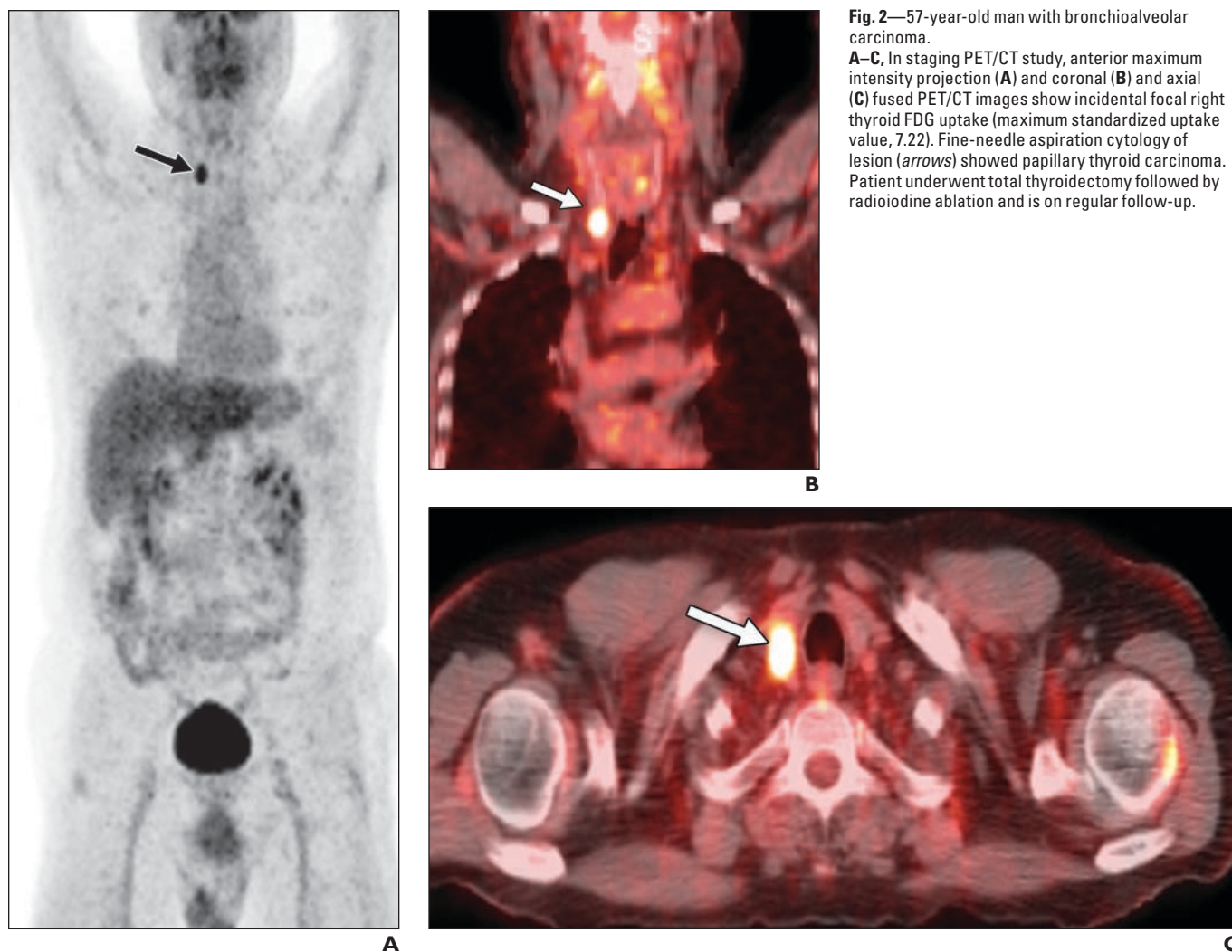


Fig. 2—57-year-old man with bronchioalveolar carcinoma. **A–C**, In staging PET/CT study, anterior maximum intensity projection (**A**) and coronal (**B**) and axial (**C**) fused PET/CT images show incidental focal right thyroid FDG uptake (maximum standardized uptake value, 7.22). Fine-needle aspiration cytology of lesion (*arrows*) showed papillary thyroid carcinoma. Patient underwent total thyroidectomy followed by radioiodine ablation and is on regular follow-up.

ies evaluating incidental focal thyroid uptake detected by FDG PET/CT ($n = 215,057$) and found a pooled malignancy risk of 36.2% (95% CI, 33.8–38.6%). In a systematic review performed by Shie et al. [40] of 18 articles on incidental focal thyroid uptake ($n = 55,160$), 62.1% of patients had benign disease, 33.2% had cancer, and 4.7% of diagnoses were indeterminate nodules. PTC was found to be the most prevalent thyroid malignancy among those who had cancer (82.2%).

FDG PET/CT in Differentiated Thyroid Carcinoma

Whole-body scan (WBS) with radioiodine (^{131}I) is the most effective method for tumor detection, staging, and treatment planning [41]. Iodine-131-WBS is useful for determining the differentiation of the tumor on the basis of its avidity to iodine, identifying remnant thyroid tissue, and evaluating for

distant metastatic disease [42]. Most well-differentiated thyroid carcinomas are relatively slow growing and can be FDG negative [43]. Therefore, the role of FDG PET/CT in the management of patients with DTC is primarily limited to postoperative follow-up. Because only 4–7% of patients with DTC present initially with distant metastasis, the routine use of an initial staging PET would not be indicated [44]. Although FDG PET does not provide information beyond that yielded by ultrasound for local preoperative assessment of thyroid cancer [28], several studies have reported that it has a high sensitivity (up to 85%) and specificity (up to 95%) for distant metastases in patients with DTC [45, 46].

After surgery, a substantial number of patients have residual or metastatic disease that is not radioiodine avid, and PET/CT has emerged as a powerful tool in the assessment of patients who have recurrent or metastat-

ic tumor not demonstrable with other imaging modalities [47]. The combination of ^{131}I -WBS and thyroglobulin measurement is a reliable indicator of the presence of metastases in 82.6% of patients with DTC after surgery [48]. However, FDG PET/CT plays a valuable role (Figs. 3 and 4) in the post-thyroidectomy workup of patients with DTC who have elevated thyroglobulin levels and a negative ^{131}I -WBS [24]. This subset of patients poses a diagnostic and therapeutic challenge because disease localization can be difficult. As DTC cells dedifferentiate, their radioiodine uptake generally decreases and their glucose metabolism generally increases [49, 50]. Although this finding is not always present, this alternating pattern of ^{131}I uptake to FDG uptake has been described as a “flip-flop” uptake pattern [51].

Many studies evaluating the role of FDG PET/CT in evaluating recurrent or metastat-

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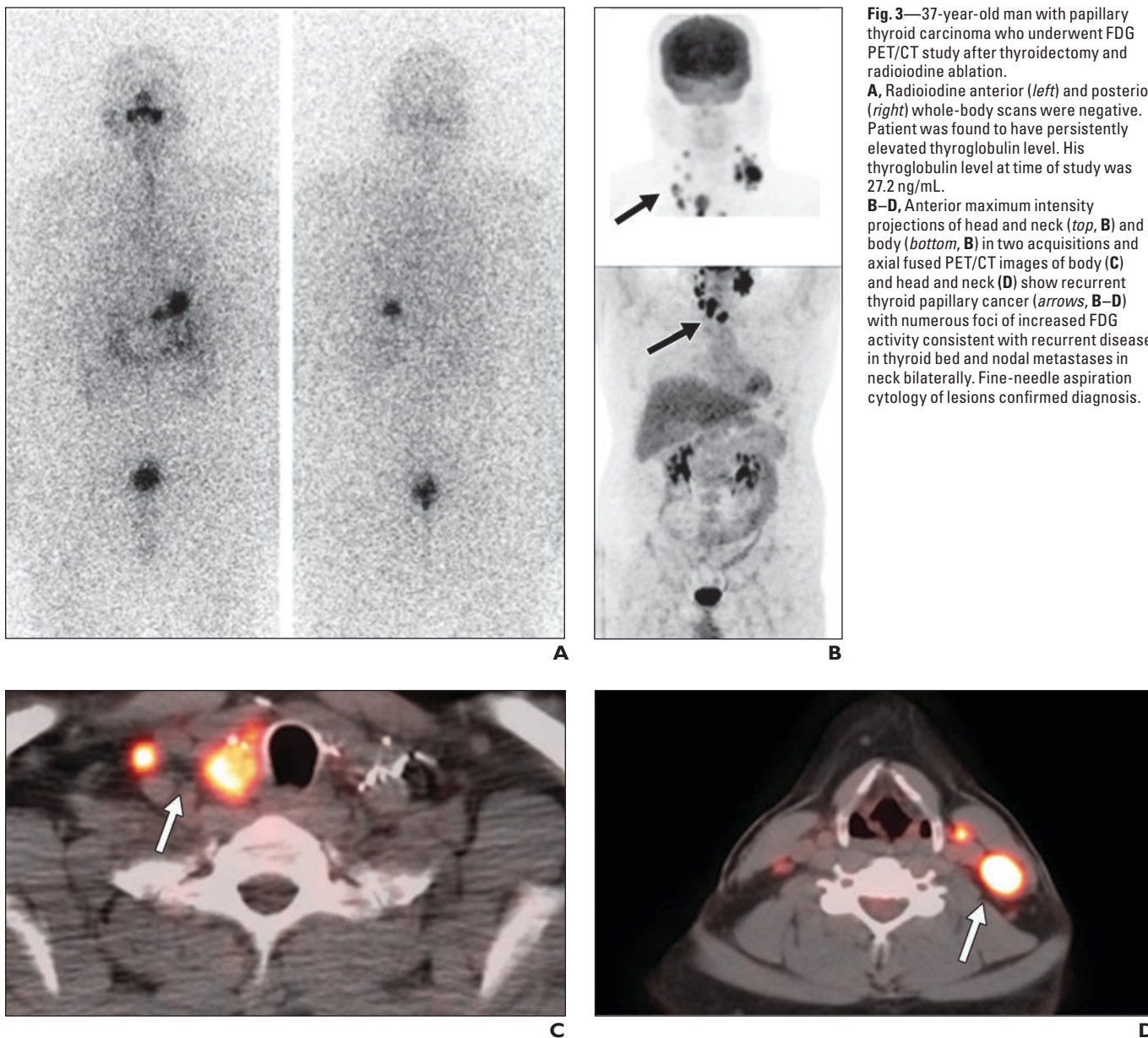


Fig. 3—37-year-old man with papillary thyroid carcinoma who underwent FDG PET/CT study after thyroidectomy and radioiodine ablation. **A**, Radioiodine anterior (*left*) and posterior (*right*) whole-body scans were negative. Patient was found to have persistently elevated thyroglobulin level. His thyroglobulin level at time of study was 27.2 ng/mL. **B–D**, Anterior maximum intensity projections of head and neck (*top, B*) and body (*bottom, B*) in two acquisitions and axial fused PET/CT images of body (**C**) and head and neck (**D**) show recurrent thyroid papillary cancer (*arrows, B–D*) with numerous foci of increased FDG activity consistent with recurrent disease in thyroid bed and nodal metastases in neck bilaterally. Fine-needle aspiration cytology of lesions confirmed diagnosis.

ic DTC have been published, and meta-analyses of such studies have been performed. Dong et al. [52] reviewed a total of 25 studies comprising of 789 patients and concluded that FDG PET/CT has a high pooled sensitivity of 93.5% for detecting DTC recurrence and metastasis in the absence of radioiodine uptake. In a similar meta-analysis of 12 studies and literature review, Miller et al. [53] found that PET/CT had a sensitivity of 94.0% for detecting recurrence of PTC. Furthermore, PET/CT is superior to a number of more conventional imaging techniques for detecting recurrent or metastatic DTC. Weber et al. [54] found that ul-

trasound provided localization of recurrent or metastatic thyroid disease in only eight of the 14 patients (57%). Seo et al. [55] reported that 21.1% of lymph-node and soft-tissue lesions missed on neck ultrasound were identified with PET/CT studies. PET/CT has also shown a clear advantage compared with PET in revealing small metastatic lesions [56]. Several studies have found a definite correlation between the thyroglobulin levels and the diagnostic accuracy of PET in these patients. A summary of the findings in these studies has been listed in Table 1. These studies show higher diagnostic ac-

curacy of PET/CT with high thyroglobulin levels. Bertagna et al. [57] reviewed the literature on the correlation between PET/CT and thyroglobulin levels and concluded that a thyroglobulin cutoff level of 10 ng/mL is reasonable, maintaining high accuracy in terms of a good compromise between sensitivity and specificity. The American Thyroid Association recommends an unstimulated cutoff of 10 ng/mL [24]. However, a recent study by Giovanella et al. [58] states that 88% of patients ($n = 102$) with a positive FDG PET/CT scan had thyroglobulin levels greater than 5.5 ng/mL. Furthermore, because dedifferentiated thyroid

TABLE I: Summary of Studies Evaluating the Relationship Between Thyroglobulin Levels and the Diagnostic Accuracy of PET/CT in Patients With Differentiated Thyroid Cancers

| Study | No. of Patients | Thyroglobulin Level (ng/mL) | Sensitivity (%) | Specificity (%) |
|----------------------|-----------------|---|-----------------|-----------------|
| Vural et al. [59] | 105 | > 38.2 (TSH stimulation) or > 1.9 (TSH suppression) | 74 | 80 |
| Zoller et al. [56] | 33 | > 20 | 88 | |
| | | < 20 | 22 | |
| Bertagna et al. [97] | 52 | > 21 | 76.5 | 83.3 |
| Schluter et al. [98] | 64 | < 10 | 11 | |
| | | 10–20 | 50 | |
| | | > 100 | 93 | |
| Shammas et al. [99] | 61 | < 5 | 60 | |
| | | 5–10 | 63 | |
| | | > 10 | 72 | |

Note—TSH = thyroid-stimulating hormone.

carcinoma cells can have a reduced capacity to produce and secrete thyroglobulin, a low thyroglobulin level is not necessarily an indication of a small tumor burden in pa-

tients with a negative ¹³¹I scan and a measurable thyroglobulin level. The impact of thyroid-stimulating hormone (TSH) levels on radioiodine scans has been established;

however, regarding the impact of TSH levels on improving accuracy of FDG PET/CT, no complete consensus exists. It has been suggested that TSH suppression can be considered in patients with low levels of thyroglobulin (< 10 ng/mL) and good compliance to hypothyroidism and that TSH stimulation with recombinant TSH should be considered in patients who are unable to tolerate symptoms of hypothyroidism [57].

In combination with thyroglobulin, FDG PET/CT provides important prognostic information (Fig. 5) and is crucial for clinical decision making for patients with DTC with a negative ¹³¹I scan. Vural et al. [59] have observed higher PET positivity in patients older than 40 years compared with younger patients (70% vs 53%). Because age at the time of detection of distant metastases is independently associated with mortality and PET positivity is higher in patients older than 40 years [59], it has been inferred that FDG uptake is associated with worse prognosis and aggressive tumor behavior [60].

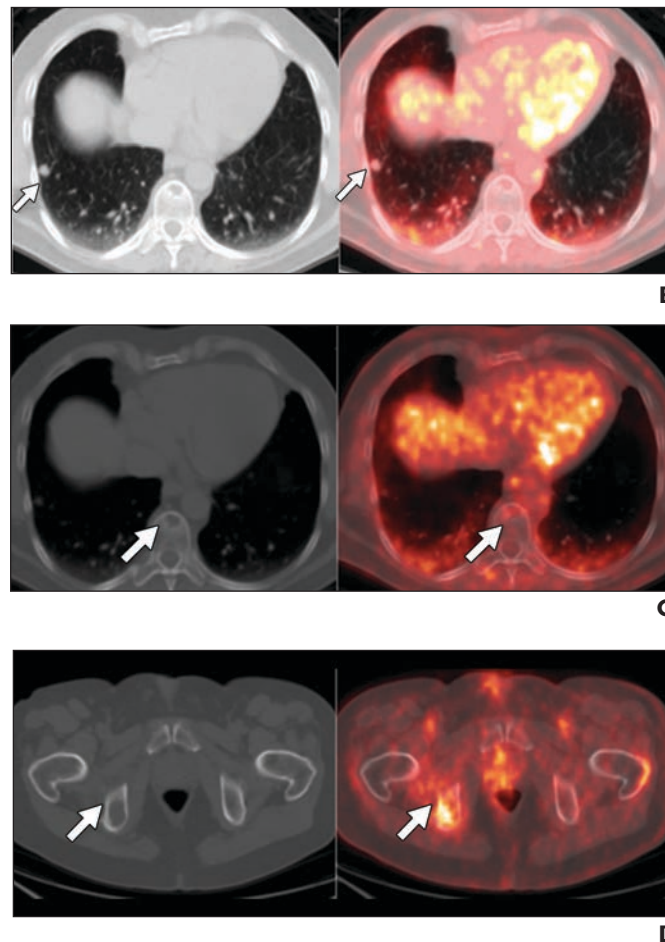


Fig. 4—62-year-old man with metastatic follicular carcinoma of thyroid who underwent FDG PET/CT study after thyroidectomy, multiple radioiodine ablations, and chemoradiation. His thyroglobulin level at time of study was 478.4 ng/mL. **A–D**, Anterior maximum intensity projection (**A**), axial contrast-enhanced CT (*left, B–D*), and fused PET/CT (*right, B–D*) images show FDG-avid metastatic lesions (*arrows, B–D*) in right lung (**B**), right acetabulum (**C**), and T10 vertebra (**D**). After study, patient underwent chemoradiation.

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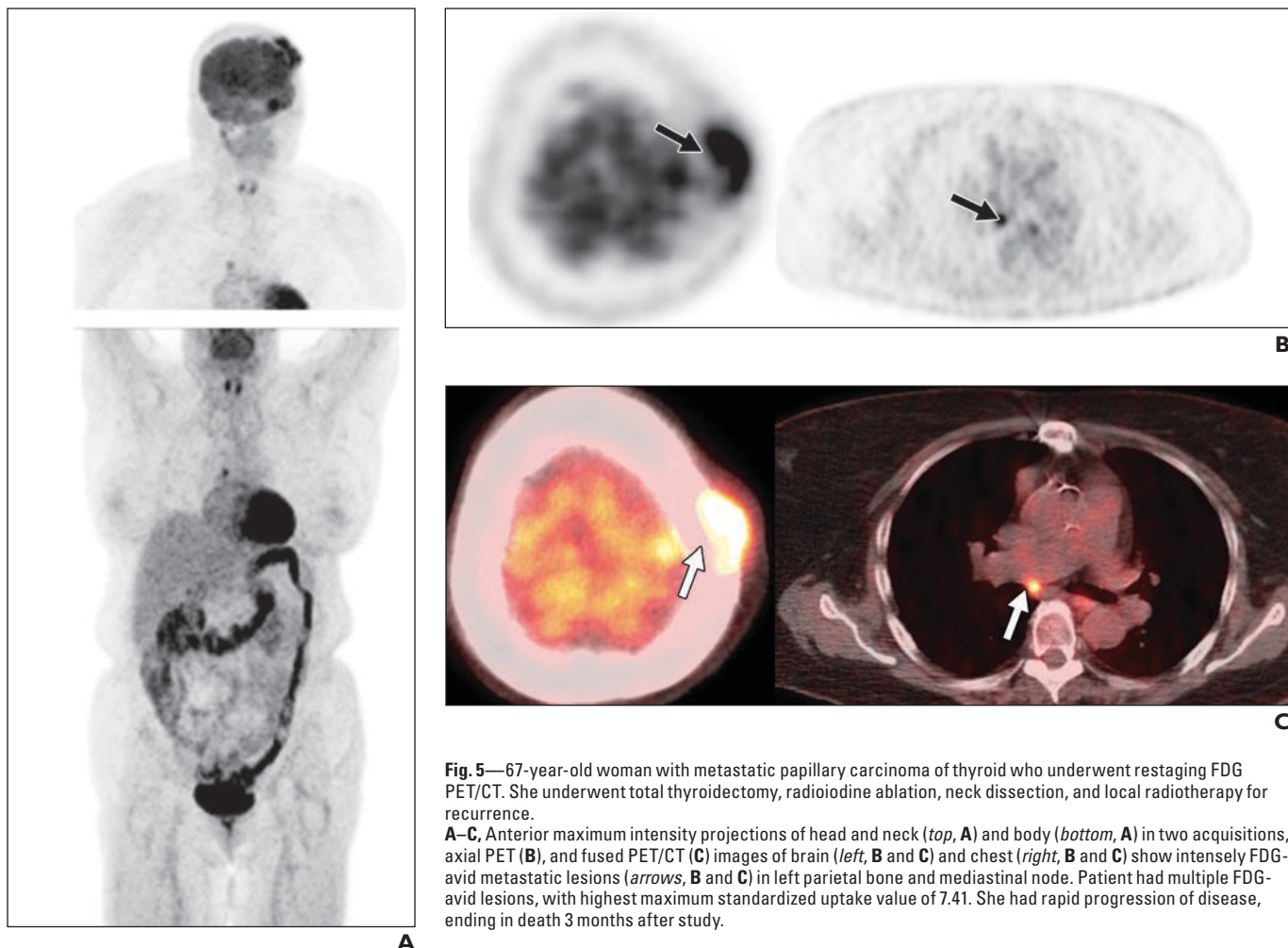


Fig. 5—67-year-old woman with metastatic papillary carcinoma of thyroid who underwent restaging FDG PET/CT. She underwent total thyroidectomy, radioiodine ablation, neck dissection, and local radiotherapy for recurrence. **A–C**, Anterior maximum intensity projections of head and neck (*top, A*) and body (*bottom, A*) in two acquisitions, axial PET (**B**), and fused PET/CT (**C**) images of brain (*left, B and C*) and chest (*right, B and C*) show intensely FDG-avid metastatic lesions (*arrows, B and C*) in left parietal bone and mediastinal node. Patient had multiple FDG-avid lesions, with highest maximum standardized uptake value of 7.41. She had rapid progression of disease, ending in death 3 months after study.

Robbins et al. [61] have shown that a positive FDG PET has a significant negative predictive value for overall survival ($p < 0.001$). Maximum standardized uptake value (SUV_{max}) has also been shown to be a significant prognostic factor. In that study [61], SUV_{max} values were categorized as either no uptake or into one of four quartiles ($n = 56$ per quartile). The 2-year survival rate was 99% in the negative group, 98% in the lowest quartile, and 52% in the quartile with the highest SUV_{max} , indicating that higher SUV_{max} of lesions correlate with decreased overall survival. The number of FDG-avid lesions, used as a surrogate for tumor volume, was also found to be an independent prognostic factor. Those authors divided the patients into four categories (no lesions, $n = 181$; 1–2 lesions, $n = 83$; 3–10 lesions, $n = 92$; > 10 lesions, $n = 51$) and found a highly significant overall reduction in survival ($p < 0.001$) as the number of FDG-avid lesions increased.

FDG PET/CT in Hürthle Cell Thyroid Carcinoma

Hürthle cell thyroid carcinoma is an aggressive histologic subtype of thyroid cancer, with a high risk of metastasis and a worse prognosis when compared with DTC [62]. Hürthle cell thyroid carcinoma seems unable to concentrate ^{131}I but is an FDG-avid tumor [63] (Fig. 6). Accurate localization of disease is essential in Hürthle cell thyroid carcinoma, because surgery and external beam radiation therapy may be beneficial.

Multiple studies have shown a high sensitivity of FDG PET for Hürthle cell thyroid carcinoma relative to other imaging modalities. A multicenter study conducted by Riemann et al. [64] found a sensitivity of 92% and specificity of 95% for FDG PET/CT in Hürthle cell thyroid carcinoma, whereas corresponding values for ^{131}I -WBS were 65% and 94% and those for ultrasound were 37% and 94% ($n = 327$). Pryma et al. [65] reported a sensitivity of 95.8% and a speci-

ficity of 95% for FDG PET/CT in Hürthle cell thyroid carcinoma ($n = 44$). They also found that FDG PET/CT had prognostic value, noting a 6% increase in mortality with an increase in SUV_{max} of one unit ($p < 0.001$). Lowe et al. [66] found that FDG PET/CT had a sensitivity of 92% for Hürthle cell thyroid carcinoma in 14 scans of 12 patients with Hürthle cell thyroid carcinoma, also noting that half of the PET scans detected tumor not seen on conventional imaging modalities, resulting in a change in disease stage and management. Plotkin et al. [67] report that FDG PET/CT had a sensitivity of 92%, specificity of 80%, positive predictive value of 92%, and negative predictive value of 80% with an accuracy of 89% for identification of Hürthle cell thyroid carcinoma ($n = 17$).

FDG PET/CT in Medullary Thyroid Carcinoma

MTC is a challenging malignancy. Despite aggressive primary treatment with total

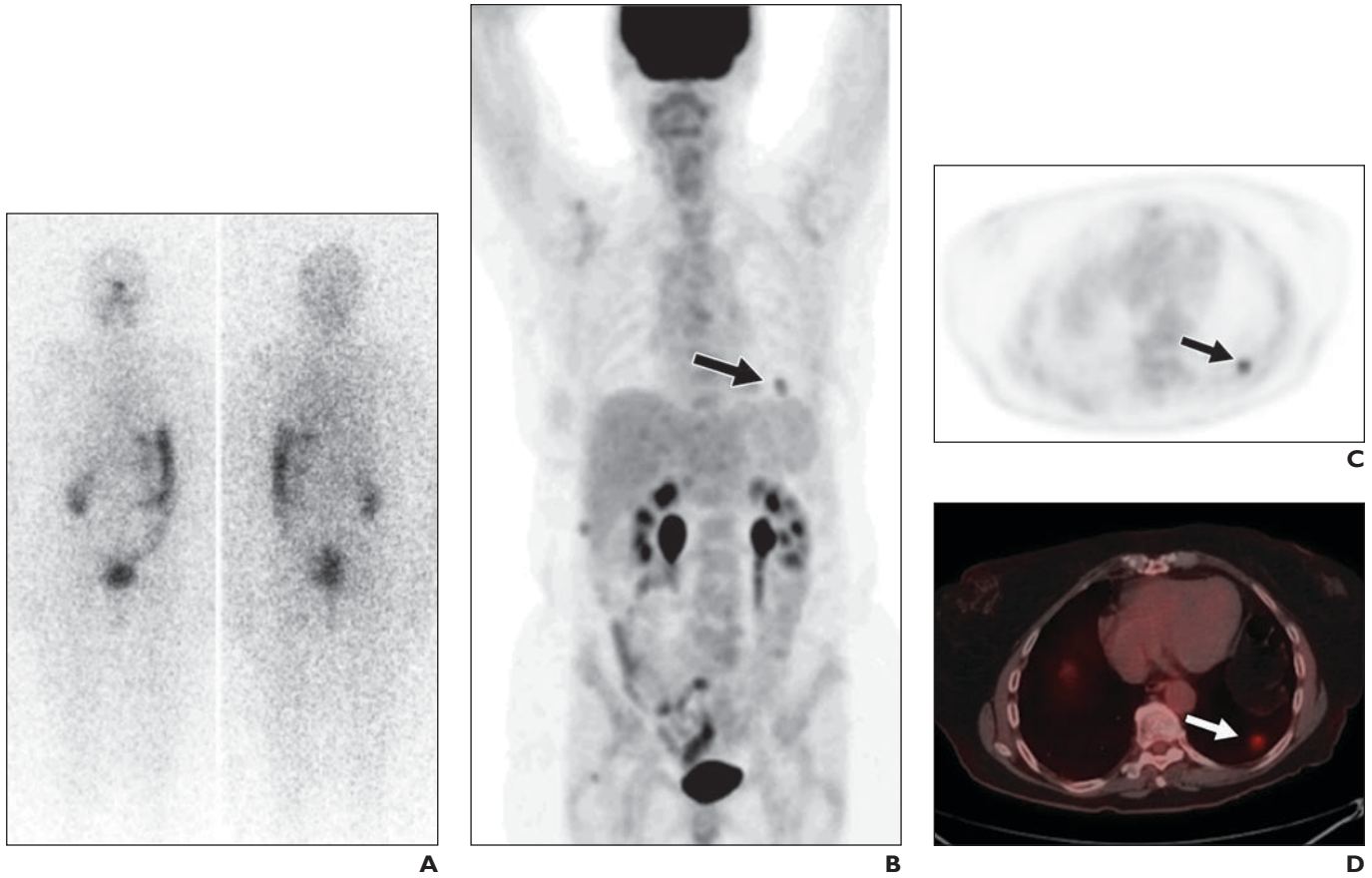


Fig. 6—74-year-old woman with Hürthle cell carcinoma who presented with increasing thyroglobulin levels and negative ^{131}I whole-body scan after thyroidectomy. **A–D**, FDG PET/CT anterior (left, **A**) and posterior (right, **A**) views, anterior maximum intensity projection (**B**), axial PET (**C**), and fused axial PET/CT (**D**) images show hypermetabolic lobulated 8-mm pulmonary nodule (arrows, **B–D**) typical for metastasis.

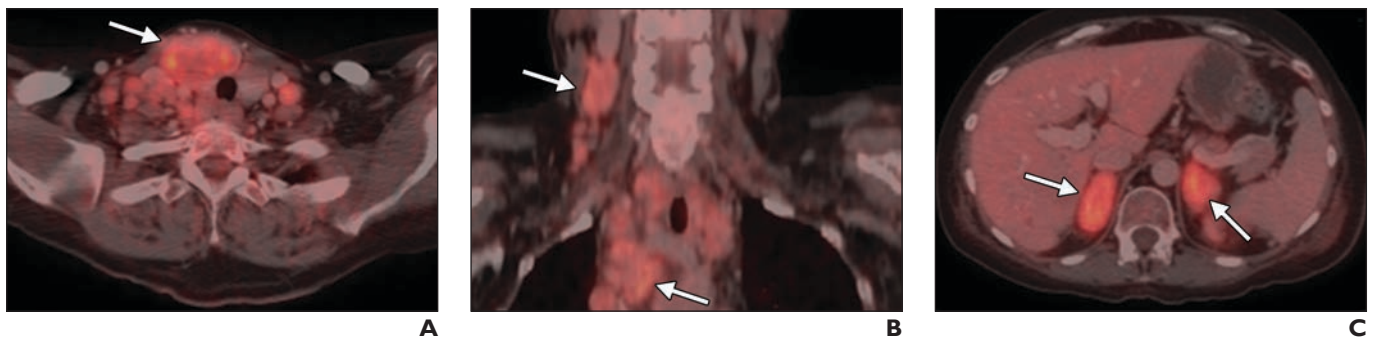


Fig. 7—52-year-old woman with thyroid mass confirmed as medullary carcinoma by fine-needle aspiration who underwent FDG PET/CT staging. **A–C**, Coronal (**A** and **C**) and axial (**B**) fused FDG PET/CT images show high FDG avidity (arrows) in thyroid (**A**), cervical and mediastinal lymph nodes (**B**), and adrenal glands bilaterally (**C**). PET/CT informed planning of subsequent total thyroidectomy with central lymph-node dissection, and mediastinal or cervical lymph-node debulking was performed. Adrenal FDG uptake resolved after thyroidectomy and debulking surgery.

thyroidectomy and modified neck lymph-node dissection, approximately 50% of patients have persistent or recurrent disease [68] (Figs. 7 and 8). Imaging of recurrent disease in MTC is difficult and still poses a major problem in the management of the disease, and FDG PET/CT has been found to be

of use in patients with biochemical evidence of recurrence (i.e., serum calcitonin and carcinoembryonic antigen) [69].

Treglia et al. [69] reported a meta-analysis of 24 studies evaluating the performance of FDG PET or PET/CT in detecting recurrent MTC. They showed that the pooled detec-

tion rate on a per patient–based analysis was 59% and that the levels of biochemical markers influenced lesion detection rates. Pooled detection rates of FDG PET or PET/CT in recurrent MTC were 75% when the calcitonin level was 1000 ng/mL or higher and 40% when it was less than 150 ng/mL. Similarly,

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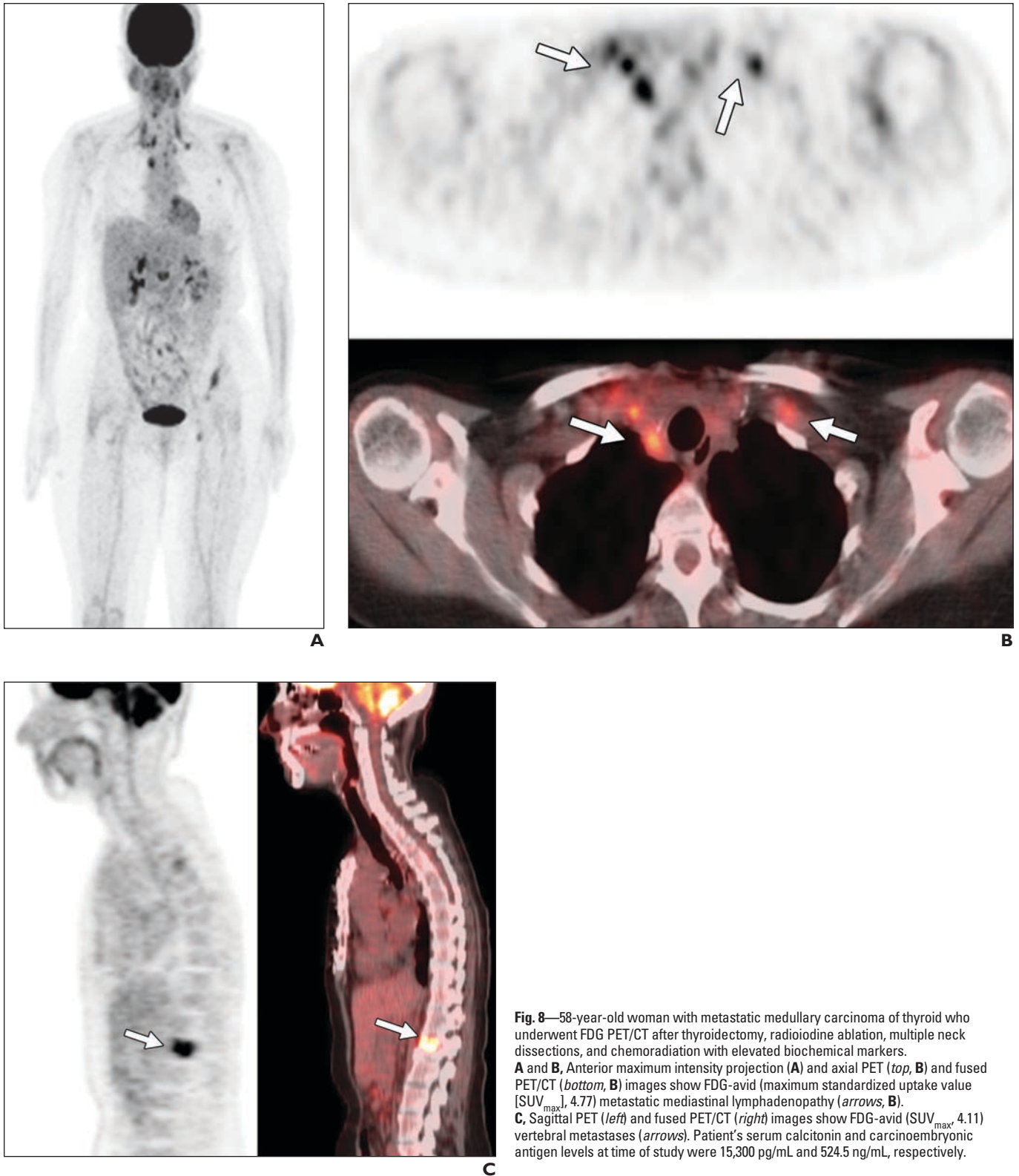


Fig. 8—58-year-old woman with metastatic medullary carcinoma of thyroid who underwent FDG PET/CT after thyroidectomy, radioiodine ablation, multiple neck dissections, and chemoradiation with elevated biochemical markers. **A** and **B**, Anterior maximum intensity projection (**A**) and axial PET (*top*, **B**) and fused PET/CT (*bottom*, **B**) images show FDG-avid (maximum standardized uptake value [SUV_{max}], 4.77) metastatic mediastinal lymphadenopathy (*arrows*, **B**). **C**, Sagittal PET (*left*) and fused PET/CT (*right*) images show FDG-avid (SUV_{max} , 4.11) vertebral metastases (*arrows*). Patient's serum calcitonin and carcinoembryonic antigen levels at time of study were 15,300 pg/mL and 524.5 ng/mL, respectively.

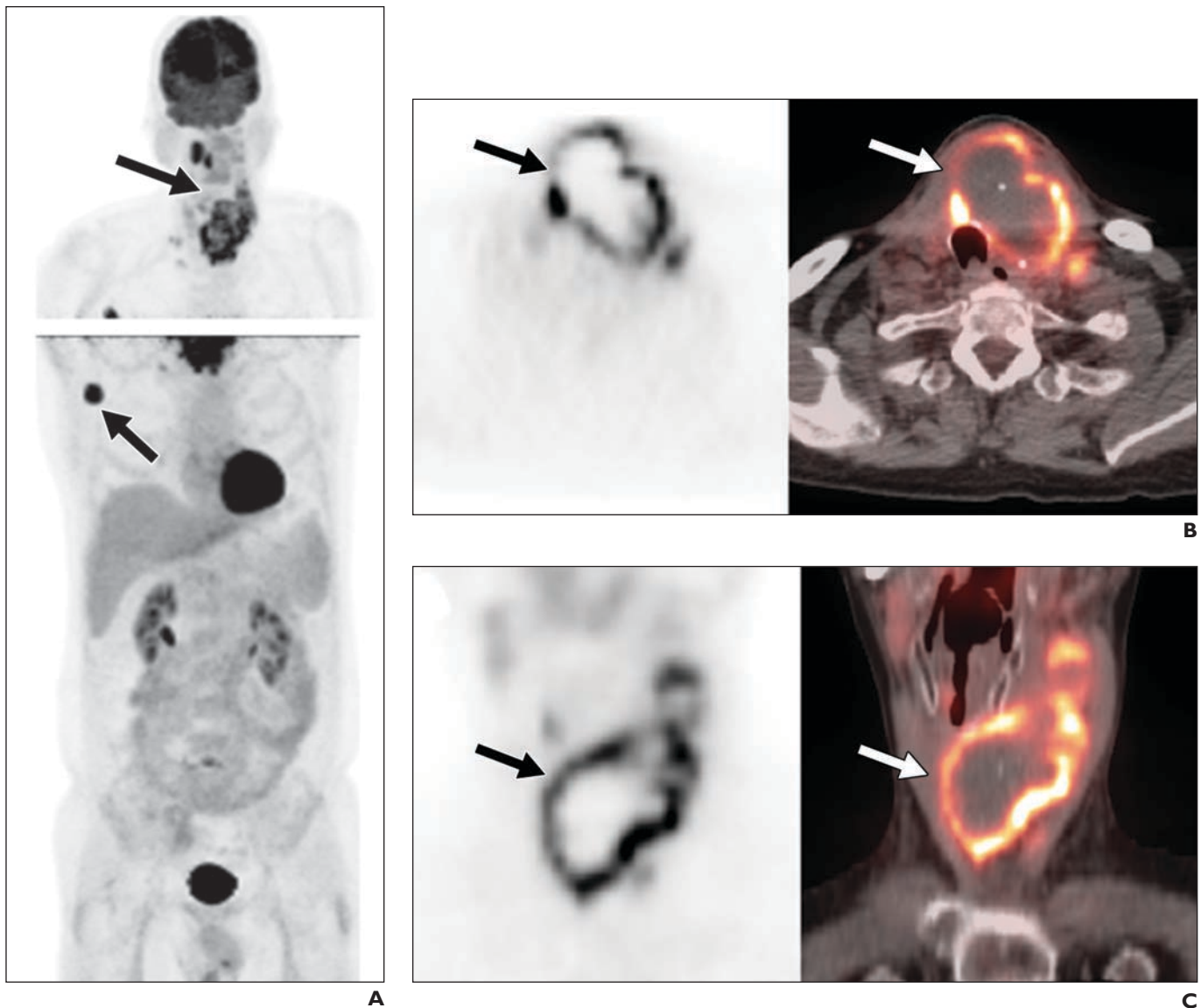


Fig. 9—65-year-old man with anaplastic thyroid cancer. **A–C**, Anterior maximum intensity projections of head and neck (*top, A*) and body (*bottom, A*), axial PET (*left, B*) and fused PET/CT (*right, B*), and coronal PET (*left, C*) and fused PET/CT (*right, C*) images show large necrotic mass (*arrows*) in lower anterior neck with intense peripheral FDG uptake (maximum standardized uptake value, 11.4) and FDG-avid right axillary lymphadenopathy. Mass was found adherent to local structures. Mass extends into upper mediastinum and displaces trachea and larynx to right.

detection rates were 69% and 45% when carcinoembryonic antigen levels were greater than 5 ng/mL and less than or equal to 5 ng/mL, respectively. The biochemical marker doubling time was also found to affect the detection rates, with shorter doubling times correlating with higher detection rates. Detection rates were 26% and 67% when the calcitonin doubling time was greater than 24 months and less than 24 months, respectively, and patients with carcinoembryonic antigen doubling times of greater than 24 months and less than 24 months had detection rates

of 33% and 91%, respectively [69, 70]. No significant difference in detection rate was found when the calcitonin levels were below 500 pg/mL or 500–1000 pg/mL [71].

MTC detection rate of FDG PET/CT was highest in patients with calcitonin levels greater than 1000 pg/mL. The overall sensitivity was only 20–36.8% when the calcitonin levels were below 1000 pg/mL [71–73]. The relatively low detection rate of disease in patients with low calcitonin levels is likely a result of a smaller tumor mass or microscopic disease [72]. Skoura et al. [71] ob-

served from 59 scans of 51 patients that, in FDG PET/CT scans positive for MTC, the mean (\pm SD) value SUV_{max} of all lesions was 3.76 ± 1.29 (range, 2–7), which is relatively low and may reflect the more indolent nature of many MTC lesions. Interestingly, it was also observed in their study that the sensitivity of FDG PET/CT for MTC recurrence in patients with multiple endocrine neoplasia (MEN) type IIA syndrome was significantly lower (23%); for patients with MEN type IIA with calcitonin levels less than 2000 pg/mL, sensitivity fell to 0%. When patients with

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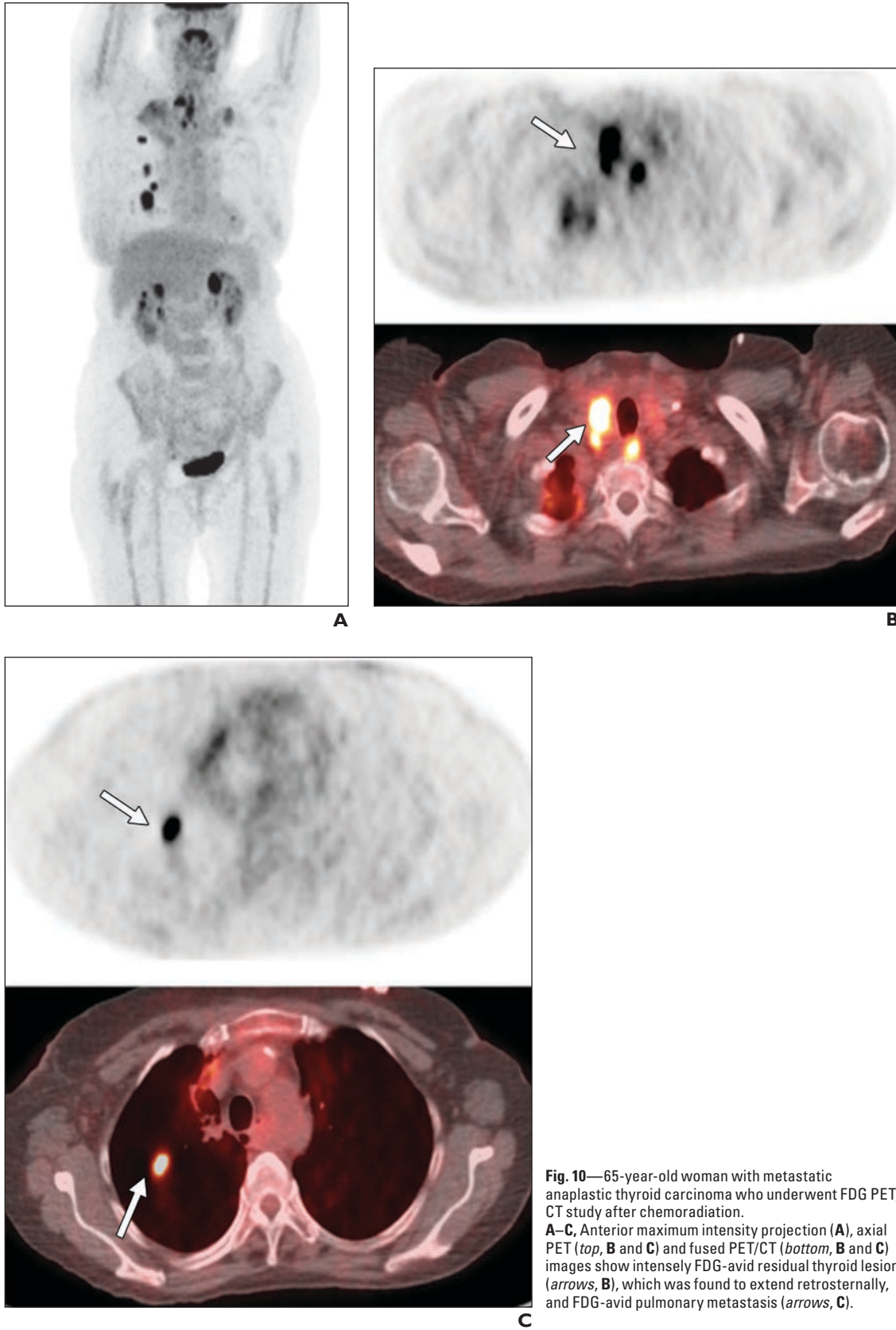


Fig. 10—65-year-old woman with metastatic anaplastic thyroid carcinoma who underwent FDG PET/CT study after chemoradiation.

A–C, Anterior maximum intensity projection (**A**), axial PET (**top, B and C**) and fused PET/CT (**bottom, B and C**) images show intensely FDG-avid residual thyroid lesion (**arrows, B**), which was found to extend retrosternally, and FDG-avid pulmonary metastasis (**arrows, C**).

C

MEN type IIA syndrome were excluded, overall per-patient sensitivity of FDG PET/CT for detecting MTC lesions increased from 44.1% to 50%. Those authors suggest that the sensitivity is better in patients with sporadic MTC or MEN type IIB than in those with MTC as part of MEN type IIA syndrome.

FDG PET/CT in Anaplastic Thyroid Carcinoma

ATC is a rapidly growing thyroid tumor; more than 75% of patients will have local invasion and 50% of patients will have distant metastases at the time of presentation (Figs. 9 and 10). ATC occurs in older age groups and is marked by rapid growth and extensive local invasion. Despite aggressive treatments, the cure and long-term survival rates are poor for these patients [8]. The most common site for distant metastases is the lungs; less common are metastases to the bone marrow and brain. About 50% of patients with ATC have a history of multinodular goiter, and about 20% have a history of DTC. Diagnostic imaging with neck ultrasound, CT, and MRI are used routinely in ATC to define the extent of the primary tumor as well as regional and distant involvement [74, 75].

ATC lesions typically have low iodine uptake and decreased thyroglobulin production due to their poorly differentiated state [76]. Furthermore, ATC lesions, whether primary or metastatic, consistently show high FDG uptake [77]. FDG PET/CT is useful at initial staging and in the early evaluation of treatment response and follow-up. The American Thyroid Association recommends FDG PET and PET/CT for the evaluation of distant metastatic disease, especially bone lesions. Other indications for FDG PET or PET/CT in ATC include evaluation of surgical candidacy, as well as follow-up imaging, with a higher sensitivity than CT alone (99.6% vs 62%; $p < 0.002$) to detect lesions [78]. FDG PET/CT may be of value to evaluate response to systemic or local therapy in patients with known persistent disease [79].

Bogsrud et al. [80] reported that PET findings had a direct impact on the management of approximately 50% of patients diagnosed with ATC ($n = 16$). Both SUV_{max} and FDG uptake volume were found to be of prognostic value for survival of patients with ATC. Poisson et al. [78] report that patients with SUV greater than 18 on FDG PET/CT had significantly worse 6-month survival rates than did those with SUV less than 18 (20%

vs 80%), as did patients with FDG uptake volume greater than 300 mL compared with patients with FDG uptake volume less than 300 mL (10% vs 90%).

Alternative PET/CT Radiopharmaceuticals

Although FDG has found wide application in thyroid PET/CT, alternative radiotracers have been evaluated extensively for specific implications in thyroid cancers. PET/CT with ^{124}I , ^{18}F -dihydroxyphenylalanine (F-DOPA), and somatostatin analogs tagged with ^{68}Ga have been shown to be useful [81, 82].

PET with ^{124}I has emerged as a valuable diagnostic tool for the detection of recurrent or residual DTC. PET with ^{124}I has greater spatial resolution than does planar ^{131}I -WBS, even at lower radioiodine activities and therefore at considerably low radiation exposure. PET with ^{124}I can provide specific dosimetric information, allows quantification of the volume of the thyroid tumor, and can be used as a surrogate marker before therapeutic intervention with ^{131}I . Simultaneous administration of the therapeutic dose of ^{131}I and a tracer dose of ^{124}I allows accurate measurement of iodine uptake during therapy [83]. PET with ^{124}I can be performed as early as 24 hours after the administration of radiotracer without sacrificing diagnostic accuracy compared with high-dose ^{131}I -WBS [84]. Metastasis localization is also improved with use of ^{124}I -PET/CT compared with conventional imaging. Lee et al. [85] compared ^{124}I -PET/CT to more conventional imaging for detection of DTC recurrence ($n = 19$), finding that five patients showing uptake on ^{124}I -PET/CT scans had lesions that were not visible on posttreatment ^{131}I scans. Of these patients, four (80.0%) were confirmed to have recurrence using either histologic or other radiologic means. One of these patients underwent further surgery and the other three received high-dose radiation therapy. Moreover, ^{124}I -PET correctly restaged all four patients. A false-positive finding was recorded for only one patient.

F-DOPA PET is also being investigated for metabolic imaging of MTC. Use of this agent is based on the postulation that F-dopa is retained by MTC metastases owing to intracellular decarboxylation, a feature of the neuroendocrine origin of MTC [86]. Beheshti et al. [87] reported a patient-based analysis ($n = 26$) of F-DOPA PET showing a sensitivity of 81%, which is considerably higher than the sensitivity of FDG PET/CT

in MTC [87]. Multiple other studies report similarly high sensitivity values [86, 88]. In a retrospective study comparing F-DOPA, FDG, and ^{68}Ga -somatostatin analog PET/CT findings in a group of patients with residual or recurrent MTC ($n = 18$) and elevated serum calcitonin levels, Treglia et al. [89] concluded that F-DOPA PET/CT was superior on both per-patient and per-lesion analyses. F-DOPA was positive in all five patients with known lesions and in eight of 13 patients with negative or inconclusive results on conventional imaging.

Gallium-68-labeled somatostatin analogs have been developed for PET of somatostatin receptors in neuroendocrine tumors. Preclinical and clinical studies have described the use of several analogs, including tetraazacyclododecanetetraacetic acid (DOTA)-Tyr³ octreotide, DOTA-Tyr³, DOTA-Thr⁸ octreotide (DOTA-TATE), and DOTA-1-Nal³-octreotide [90–93]. These analogs have a high affinity for somatostatin receptors, which are overexpressed in neuroendocrine tumor cells [94, 95]. Conry et al. [96] compared ^{68}Ga -DOTA-TATE PET/CT and FDG PET/CT in 18 patients with MTC and found that, although the sensitivity was marginally lower for ^{68}Ga -DOTA-TATE (72% vs 78%), this difference was marginally statistically insignificant ($p = 0.056$). However, the previously mentioned retrospective study by Treglia et al. [89] found that ^{68}Ga -somatostatin analogs had a lower sensitivity than F-DOPA PET/CT (33.3% vs 72.2%) and provided no additional information in any patient. Furthermore, they report that ^{68}Ga -somatostatin analog PET/CT missed all liver lesions detected by FDG PET/CT and F-DOPA PET/CT, which may be explained by a low lesion-to-background ratio caused by low hepatic expression of somatostatin receptors and physiologic tracer uptake by the liver.

Conclusion

FDG PET/CT has a role in the management of various thyroid cancers. Incidental focal thyroid uptake on PET/CT has a high risk of malignancy, 24–36%, necessitating further diagnostic workup with ultrasound and fine-needle aspiration biopsy. PET/CT has proven useful for the detection of recurrent or metastatic disease, as well as provision of prognostic information in patients with DTC and elevated thyroglobulin levels with negative iodine scintigraphy. FDG PET/CT has also been shown to have high sensitivity and specificity and to provide prognos-

tic information in patients with Hürthle cell thyroid carcinoma. ATC lesions have high FDG avidity, and PET/CT has been found useful in the clinical management of patients with ATC. Although its utility is limited in patients with MEN type IIA syndrome, FDG PET/CT is useful in patients with sporadic MTC or MEN type IIB syndrome, and elevated biochemical markers are associated with positive studies in patients with MTC.

The value of non-FDG PET/CT in thyroid cancer management is evolving. PET with ¹²⁴I has greater spatial resolution than does planar ¹³¹I-WBS even at lower radioiodine activities. F-DOPA and somatostatin analogs labeled with ⁶⁸Ga may be valuable in the evaluation of MTC in the future.

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