



Paul Desire Trouillebert, 1829-1900. *Au Bord de La Loire a Montsoreau*. Oil on canvas, 15" x 22¼".
Courtesy of the Callan Fine Art gallery, New Orleans, Louisiana.

*Current literature indicates that
FDG-PET has a role in the follow-up
of medullary and anaplastic
thyroid carcinomas.*

Review of Fluorine-18-2-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography (FDG-PET) in the Follow-Up of Medullary and Anaplastic Thyroid Carcinomas

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Background: *The goal of posttreatment follow-up for medullary and anaplastic thyroid cancer (MTC and ATC) is the early diagnosis of recurrence or metastases. However, routine follow-up protocols, including physical examination and clinically oriented investigations, are not standardized, and their sensitivity in accurately detecting recurrent or metastatic disease is often suboptimal. A valuable addition to posttreatment follow-up of oncology patients is positron emission tomography using fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG-PET).*

Methods: *We review the role of FDG-PET imaging in the follow-up of patients previously treated for MTC and ATC.*

Results: *Based on the encouraging literature data, FDG-PET appears to be useful in detecting recurrent or metastatic disease in patients with MTC and ATC, providing a higher sensitivity (66% to 100%) and specificity (79% to 90%) than conventional imaging methods. However, the PET technique is limited by less accurate spatial assignment of small lesions, especially in the lung and liver.*

Conclusions: *Supporting evidence indicates that FDG-PET has a significant role in the follow-up of patients with MTC and ATC.*

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Abbreviations used in this paper: PET = positron emission tomography, FDG = fluorine-18-2-fluoro-2-deoxy-D-glucose, MTC = medullary thyroid carcinoma, ATC = anaplastic thyroid carcinoma, CT = computed tomography, MRI = magnetic resonance imaging, SUV = standardized uptake value, CLT = calcitonin.

Introduction

The primary treatment for most thyroid cancers is surgery. After the initial treatment, follow-up methods for patients with thyroid cancer differ according to the origin of their primary disease. The World Health Organization classifies the major types of primary thyroid carcinomas as papillary, follicular, medullary, and anaplastic.¹ Each of these morphologic patterns has a distinctive biology and clinical significance. Anaplastic thyroid carcinoma (ATC) and particularly medullary thyroid carcinoma (MTC) have the biological capability of secreting specific tumor markers that have been utilized for the diagnosis and follow-up of these malignancies.² Despite the availability of numerous imaging modalities, localization of recurrence or metastases in patients with MTC or ATC and elevated serum tumor marker levels is often problematic. Moreover, since curative outcome and patient survival depend on the surgical removal of all tumor tissue, early diagnosis of recurrence or metastases is important.

Many studies have demonstrated the clinical application of fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in several types of cancers, including lung, head and neck, breast, and colorectal cancers, as well as lymphoma, melanoma, and brain tumors.^{3,4} Although the use of FDG-PET to differentiate between benign and malignant tumors in the preoperative evaluation of thyroid nodules is controversial, it is a valuable diagnostic tool in the postoperative follow-up of differentiated thyroid cancer.^{5,7} Also, supporting evidence indicates that FDG-PET has a significant role in the follow-up of patients with MTC and ATC.⁸⁻¹⁰ The metabolic imaging findings by PET may precede the morphologic changes evidenced by computed tomography (CT) or magnetic resonance imaging (MRI) by several weeks or months. This difference provides the rationale to assess the role of FDG imaging in the posttreatment evaluation of thyroid cancer.

The FDG-PET Imaging Protocol

[¹⁸F]FDG is the principal radiotracer for clinical PET imaging. ¹⁸F is produced in a cyclotron, and the radiopharmaceutical is usually then synthesized locally by simple radiochemistry. Due to its relatively short half-life (110 minutes), many centers now have the cyclotron facility and camera on site to ensure a supply of [¹⁸F]FDG. However, manufacturers can deliver [¹⁸F]FDG to locations within a certain distance, and a delivery system is already established in some countries.

FDG is trapped within the metabolically active tumor cells, which provides the basis for functional imaging. FDG imaging is usually performed with dedicated PET scanners. In our institute, we routinely perform FDG studies with a dedicated PET scanner (SET 2400W, Shimadzu,

Kyoto, Japan) that has a 59.5-cm transaxial field of view and a 20.0-cm axial field of view, which produces 63 image planes with a 3.125-mm interval between consecutive images. Transaxial resolution at the center of the field of view is 4.2 mm full width at half maximum (FWHM). The ordered-subsets expectation maximization algorithm is used to reconstruct PET images.

PET examination of patients with MTC is performed at least 2 months after initial treatment, when tumor markers are usually elevated and conventional imaging modalities are either negative or inconclusive to detect recurrent or metastatic disease. PET images are routinely obtained 40 to 60 minutes after 5–6 MBq/kg of FDG is given intravenously to patients in a fasting state. Fasting is necessary to minimize competitive inhibition of FDG uptake by blood glucose.¹¹ At least 4 hours of fasting is recommended by many investigators. At some centers, serum glucose is measured before the tracer injection; if it is higher than 200 mg/dL, the PET scan is deferred until the patient's glucose level is normal. In diabetic patients, the blood sugar should be controlled by either oral hypoglycemic agents or insulin before scanning. In a standard protocol of thyroid cancer imaging, the patient should be relaxed prior to and after the injection of FDG. Tension of the neck muscles can result in focal uptake, which can be misinterpreted as nodal metastases.¹² Patients should avoid talking and chewing to avoid uptake of FDG in the laryngeal, facial, pharyngeal, and masticatory muscles, which can also affect interpretation of the images.

Whole-body scans are usually performed to evaluate patients with known malignancy. However, metastasis is rarely seen in the legs. At our center, we routinely scan patients from the skull through the mid-thigh region. Emission scans typically take 40 minutes to cover 100 cm. Emission scans are adjusted for signal attenuation by applying a correction derived from a ⁶⁸Ge/⁶⁸Ga transmission scan of the same region. Transmission scans are typically acquired for 18 minutes. In our institute, we acquire an 8-minute simultaneous emission-transmission scan for attenuation correction. Images are viewed in the transaxial, coronal, and sagittal planes from a computer monitor that allows coregistration of all three orthogonal views. Since PET images cannot accurately display the anatomical location of tumors, CT or MRI is usually correlated to interpret FDG images. Maximum-intensity projection images are sometimes helpful in determining abnormal focuses of tracer uptake. PET-CT devices have recently been introduced that are able to provide, in one session, metabolic information about tumor behavior and precise anatomic localization of the disease.^{13,14}

FDG images, like other imaging methods, are usually interpreted qualitatively, and an area of abnormality is identified by comparison with background activity. Using attenuation-corrected images, a semiquantitative parameter standardized uptake value (SUV) determination is a widely used index in clinical FDG-PET studies to differen-

tiate malignant from benign tumors¹⁵ and to assess the efficacy of therapy.¹⁶ SUV is calculated as follows:

$$\text{SUV} = \frac{\text{radioactive concentration in the tumor: MBq/g}}{\text{(injected dose [MBq]/patient's body weight [g])}}$$

An empirical value for SUV is selected (2.5), and lesions with values of more than 2.5 are usually considered to be malignant. According to some investigators, the use of SUV-lean (a weight-independent index for blood) is superior to SUV in oncologic PET studies.¹⁷ However, the interpretation of FDG images depends on knowledge and experience of normal tracer biodistribution, and the use of SUV is not always helpful.¹⁸

FDG-PET in Monitoring Treated MTC

MTC is a neoplasm of the parafollicular C cells and belongs to the neuroendocrine tumor group.¹⁹ C cells are derived from the neural crest and secrete calcitonin (CLT), as well as other polypeptides such as carcinoembryonic antigen (CEA), vasoactive intestinal polypeptide, and somatostatin. MTC may occur either sporadically or in a hereditary form as familial MTC that includes multiple endocrine neoplasia type IIA, multiple endocrine neoplasia type IIB, and isolated familial MTC.^{20,21} Both sporadic and familial MTCs are characterized by relatively slow tumor growth but early lymphatic metastatic spread.²² Metastases are already present in 35% of patients at the time of initial diagnosis, and the cervical and mediastinal lymph nodes are most frequently affected.¹⁹ Due to the CLT secretion of C cells, the hormone has been used as a tumor marker for diagnosis and follow-up of MTC.^{2,23} CEA also serves as a tumor marker for MTC.²⁴ Persistent elevation of tumor marker levels or the CLT level measured 8 to 12 weeks postoperatively suggests the presence of residual or recurrent disease. In some cases, the CLT level may be false positive or false negative, and thus CEA is useful as the marker for MTC. Therefore, measurement of both CLT and CEA may be useful in the postoperative follow-up of patients with MTC.²⁴ Since surgical resection is the only curative therapeutic treatment, early diagnosis and localization of recurrent or metastatic lesions by means of diagnostic imaging are important.^{19,22} The detection of recurrence or metastases of MTC, however, remains difficult, and efforts are ongoing to develop reliable methods to localize residual and remote metastases of MTC.

There is no single sensitive diagnostic imaging method to reveal all MTC recurrence or metastasis. Morphologic imaging techniques such as ultrasonography, CT, MRI, and different scintigraphic procedures are usually performed in MTC patients who have elevated tumor marker levels for localizing the responsible tumor sites. The scintigraphic studies used in the evaluation of MTC

include thallium chloride (²⁰¹Tl), ^{99m}Tc-sestamibi (MIBI), pentavalent ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc(V)-DMSA), ¹¹¹In-pentetreotide (SRS), anti-CEA antibodies, and radioiodinated meta-iodobenzylguanidine (¹²³I/¹³¹I-MIBG), with reported sensitivities and specificities in the literature on the basis of histologic confirmation as the gold standard.^{25,31} Radiolabeled pentagastrin may represent a useful new class of receptor-binding peptides for diagnosis and therapy of a variety of tumor types, including MTC and small-cell lung cancer.³² Furthermore, selective venous catheterization may sometimes be helpful for the localization of pentagastrin-stimulated cervical and mediastinal MTC metastases, and it can be applied as a guide during surgery.²² However, in all of these methods, the sensitivity is low, especially for small lesions. The diagnostic performance of conventional nuclear medicine procedures is unsatisfactory due to variable tracer uptake and the lower spatial resolution. Despite high anatomical resolution, the morphologic imaging procedures are restricted to depiction of organ shape and tissue structure, and assessment of lymph node status is consequently limited.³³

Studies of the clinical role of FDG-PET in the diagnosis and staging of recurrent and metastatic MTC have shown encouraging results.^{8,10,34,35} In a prospective study of 10 postoperative patients with MTC, Musholt et al³⁵ compared the accuracy of FDG-PET with that of CT/MRI and found that FDG-PET imaging was more sensitive in the detection of recurrent or metastatic disease. PET was positive in 31 lesions in 9 patients (including 4 false-positive findings) and CT/MRI was positive in only 11 lesions in 4 patients (including 1 false-positive finding). In addition, PET was false negative in 10 confirmed small hepatic and cervicomedial metastatic lesions, whereas CT/MRI was false negative in 20 lesions. In contrast, Hoegerle et al³⁶ found less sensitivity for FDG-PET in a study of 11 patients including both primary and recurrent tumors by PET and other imaging methods. Their calculated sensitivities for primary and recurrent MTC and lymph node metastases were 66% and 88% for ¹⁸F-DOPA PET, 66% and 44% for [¹⁸F]FDG-PET, 66% and 50% for SRS, and 100% and 69% for CT/MRI, respectively. The overall specificity was 90% for PET and SRS, respectively, and 67% for CT/MRI. Adams et al³⁷ studied 8 patients with elevated CLT levels in whom FDG-PET was performed compared with ^{99m}Tc(V)-DMSA and ¹¹¹In-DTPA scanning. FDG-PET demonstrated 38 lesions in 7 patients; 9 lesions were verified by surgical histology in 2 patients as being metastatic cancer, whereas ^{99m}Tc(V)-DMSA and ¹¹¹In-DTPA-D-Phe dual scintigraphy detected only 3 lesions in 2 patients. In another study of 20 patients by FDG-PET imaging during follow-up, a sensitivity of 76% was found on patient-based analysis and 88% on lesion-based analysis.¹⁰

Data from more recent publications has shown promising results by FDG-PET imaging in patients with MTC. Roelants et al³⁸ reported a case with rising CLT level during follow-up. FDG-PET demonstrated an abnormal

lesion in left lateral neck region that was not detected by conventional radiologic and radionuclide imaging. In a comparative data analysis of 100 PET examinations in 85 patients, PET showed the highest lesion detection probability (68%) for MTC.³⁹ The calculated sensitivity and specificity were 78% and 79%, respectively, for histologically confirmed diagnosis of 55 lesions in that study. FDG-PET was also useful in patients with lower tumor marker values when pathologic findings were obtained with morphologic imaging (ultrasonography, CT, or MRI). A study by Szakall et al⁴⁰ suggested that FDG-PET was a highly sensitive method for detecting metastases in MTC patients with elevated serum CLT levels. In this study, the findings of conventional imaging were compared with those of FDG-PET in the investigation and restaging of 40 MTC patients. PET identified positive lesions in at least one of the lymphatic regions [38/40 (95%)]. PET detected 270 lesions in 38 patients with an increased tracer accumulation, whereas only 141 were detected by CT and 116 by MRI. In 25 of 38 patients, the positive PET findings were validated by histopathologic and subsequent radiologic examinations. Although lesions in the remaining 13 patients were not verified immediately by the above methods, clinical follow-up showed no contradiction with the PET findings. PET demonstrated more lesions in the neck and the mediastinum than the other imaging methods found, but it failed to detect many small lesions in the lung and liver. The lack of attenuation correction in their study and the relatively low sensitivity of PET for small pulmonary metastases were the probable reasons of decreased tumor detection rate in the lung and liver, especially for the small lesions. In addition, the slow growth rate and low proliferation index of neuroendocrine tumors, resulting in usually normal glucose metabolism, may be other causes of decreased detection rate of small MTC foci with FDG-PET in patients with elevated tumor

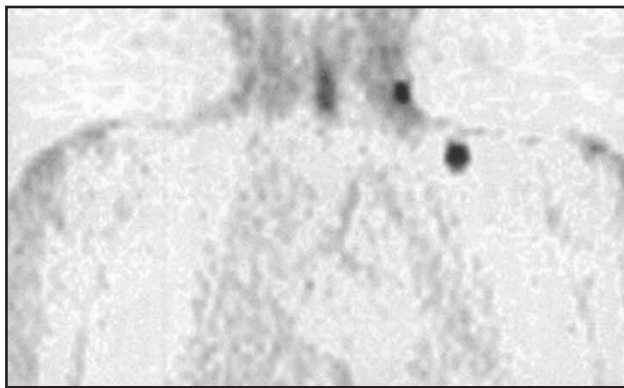


Fig 1. — FDG-PET shows increased tracer accumulation in lymph nodes in the left lateral cervical compartment and left supraclavicular region in a 38-year-old man during follow-up after surgical treatment of MTC. Radiologic methods detected lymph node only in the left supraclavicular region. Metastasis of MTC was confirmed by histopathology in the lymph nodes of both regions. Reprinted from permission of the Society of Nuclear Medicine. From Szakall S Jr, Esik O, Bajzik G, et al. 18F-FDG PET detection of lymph node metastases in medullary thyroid carcinoma. *J Nucl Med.* 2002;43:66-71.

markers.³⁷ In a subsequent study of 52 patients, Szakall et al⁴¹ found at least 1 abnormal lesion in 49 patients by FDG-PET, in 35 by CT, in 32 by MRI, and in 3 by MIBG. FDG-PET was more sensitive in localizing metastatic lymph node involvement, especially in the supradiaphragmatic region, compared with other imaging modalities.

As the most recent nuclear medicine imaging modality, FDG-PET appears to be a promising functional imaging procedure in the staging and follow-up of patients with MTC. Figs 1 and 2 show metastases detected with FDG-PET in MTC patients with histologically proven metastases in the neck and breast. A recent prospective study of 26 patients reported that FDG-PET is superior to conventional imaging modalities for the detection of recurrent or metastatic MTC.⁴² The sensitivity was 96% for FDG-PET, 41% for ¹¹¹In-octreotide, 57% for ^{99m}Tc(V)-DMSA, and 87% for morphologic imaging including bone scintigraphy on a lesion-based analysis. The Table shows the diagnostic performance of FDG-PET during the follow-up of MTC patients from some of the published reports.

As PET-CT technology becomes more widely available, studies are beginning to appear that document the

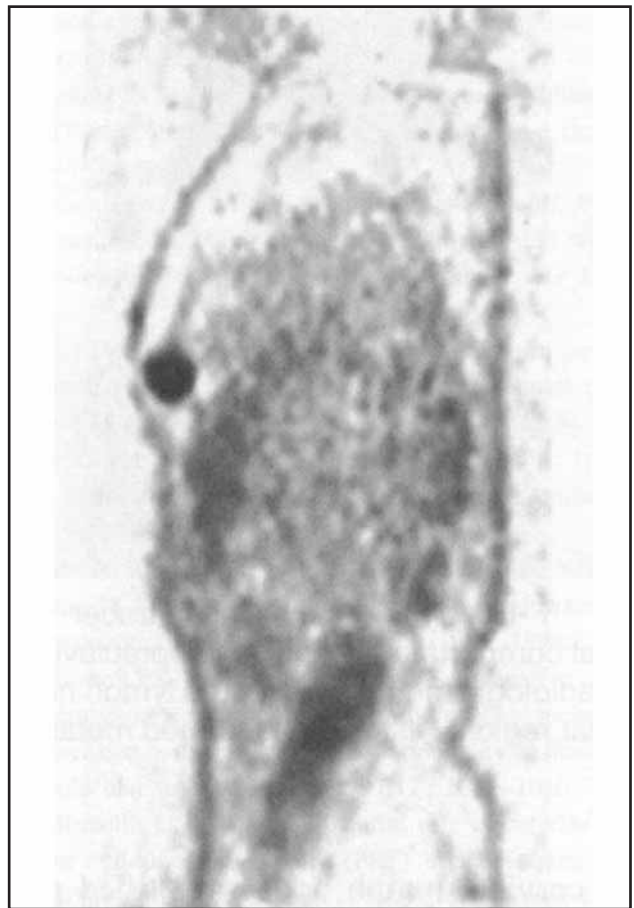


Fig 2. — The sagittal slice of FDG-PET scan in a 51-year-old woman shows high FDG uptake in the right breast, which was a histologically confirmed breast metastasis of MTC. Reprinted with permission from the Society of Nuclear Medicine. From Szakall S Jr, Esik O, Bajzik G, et al. 18F-FDG-PET detection of lymph node metastases in medullary thyroid carcinoma. *J Nucl Med.* 2002;43:66-71.

Diagnostic Performance of FDG PET and Other Imaging Methods in Detecting Recurrence or Metastases of MTC: Summary of Literature

Authors (year)	No. of Lesions Detected by		Comments
	FDG-PET	Other Imaging	
Musholt et al ³⁵ (1997)	27/37 (73%)	10/30 (33%) CT/MRI	Recurrence or metastasis was confirmed in 26 lesions by surgery and histology, and the remaining lesions were assessed clinically.
Adams et al ³⁷ (1998)	38 (100%)	3 (NA) DMSA DTPA	FDG-PET findings were verified by histologic confirmation and follow-up. DMSA-DTPA dual scintigraphy detected only 3 lesions in 2 patients in this study.
Brandt-Mainz et al ¹⁰ (2000)	22/25 (88%)		FDG-PET findings were confirmed by histologic examination (11) and follow-up (14 lesions, including 3 false-negative findings).
Diehl et al ³⁹ (2001)	32/41 (78%)	8/16 (50%) CT 14/17 (82%) MRI 1/4 (25%) MIBI 3/9 (33%) DMSA 3/12 (25%) SMS	Among the 55 histologically confirmed lesions, FDG-PET was true positive in 32, false negative in 9, false positive in 3, and true negative in 11 lesions. The number of lesions were variable in other modalities but the sensitivity was inferior to FDG-PET except MRI.
Szakall et al ⁴⁰ (a) (2002)	38/40 (95%)	29/40 (95%) CT 23/40 (57.5%) MRI 3/40 (NA) MIBG	The histologic and follow-up radiologic verification were obtained in 25 of 40 patients. The PET findings in remaining patients were correlated with clinical observation only.
de Groot et al ⁴² (2004)	46/48 (96%)	11/27 (41%) ¹¹¹ In-octreotide 24/42 (57%) DMSA 34/39 (87%) MI + BS	The positive FDG-PET findings were validated by histologic and other imaging confirmation.

Data are expressed as number of lesions except (a), in which number of patients is considered (sensitivity).
 CT/MRI = computed tomography/magnetic resonance imaging
 DMSA = ^{99m}Tc(V)-DMSA scintigraphy
 DTPA = ¹¹¹In-DTPA-D-Phe scintigraphy
 MIBI = ^{99m}Tc-sestamibi scintigraphy
 SMS/SRS = somatostatin receptor scintigraphy
 MIBG = ^{123I}/^{131I}-MIBG scintigraphy
 NA = not applicable (no statistical value)
 MI = morphologic imaging (CT, MRI, US)
 BS = bone scintigraphy

use of PET-CT in a variety of cancers, including thyroid cancer.¹³ PET-CT offers many advantages: it facilitates the interpretation of PET findings and can offer adequate anatomic information that results in increased diagnostic accuracy.¹⁴

FDG-PET in the Follow-Up of Anaplastic Thyroid Cancer

Clinically, ATC is distinct from medullary and differentiated thyroid cancer. ATC is relatively rare, accounting for 1% to 1.6% of all thyroid cancers. It occurs in an older age group and is marked by rapid growth and extensive local invasion usually. The diagnosis of ATC is usually confirmed by fine-needle aspiration biopsy. The prognosis is poor, and survival beyond 1 year is uncommon. Thus, there is no real use for an elaborate staging system in these patients. However, morphologic imaging techniques such as ultrasonography, CT, or MRI have a role in the evaluation of ATC. No major publications have reported the use of functional radionuclide imaging techniques in ATC, which may be due to the lack of clinically relevant results. Imaging

with ¹³¹I scan is not usually beneficial and serum thyroglobulin measurements may be false negative.

Although FDG-PET has not been significantly studied in patients with ATC, it is assumed that as a metabolic imaging modality PET can play a role in the primary staging and in follow-up after initial treatment. PET has the ability to provide whole-body scanning in the same imaging session, and it can help to avoid repeated, time-consuming, and unfruitful conventional imaging procedures. It has been shown that imaging from head to the upper thigh influences clinical management of patients by detecting distant metastases or secondary tumors early in head and neck cancer.⁴³ A limited number of reports of FDG-PET studies in patients with ATC are available. Jadvar et al⁴⁴ described that FDG-PET correctly detected anaplastic thyroid cancer along with other rare tumors evaluation. Conti et al⁹ found positive findings in a patient with anaplastic carcinoma in a study of thyroid cancer by FDG-PET. McDougall et al⁴⁵ also reported positive FDG-PET findings in the evaluation of patients with recurrent anaplastic thyroid cancer. Thus, FDG-PET may have a positive impact in the follow-up of patients with ATC after initial resection for the detection of residual or metastatic

disease and also in patients with advanced disease who underwent chemotherapy (to prolong survival) for assessing therapeutic response. Additional well-designed studies are needed to validate such an expectation in terms of diagnostic accuracy and impact on survival.

Conclusions

There is no single sensitive method for the diagnosis of all recurrences or metastases of MTC. The routine protocols are not well systematized, and they are unable to provide an optimal sensitivity for detecting a recurrent or metastatic disease, especially in asymptomatic patients. FDG-PET appears to be useful for detecting recurrent or metastatic disease in patients with MTC with high sensitivity and specificity, particularly the cervical, supraclavicular, and mediastinal lymph node metastases. However, the method has limitation in detecting very small lesions in the lung and liver, although PET can detect malignancy efficiently even in normal-sized lymph nodes. In the future, FDG-PET may have a role in staging and follow-up of ATC. Therefore, the use of such a highly sensitive, noninvasive, whole-body imaging technique in combination with highly specific biochemical markers may provide an added value in posttherapy surveillance of patients.

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