Oncological Applications of FDG PET Imaging: Brain Tumors, Colorectal Cancer Lymphoma and Melanoma*

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This article will focus primarily on body oncology diagnosis, staging and therapy monitoring using fluorodeoxyglucose (FDG) PET imaging. Common pitfalls and artifacts in body FDG imaging will be covered. Examples of diagnosis, staging and therapy monitoring of brain tumor, colorectal cancer, lymphoma and melanoma will be given. Importance of correlation with anatomic imaging and practical use of FDG imaging in patient management will be stressed.

Key Words: emission CT; fluorine; glucose; metabolism; neoplasms

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Keeping abreast of the rapid advances in imaging technologies is a challenge for both radiologists and clinicians who must integrate these technologies for optimal patient care and outcome at minimal cost. New developments in CT, MRI and ultrasonography continue to improve anatomic image quality, leading to improvements in lesion detection, tissue characterization and relationship to vascular structures.

Although functional imaging has limitations related to resolution and lack of landmarks, it can be of tremendous help in identifying or characterizing malignant lesions not seen or equivocal on anatomic imaging. Anatomic and functional images provide complementary information and, in many circumstances, registration of both sets of images is necessary for correct interpretation. Registration can be done visually or with various computerized methods that are becoming more readily available.

Functional imaging with single photon emitters used in the detection and staging of malignancies has well-known limitations. ^{67}Ga exhibits interference from physiologic hepatic and colonic activity, which results in poor accuracy in imaging intra-abdominal tumors, and accumulation at inflammatory sites diminishes the specificity of ^{67}Ga for detecting malignant lesions. ^{201}Tl imaging has similar problems related to its physical and biologic properties; and radioimmunoscintigraphy is limited by difficulties with antigen modulation and variable depiction of tumor and nontumor cells, as well as by physiologic hepatic and bowel excretion. Positron imaging is unique in one respect: positron emitters allow labeling of radiopharmaceuticals that closely mimic endogenous molecules, and there are continuous developments of new biological tracers. ^{18}F-fluorodeoxyglucose (FDG), which allows the evaluation of glucose metabolism, is the most commonly used tracer in oncology because of the practical half-life of ^{18}F (110 min) compared with other positron emitters. This article will therefore focus on FDG imaging. Although FDG shares some of the limitations of single photon emitters, the relatively high ratio of tumor-to-background contrast in most malignant lesions and the better resolution of PET accounts for the high reported sensitivity and specificity of FDG imaging.

Tumor cells demonstrate increased glucose metabolism (*1*) which is due, in part, to increased numbers of glucose transporter proteins and increased intracellular enzyme levels of hexokinase and phosphofructokinase, among others, that promote glycolysis (*2–4*). PET imaging with the glucose analog FDG can be used to exploit the metabolic differences between benign and malignant cells for imaging purposes (*5,6*). Although variations in uptake are known to exist among tumor types, elevated uptake of FDG has been demonstrated in various malignant primary tumors. Therefore, various indications for FDG imaging have been investigated, including differentiation of benign from malignant lesions, staging malignant lesions, detection of malignant recurrence and monitoring tumor therapy.

Increasing cost-effectiveness and decreasing the number of invasive procedures are currently two of the major trends in health care. Pursuant to these goals, considerable attention has recently been directed toward the use of metabolic imaging using PET and FDG in the evaluation of patients with cancer. Metabolic imaging, used in the appropriate setting, allows significant reduction in the use of more costly and invasive surgical methods for diagnosing and staging disease in patients with suspicious lesions.

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Although PET imaging may decrease the cost of health care by reducing the number of invasive procedures, implementation of clinical PET has been hindered by the high cost of PET systems, the need for immediate access to a source of ^{18}F (i.e., a cyclotron and support laboratory must be close to the site of use, because of the 110-min half-life of ^{18}F), the high maintenance and operating expenses of scanners and cyclotrons and the limited reimbursement for clinical procedures by third-party payers. These combined factors have resulted in the development by manufacturers of gamma camera systems capable of performing positron imaging. These systems can be used to image conventional radiopharmaceuticals used in general nuclear medicine and positron-emitting radiopharmaceuticals. The performance of these camera-based PET systems has improved markedly over the past few years with the introduction of thicker NaI(Tl) crystals, iterative reconstruction algorithms and attenuation correction.

These new developments in medical imaging instrumentation have contributed to the expansion of the number of cyclotrons in the last decade and have driven the concept of commercial FDG distribution centers, which makes FDG more available. The expense of purchasing and operating a cyclotron is no longer necessary to perform FDG imaging. There are approximately 200 cyclotrons in operation throughout the world. The largest concentration of cyclotrons for medical radionuclide production is in the U.S. (n = 66), followed by Europe (n = 48) and Japan (n = 33). Most of these cyclotrons produce ^{18}F, and FDG is compounded and used on site. Approximately 20 of these cyclotron sites distribute positron-emitting radiopharmaceuticals from a central cyclotron to satellite hospitals that have the imaging equipment. The cost of producing FDG by these distribution centers will decrease as there is an increased demand, and because the many applications of FDG imaging are becoming established, the number of patients who will benefit from FDG imaging is increasing.

Widespread implementation of FDG imaging has also been hindered in the U.S. by the lack of reimbursement by third-party payers. In the early 1990s, certain brain tumors and epilepsy cases became the first clinical indications approved for FDG imaging by some private insurance companies. In 1997, a Blue Cross/Blue Shield technology assessment panel concluded that the data found in the literature supported the use of FDG PET imaging in the evaluation of solitary pulmonary nodules and the staging of non–small-cell lung cancer. Other third-party payers now have policies for paying for FDG imaging performed for these indications. In January 1998, the Health Care Financing Administration (HCFA), which regulates Medicare, started reimbursement for solitary pulmonary nodules that are <4 cm in size and indeterminate on CT scan and for the initial staging of pathologically diagnosed non–small-cell lung cancer. The restrictions of coverage are controlled by G-codes that incorporate information such as studies performed before and after the PET scan. For example, a biopsy will not be reimbursed for patients who have a negative PET scan, unless it has been preapproved. HCFA is currently reviewing data supporting reimbursement for patients with brain tumors, colorectal cancer, lymphoma, melanoma and head and neck cancer. The results of the review should be available in 1999.

This article includes applications of FDG PET imaging for brain tumors, colorectal cancer, lymphoma and melanoma.

TECHNICAL CONSIDERATIONS

Emission images are obtained after the intravenous administration of 370 MBq (10 mCi) FDG. Current PET systems provide for the correction of soft-tissue attenuation, which is measured by transmission scanning using an external positron source. Registration of the transmission and emission is necessary to provide images corrected for soft-tissue attenuation. In addition, the detectors are calibrated with an external source of known activity (^{68}Ge), and, therefore, the true count rate can be determined in a region of interest drawn on the images corrected for attenuation. Dynamic scanning of an organ or lesion of interest after injection of FDG and dynamic arterial blood sampling to obtain tissue and plasma tracer concentration over time allow quantification of the actual metabolic rate using tracer kinetic modeling. This approach is time consuming, cumbersome and more invasive than obtaining a static image after the radiopharmaceutical concentration has reached a plateau at the time of acquisition, usually 60 min after intravenous FDG administration. In oncology, true quantitation of glucose metabolism is usually not performed because of the absence of knowledge concerning the lumped constant for the quantification, and dynamic imaging is not possible over the entire body. Static imaging of the entire body offers the advantage of detecting additional unsuspected lesions in addition to evaluating a specific lesion. Evaluation of static PET images can be performed visually or semiquantitatively using the standardized uptake ratio (SUR) or a lesion-to-background ratio. The SUR is the activity in the lesion in microCuries per milliliter divided by the weight of the patient in kilograms and the dose of FDG in milliCuries. Semiquantitative evaluation offers a more objective reporting of the uptake in the lesion. However, it does depend on accurate soft-tissue attenuation correction that may be affected by movement of the patient or error in repositioning the patient on the table between the transmission and emission scans, leading to inadequate registration of transmission and emission images. Modifications of the SUR that may improve the semiquantitative evaluation of FDG uptake include using the body surface area (*7*) or the lean body weight (*8*) instead of the weight of the patient; this is significant because the distribution of FDG is higher in muscle than in fat. FDG uptake is significantly influenced by plasma glucose levels, because uptake is decreased when the plasma glucose level is elevated (*9–11*). Correction for the blood glucose level of the patient can also be done, but to

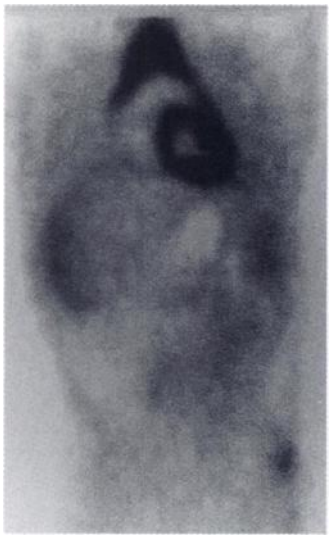

FIGURE 1. FDG PET scan without attenuation correction of 12-y-old boy evaluated for possible recurrent lymphoma. This coronal image shows physiological myocardial uptake. Uptake in mediastinum has typical shape of thymus.

date there are no strong supportive data that it increases the sensitivity of FDG PET for tumor detection.

NORMAL DISTRIBUTION OF FDG

FDG is an analog of glucose and is used as a tracer of glucose metabolism. Therefore, the distribution of FDG is not limited to malignant tissue. FDG enters the cells by the same transport mechanism as glucose and is intracellularly phosphorylated by hexokinase into FDG-6-phosphate (FDG-6-P). In tissue with low concentration of glucose-6-phosphatase such as the brain, myocardium and most malignant cells, FDG-6-P does not enter into further enzymatic pathways and accumulates intracellularly proportionally to the glycolytic rate of the cell. Some tissue such as liver, kidney, intestine, muscle and some malignant cells may have various degrees of activity of glucose-6-phosphatase, and therefore do not accumulate FDG-6-P to the same extent. To interpret FDG images, one must be familiar with the normal distribution of FDG, physiological variations and benign conditions that accumulate FDG (*12–14*).

The cortex of the brain normally uses glucose as its substrate; therefore, FDG accumulation is normally high. The myocardium, on the other hand, can use various substrates according to substrate availability, hormonal status and other factors including myocardial ischemia. In a typical fasting state, the myocardium primarily uses free fatty acids, but post-prandially or after a glucose load it preferentially uses glucose (Fig. 1). When the chest is evaluated with FDG to assess the presence of malignant lesions, a long fasting state (12 h) is preferable to avoid artifacts caused by cardiac activity. For evaluation of coronary artery disease, a glucose load is usually given to promote cardiac uptake of FDG. Unlike glucose, FDG is excreted by the kidneys into the urine. Accumulation of FDG in the renal collecting system may create artifacts that obscure evaluation of that region. This can be avoided by keeping the patient well hydrated to promote diuresis. In addition, hydration and frequent voiding is advised to limit radiation to the genitourinary tract. Some institutions have advocated the administration of diuretics (furosemide, 20 mg intravenously, 20 min after FDG administration) (Fig. 2). For adequate visualization of the pelvis, placement of a Foley catheter in the bladder with irrigation has been useful in our experience.

In the resting state, there is little accumulation of FDG in the muscular system, but after exercise, increased accumulation of FDG in selected muscular groups may mislead the interpretation. For example, in the evaluation of head and neck cancer, uptake in the muscles used for mastication or laryngeal muscles may mimic metastases. Therefore, it is important to keep the patient in the resting state (no eating or talking) during the distribution phase after FDG injection. Hyperventilation may induce uptake in the diaphragm and stress-induced muscle tension is often seen in the trapezius and paraspinal muscles. Muscle relaxants such as benzodiazepines (diazepam, 5–10 mg orally, 30–60 min before FDG administration) may be helpful in these tense patients. Figure 3 shows a patient evaluated for recurrent lymphoma. The scan without administration of muscle relaxant could be

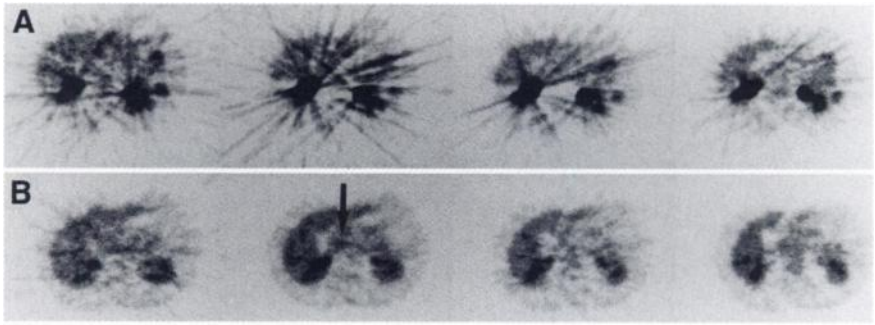

FIGURE 2. FDG PET scan with attenuation correction of 38-y-old man evaluated for pancreatic carcinoma. (A) Consecutive transverse images through abdomen show marked activity in renal pelvis creating artifact over region of pancreas. (B) Corresponding consecutive slices repeated after hydration and furosemide administration show focus of uptake corresponding to head of pancreas (arrow).

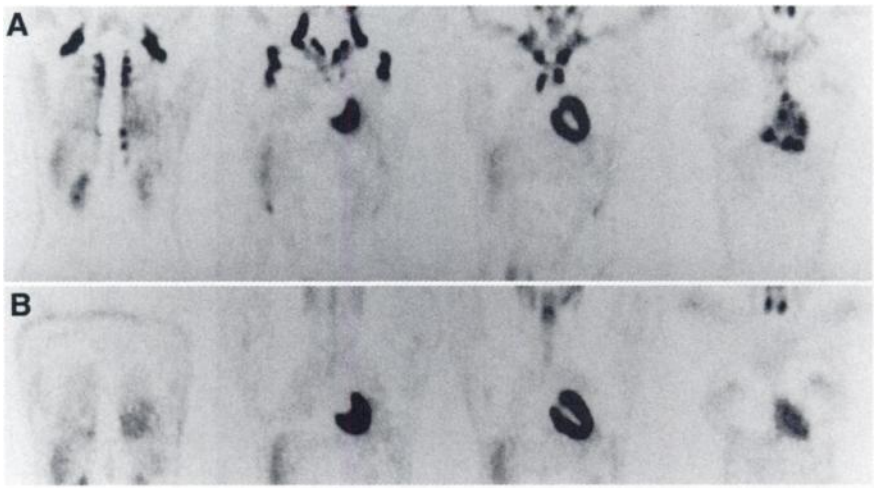

FIGURE 3. FDG PET scan without attenuation correction of 10-y-old boy evaluated for recurrent lymphoma. (A) Selected coronal images demonstrate foci of uptake in lower neck and scattered throughout mediastinum. Some of these foci are symmetrical and can be definitively identified as muscular uptake but others cannot. (B) FDG PET images were repeated after administration of diazepam (5–10 mg orally 30–60 min before FDG administration), foci of uptake are no longer seen, indicating that it was due to muscular uptake.

misinterpreted as recurrent lymphoma, whereas after administration of diazepam, the scan is normal, indicating muscular uptake.

Another source of misinterpretation is uptake in the gastrointestinal tract, which varies from patient to patient. There is usually uptake in the lymphoid tissue of Waldeyer's ring, and prominent uptake in the cecum of many patients may also be related to abundant lymphoid tissue in the intestinal wall. The wall of the stomach is usually faintly seen and can be used as an anatomic landmark, but occasionally the uptake can be relatively intense (Fig. 4). Uptake along the esophagus is also common, especially in the distal portion and when there is esophagitis; the esophagus is best identified on sagittal views (Fig. 5).

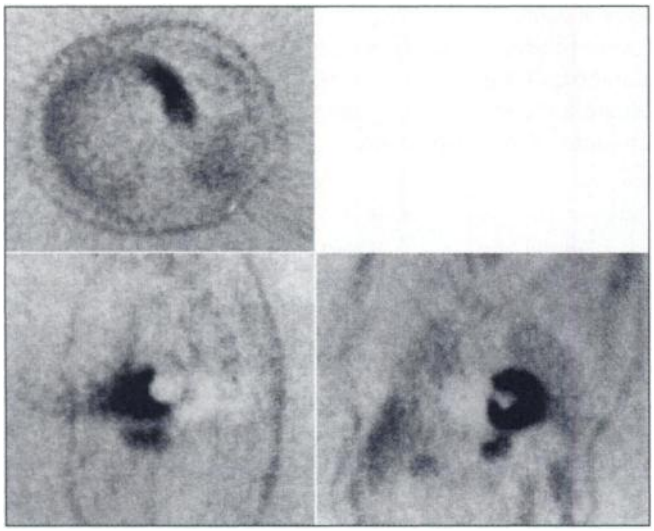

FIGURE 4. FDG PET scan without attenuation correction of 67-y-old man evaluated for metastatic melanoma. These transverse (top), coronal (bottom right) and sagittal (bottom left) images show physiological uptake in stomach.

Thymic uptake can be present in children and in patients with regenerating hemopoietic tissue after chemotherapy (Fig. 1). Its typical "V" shape usually allows differentiation from residual lymphoma. Marked diffuse bone marrow uptake is also frequently seen after chemotherapy and occasionally prevents evaluation of the bone marrow for malignant involvement. In our experience, FDG uptake in the bone marrow is sufficiently low 1 mo after completion of chemotherapy to avoid that problem. Diffuse thyroid uptake can be seen in thyroiditis and Graves' disease or can be a normal variant (Fig. 6).

Inflammation in general can cause FDG uptake that can be severe enough to be confused with malignant lesions when there is granulomatous inflammation such as tuberculosis, sarcoidosis, histoplasmosis and aspergillosis among others.

If the radiopharmaceutical extravasates into the soft tissue at the site of injection, the tracer may accumulate in draining benign lymph nodes due to lymphatic reabsorption. Therefore, when PET is performed for staging malignancies such as melanoma or breast cancer, FDG should be injected through an intravenous catheter in the arm opposite the primary lesion.

To avoid misinterpretation of FDG images, it is important to standardize the environment of the patient during the uptake period; to examine the patient for postoperative site, tube placement, stoma, etc.; and to know the history and time of invasive procedures or therapeutic interventions. In addition, a 4-h fasting period is recommended, including no consumption of beverages with sugar and no intravenous dextrose; a 12-h fasting period is preferred if the chest is evaluated, to prevent myocardial uptake. Drinking water should be encouraged to keep the patient hydrated and to promote diuresis, which will limit artifacts from the renal collecting system and radiation to the bladder. During the

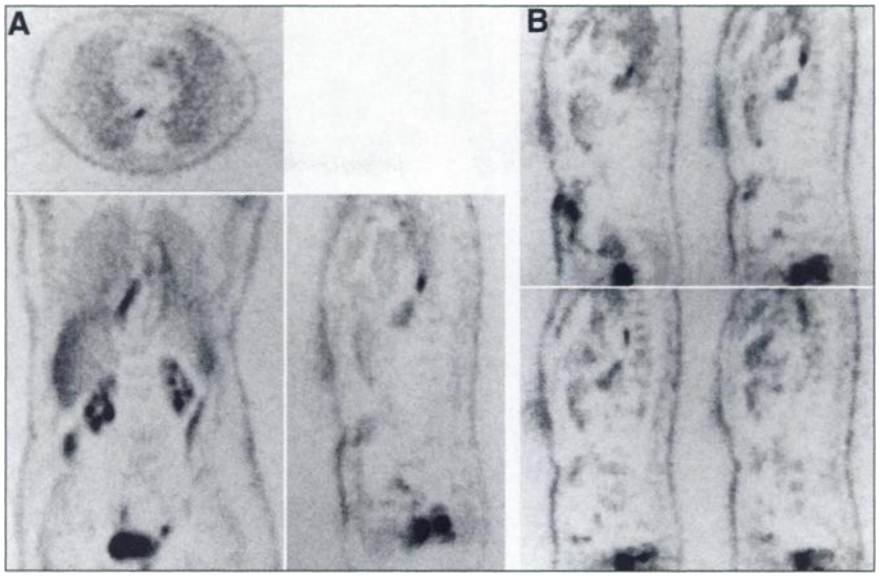

FIGURE 5. FDG PET scan without attenuation correction of 68-y-old woman with hiatal hernia evaluated for recurrent/metastatic ovarian carcinoma. (A) Transverse image (top) of chest shows focus of uptake posteriorly near midline. On coronal (bottom left) and sagittal (bottom right) images, uptake is linear typical for esophagus. Wider area of uptake at gastroesophageal junction corresponds to hiatal hernia. (B) On consecutive sagittal images, uptake in esophagus can be traced up to neck.

distribution phase, the patient should be relaxed and avoid talking, chewing and any muscular activity. For evaluation of the brain, sedatives should not be administered before the end of the distribution phase.

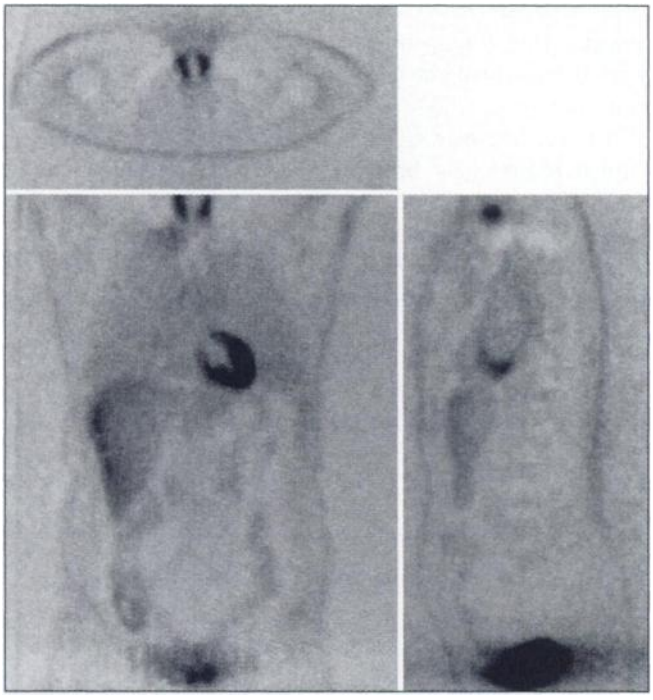

FIGURE 6. FDG PET scan without attenuation correction of 53-y-old woman evaluated for lung carcinoma. Transverse (top), coronal (bottom left) and sagittal (bottom right) images show diffuse uptake in thyroid gland. This has been reported in patients without thyroid pathology and in patients with thyroiditis and Graves' disease.

BRAIN TUMORS

Patronas et al. (*15*) demonstrated that metabolic imaging with FDG can differentiate recurrent brain tumor from radiation necrosis. Since then, however, evaluation of cerebral tumors has been recognized as a valid indication for FDG PET imaging, after various investigators have documented the usefulness of metabolic imaging to differentiate low-grade from high-grade gliomas (*16*), to determine the prognosis in patients with these lesions (*17*) and to differentiate recurrent tumor from changes due to therapy. Furthermore, FDG PET has been used to differentiate lymphoma from toxoplasmosis in patients with acquired immune deficiency syndrome (*18*). Other types of central nervous system tumors such as meningiomas (*19*) and schwannomas (*20*) have also been evaluated with FDG PET. The glucose metabolic rate in these tumors appears to be a good predictor of their biologic behavior and aggressiveness. Metastases of various non-central nervous system primary tumors seem to have more variable FDG uptake (*21*). Pituitary adenomas are benign tumors but usually have marked FDG uptake (*22*).

Different regions in the brain have been used for reference uptake in semiquantitative analysis (*16–21,23*) including white matter and contralateral unaffected gray matter.

After several years of experience with PET at our institution, patient treatment may be determined on the basis of the results of PET, if access to the lesion for biopsy is difficult. In other cases, PET may help provide guidance during biopsy at the site of maximum activity, because some tumors such as cerebral gliomas may be well differentiated in some regions and contain highly atypical cells in others. Numerous investigators have demonstrated that PET pro-

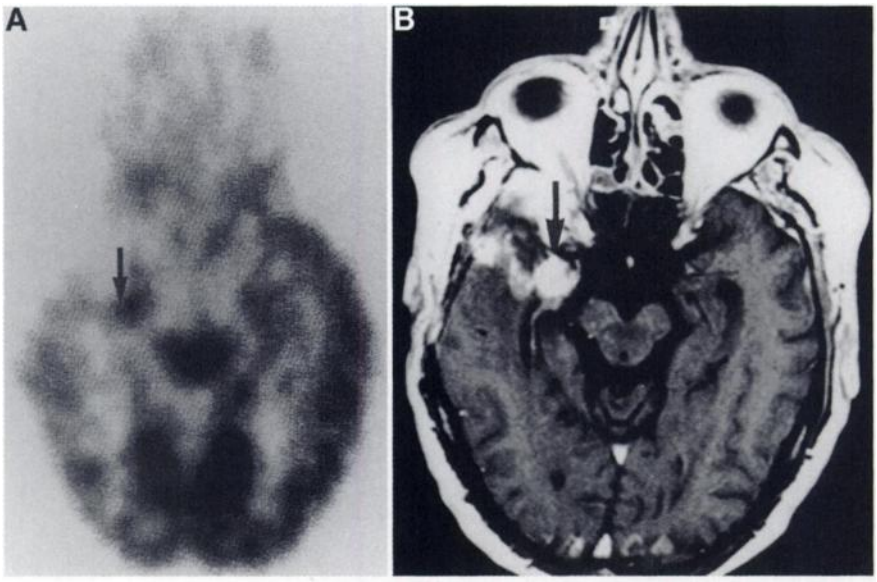

FIGURE 7. Recurrent glioblastoma multiforme after radiotherapy and chemotherapy in 45-y-old woman. (A) PET image with attenuation correction shows focus of FDG uptake (arrow) with accumulation similar to that of normal cortex consistent with recurrent high-grade tumor. This finding was confirmed by biopsy. (B) Corresponding gadolinium-enhanced T1-weighted MR image demonstrates large enhancing mass in right mesial temporal lobe (arrow).

vides critical information for the management of patients with cerebral neoplasms. Figure 7 shows an example of a patient with recurrent high-grade glioma after radiation therapy.

COLORECTAL CARCINOMA

Detection and Staging of Recurrent Colorectal Carcinoma

In 1996, there were approximately 133,500 new cases of colorectal carcinoma diagnosed in the U.S., and 54,900 patients died of their neoplasm that same year. Approximately 14,000 patients per year present with isolated liver metastases at their first recurrence (*24*), and about 20% of these patients die with metastases exclusively to the liver. Hepatic resection of the metastases is the only curative therapy in these patients but is associated with a mortality of 2%–7% (*25*) and has the potential for significant morbidity. Early detection and prompt treatment of recurrences may lead to a cure in up to 25% of patients (*26*). However, the size and number of hepatic metastases and the presence of extrahepatic disease affect the prognosis. The poor prognosis of extrahepatic metastases is believed to be a contraindication to hepatic resection (*27*). Therefore, accurate noninvasive detection of inoperable disease with imaging modalities plays a pivotal role in selecting patients who would benefit from surgery.

The measurement of serum levels of carcinoembryonic antigen (CEA) may be used to monitor the detection of recurrences with a sensitivity of 59% and specificity of 84% but does not localize recurrent lesions (*28*). CT has been the conventional imaging modality used to localize recurrence, but it fails to demonstrate hepatic metastases in up to 7% of

TABLE 1
Staging Colorectal Carcinoma

Author (ref)	Year	No. of patients	CT Sensitivity (%)	CT Specificity (%)	CT Accuracy (%)	PET Sensitivity (%)	PET Specificity (%)	PET Accuracy (%)
Yonekura et al. (*35*)	1982	3				100	100	100
Strauss et al. (*36*)	1989	29				100	100	100
Ito et al. (*37*)	1992	15				100	100	100
Gupta et al. (*38*)	1993	16	60	100	65	90	66	87
Falk et al. (*39*)	1994	16	47	100	56	87	67	83
Schiepers et al. (*40*)	1995	76			65–93			95–98
Vitola et al. (*33*)	1996	24	86	100	76	90	100	93
Delbeke et al. (*34*)	1997	61	79	58	76	93	89	92
Valk et al. (*41*)	1998	99	69	96		93	98	
Ruhlmann et al. (*42*)	1997	59				100	67	
Total		454	47–86	58–100	56–93	87–100	66–100	63–100

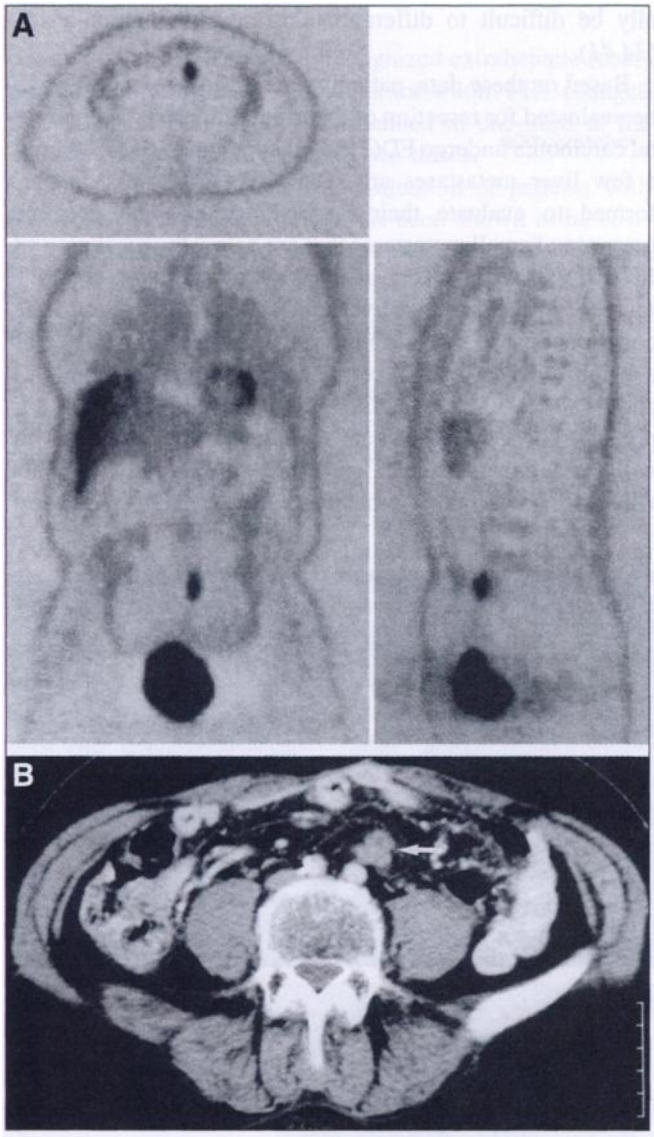

FIGURE 8. 60-y-old woman with history of colectomy for colorectal carcinoma was referred for resection of solitary liver metastasis. FDG PET scan was obtained for preoperative staging. (A) FDG PET images without attenuation correction shows focus of uptake in the mid-upper pelvis to left of midline, in addition to liver metastasis (not shown). (B) Correlation with corresponding CT image shows soft-tissue density in left iliac region (arrow) consistent with lymph nodes involved by tumor. This was overlooked when CT scan was first interpreted without PET scan.

patients and underestimates the number of lobes involved in up to 33% of patients (*29*). In addition, metastases to the peritoneum, mesentery and lymph nodes are commonly missed on CT, and the differentiation of postsurgical changes from tumor recurrence is often equivocal (*30*). CT portography (superior mesenteric arterial portography) is more sensitive (80%–90%) than CT (70%–80%) for detection of hepatic metastases (*31*) but has a considerable rate of false-positive findings, lowering the positive predictive value (*32*).

FDG PET is extremely useful for detecting both hepatic and extrahepatic metastases from colorectal carcinoma (*33,34*). Three indications for functional imaging are now well established in patients with suspected recurrent colorectal carcinoma: (a) rising CEA levels in the absence of a known source; (b) equivocal lesion on conventional imaging; and (c) preoperative staging before curative resection of recurrent disease. Several studies have demonstrated a strong potential role for FDG PET as a functional imaging modality for detecting and staging recurrent colorectal carcinoma (Table 1) (*35–44*).

In the study of Delbeke et al. (*34*), the sensitivity and accuracy of FDG PET in detecting metastatic colorectal carcinoma are in the same range as those reported by other investigators (*33,35–40*). FDG had a higher accuracy (92%) than CT (78%) and CT portography (80%) in detecting liver metastases, and although the sensitivity of FDG PET (91%) was lower than CT portography (97%), the accuracy was much higher, particularly at postsurgical sites. In addition, PET imaging allows evaluation of the entire body without additional radiation to the patient and can identify metastatic disease to the chest, abdomen or pelvis that can guide follow-up CT of these regions to evaluate the exact anatomic location and potential resectability of these lesions. Outside the liver, FDG PET is especially helpful in detecting nodal involvement, differentiating local recurrence from postsurgical changes and evaluating the malignancy of indeterminate pulmonary nodules, indications for which CT has known limitations. PET changed the surgical management in 28% of patients, either by identifying a resectable metastasis or by demonstrating unresectable extrahepatic metastases that were unsuspected clinically, not seen or equivocal on CT. Figure 8 shows a patient referred for resection of a solitary

TABLE 2
Clinical Impact of FDG PET in Patients with Colorectal Carcinoma

Author (ref)	Year	No. of patients	Accuracy PET (%)	Detection of unsuspected metastases (%)	Clinical impact (%)
Beets et al. (*45*)	1994	35			40 (14/35)
Schiepers et al. (*40*)	1995	76	95–98	13 (10/76)	
Lai et al. (*46*)	1996	34		32 (11/34)	29 (10/34)
Delbeke et al. (*34*)	1997	61	92	28 (17/61)	28 (17/61)
Valk et al. (*41*)	1998	155		36 (35/96)	34 (17/73)
Total		378		27 (73/267)	29 (58/203)

liver metastasis; FDG PET imaging detected an extrahepatic metastasis, making this patient have a poor prognosis (poor surgical candidate). The impact of FDG PET on surgical management of the same magnitude has been demonstrated by numerous investigators (Table 2) (*34,40,41,45,46*). Among the combined 378 patients of these studies, PET detected unsuspected metastases in 27% and had a clinical impact in 29%.

False-negative lesions can be due to partial-volume averaging, leading to underestimation of the uptake in small lesions (<1cm) or in necrotic lesions with a thin viable rim, classifying these lesions as benign instead of malignant.

Some inflammatory lesions, mainly granulomatous, can have FDG uptake presumably due to activated macrophages and can be mistaken for malignancies (*47*). FDG uptake normally present in the gastrointestinal tract can occasionally be difficult to differentiate from a malignant lesion (*34,41*).

Based on these data, patients referred to our institution to be evaluated for resection of recurrent or metastatic colorectal carcinoma undergo FDG PET scan preoperatively. If only a few liver metastases are seen, CT portography is performed to evaluate their resectability and the possible presence of small metastases that are below the resolution of PET. If extrahepatic foci of uptake are present on the PET images (with or without liver metastases), a CT scan of the corresponding region is obtained to confirm the presence of a lesion, even equivocal (versus normal bowel, for example) and evaluate its resectability. In our experience, this approach allows more accurate selection of the patients who will benefit from surgery and, more importantly, patients who will not benefit from laparotomy and liver resection

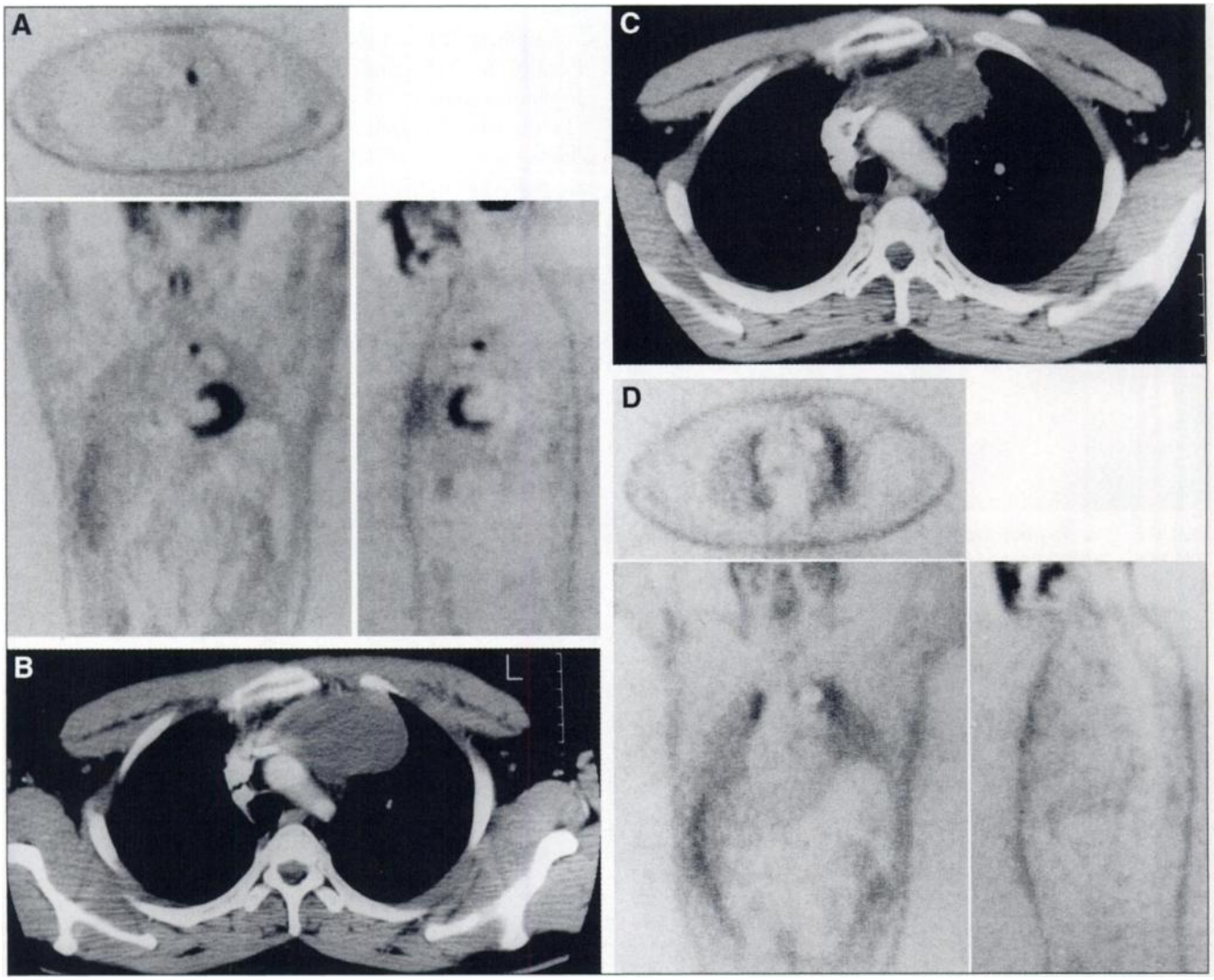

FIGURE 9. 26-y-old man treated with 9 mo chemotherapy for lymphoma was evaluated for residual disease. (A) FDG PET images (without attenuation correction) show photopenic region corresponding to necrotic portion of mass and focus of uptake at superior and medial portion of mass, indicating residual viable tumor. Patient was treated with more chemotherapy and radiation therapy followed by bone marrow transplant. (B) CT image shows persistent large anterior mediastinal mass with central necrosis. (C) CT scan 5 mo later still shows large anterior mediastinal mass. (D) Corresponding FDG PET images (without attenuation correction) show no FDG uptake at that time, indicating good response to therapy.

because of unsuspected or unrecognized extrahepatic recurrence. Among the 28% of patients for whom PET changed the management, surgery was planned in one-third of the patients and avoided in the other two-thirds.

Including FDG PET in the evaluation of patients with recurrent colorectal carcinoma has been shown to be cost-effective in studies using both a retrospective review of costs (*41*) and using decision tree sensitivity analysis (*48*).

Monitoring Therapy of Colorectal Carcinoma

FDG PET is also useful in monitoring therapy for colorectal carcinoma. Two studies have shown that FDG PET can differentiate local recurrence from scarring after radiation therapy (*35,36*). However, FDG uptake immediately following radiation may be due to inflammatory changes and is not always associated with residual tumor (*49*). The time course of FDG uptake after radiation has not been studied systematically; it is, however, generally accepted that 6 mo after radiation therapy, FDG uptake is associated with tumor recurrence. Findlay et al. (*50*) monitored liver metastases from colorectal carcinoma after chemotherapy with fluorouracil in 18 patients. They were able to discriminate responders from nonresponders at 4–5 wk into their treatment by measuring FDG uptake before and during therapy. Regional therapy to the liver by chemoembolization can also be monitored with FDG PET images. FDG uptake decreases in responding lesions. The presence of residual uptake in some lesions can help in guiding further regional therapy (*51*).

LYMPHOMA

Although the incidence of Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) is only 8% of all malignancies, they are potentially curable malignancies. The extent of the disease is the most important factor influencing relapse-free and total survival of patients (*52*). Conventional methods for staging (CT and ^{67}Ga) imaging have limitations (*53,54*). Although ^{67}Ga plays a role in the evaluation of the presence of viable tumor in residual masses, it is not superior to CT in staging untreated lymphoma (*55*).

Both HD and NHL have marked FDG uptake, and FDG imaging is useful both for staging and monitoring therapy (*56–69*). Several of these studies have shown that there is a correlation between the degree of FDG uptake and the grade of the lymphoma (*58–61*). There is, however, a large overlap between low- and high-grade lymphoma.

Because lymphoma is not treated surgically and all presumed lesions cannot undergo biopsy, from an ethical and practical point of view, the true sensitivity, specificity and accuracy of the imaging modalities used for staging cannot be evaluated. Data found in the literature usually compare two imaging modalities: concordant sites of disease are considered true disease, and discordant sites are discriminated by biopsy, when possible, or by clinical and radiological follow-up.

Staging Lymphoma

In a pilot study of 16 patients, Newman et al. (*53*) showed that FDG PET is more accurate than CT in staging lymphoma. In a more recent study comparing PET with conventional staging in 18 patients, both staging algorithms detected 33 of 37 lesions, but the lesions detected were not the same (*62*). PET and conventional staging was concordant in 14 of 18 patients, PET was better than conventional staging in 3 patients and PET was worse in 1 patient. The authors compared the actual cost of both staging algorithms in these patients ($36,250 for PET and $66,292 for conventional staging), demonstrating the cost-effectiveness of PET

TABLE 3
Staging Melanoma

				CT			PET		
Authors	Year	No. of patients	No. of lymph node stations	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Gritters et al. (*71*)	1993	12					100	100	100
Steinert et al. (*72*)	1995	33	53				92	77	
Boni et al. (*73*)	1995	15					91		
Blessing et al. (*74*)	1995	20	83				74	93	
Damian et al. (*75*)	1996	100	415				93		
Wagner et al. (*76*)	1997	12	14				100	100	
Rinne et al. (*77*)	1998	52*			80		100	94	
		48†		85	68	77	100	95	98
			121	57	45	56	92	95	98
Macfarlane et al. (*78*)	1998	23	24				85	91	88
Holder et al. (*79*)	1998	103		55	84		94	83	
Steinert et al. (*80*)	1998	55	108				89		
Total		406		55–85	45–84	56–77	74–100	77–100	88–100

*Initial evaluation.
†Follow-up.

(*62*). Similar findings were reported by Moog et al. (*63*) in a study including 27 patients with HD and 33 patients with NHL. In these patients, PET showed lymphomatous involvement of 25 additional regions compared with CT (7 true-positive, 2 false-positive, 16 unresolved). CT showed 6 additional regions involved compared with PET (3 false-positive, 3 unresolved). Staging was changed due to PET in 4 patients. In another study, Moog et al. (*64*) demonstrated that FDG PET imaging may provide more information than CT for detection of extranodal lymphoma. Lymphomatous involvement of the bone marrow is detectible on FDG PET images in a high proportion of patients, reducing the need for staging bone marrow biopsy (*65*). In some patients, FDG PET imaging detects bone marrow involvement when the posterior iliac crest biopsy is normal (*66*).

Monitoring Therapy and Detection of Persistent or Recurrent Lymphoma

Although the sensitivity of CT and FDG imaging may be comparable in diagnosing untreated lymphoma, CT is unable to distinguish between active or recurrent disease and residual scar tissue after therapy (*67*).

In a study of 34 patients with lymphoma, 32 had a residual mass on CT after therapy (*68*). Of these 32 patients, FDG

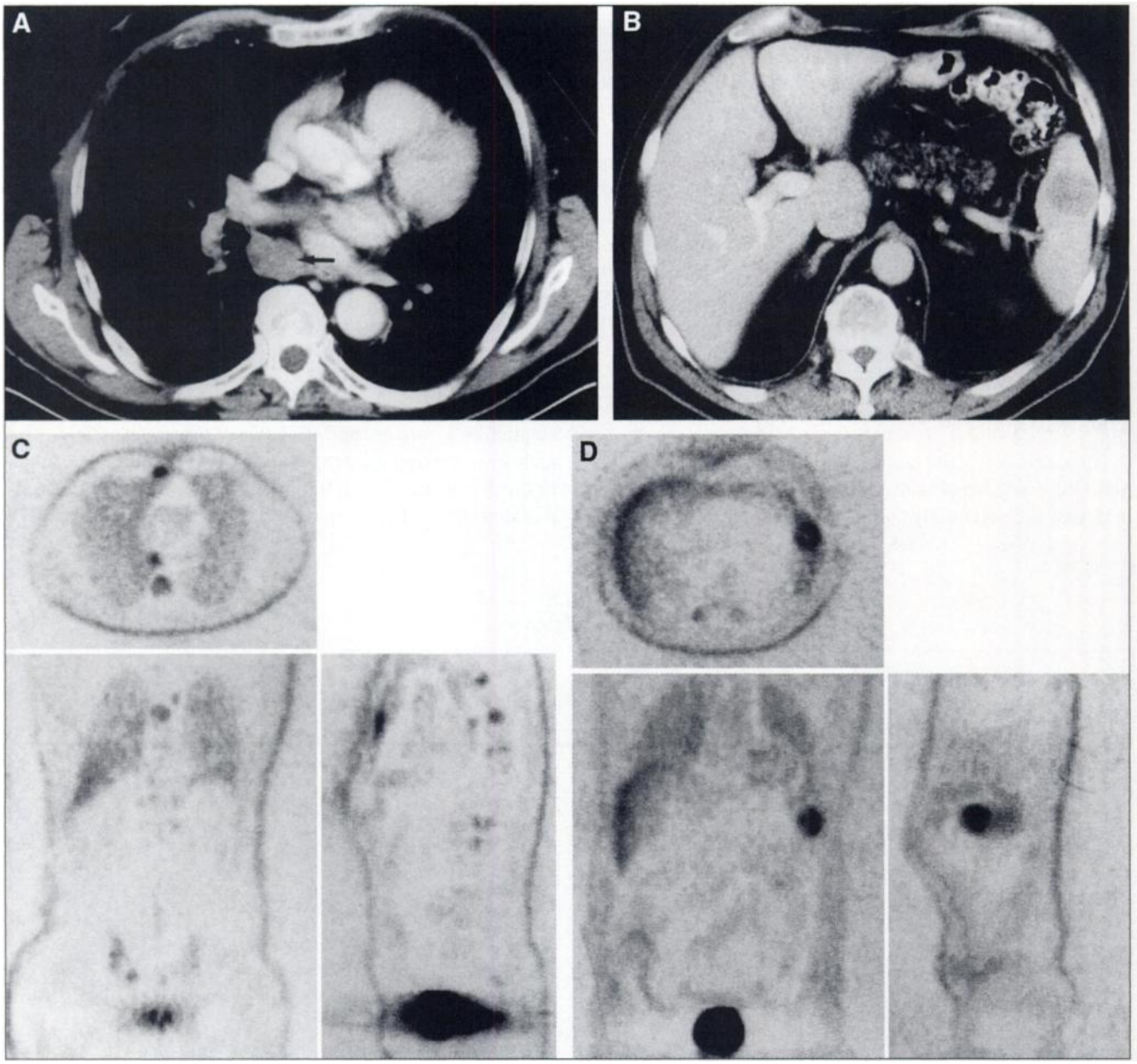

FIGURE 10. 75-y-old man with melanoma behind left ear resected 6 mo previously was evaluated for metastases. CT scans show 2.5-cm soft tissue nodule in azygoesophageal recess (arrow, A) consistent with metastasis (A) and spleen lesion (B). (C and D) Corresponding PET images confirm that both mediastinal and spleen lesion were malignant and also show unsuspected metastases to spine (C).

PET imaging showed no residual uptake in 17 patients and accurately predicted complete remission (*68*). Figure 9 shows a patient with lymphoma for whom FDG PET was useful in monitoring and guiding therapy. Another study demonstrated that standard chemotherapy of patients with NHL causes a rapid decrease of tumor FDG uptake as early as 7 d after treatment and continues to decline during therapy (*69*). Uptake at 42 d after therapy was superior in predicting the long-term outcome.

MELANOMA

Melanoma is the most aggressive of skin cancers and is increasing in frequency, particularly in Caucasians in areas of high sun exposure. Melanoma frequently spreads to regional lymph nodes once the vertical growth phase develops and is then likely to metastasize to any organ. The presence of lymph node metastases is well established as a crucial prognostic indicator of this disease. The accurate staging of disease extent in malignant melanoma remains difficult. For early-stage melanoma, the approach developed recently is identification, surgical resection and pathological examination of the sentinel lymph node. The sentinel node is the first draining node of the lymphatic bed draining a malignant tumor. If the sentinel node is free of tumor, the remainder of the nodes in that basin are likely to be free of tumor, which obviates more radical lymph node dissection (*70*).

For high-risk melanoma, FDG PET imaging may be useful in detecting subclinical lymph nodes noninvasively and metastases to other organs. In a pilot study for staging melanoma in 12 patients, PET correctly identified 7 of 7 negative superficial lymph nodes and 6 of 6 superficial lymph nodes involved by tumor (*71*). For deep lymph nodes and visceral metastases, PET detected 15 of 15 metastases. However in that study, the sensitivity of PET to detect small pulmonary metastases was lower than that of CT. In another study using whole-body FDG PET imaging in 33 patients with 53 lesions, FDG PET had a sensitivity of 92% to detect malignant lesions and a specificity of 77% without and 100% with clinical information (*72*). The findings on PET affected therapy in 4 of 29 patients. Subsequent studies totaling 406 patients (Table 3) have demonstrated the high accuracy of FDG PET to identify both nodal and visceral metastases from melanoma (*71–80*). False-positives included other malignancies, Warthin's tumor, leiomyoma of the uterus, endometriosis and inflammatory lesions; false-negatives were skin lesions without mass effects and small lesions (<0.5 cm). In a prospective study of 100 patients with high-risk melanoma (thickness >1.5 mm) comparing FDG PET imaging and conventional diagnostic methods, PET was superior in staging melanoma at primary diagnosis and during follow-up both on a patient and lesion basis (Table 3) (77). Potentially, patients that have a negative FDG PET scan could be followed by close clinical observation. A retrospective review of the actual cost was performed and showed that including PET in the evaluation of patients with suspected metastatic melanoma saved approximately $1800 per patient, with a net savings-to-cost ratio of more than 2:1 (*81*). Figure 10 shows a patient with metastatic melanoma to the mediastinum and spleen on CT. FDG PET demonstrated additional unsuspected metastases to the skeleton.

CONCLUSION

The applications for FDG PET are rapidly growing and becoming more accepted in the field of oncology. FDG PET imaging does not replace other imaging modalities such as CT but appears to be very helpful in specific situations in which CT has known limitations, such as differentiation of benign from malignant indeterminate lesions on CT, differentiation of post-therapy changes versus recurrent tumor, differentiation of benign from malignant lymph nodes and monitoring treatment. The addition of FDG PET in the evaluation of oncology patients in well-defined algorithms including a combination of imaging studies appears to be cost-effective by accurately identifying patients that will benefit from invasive procedures and thus saving unnecessary costly procedures on patients who will not benefit from them.

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