Integrated PET/CT: Current Applications and Future Directions[1]

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For the past 5 years, combined positron emission tomography (PET) and computed tomography (CT), or PET/CT, has grown because the PET portion provides information that is very different from that obtainable with other imaging modalities. However, the paucity of anatomic landmarks on PET images makes a consistent "hardware fusion" to anatomic cross-sectional data extremely useful. Clinical experience indicates a single direction: Addition of CT to PET improves specificity foremost, but also sensitivity, and the addition of PET to CT adds sensitivity and specificity in tumor imaging. Thus, PET/CT is a more accurate test than either of its individual components and is probably also better than side-by-side viewing of images from both modalities. The synergistic advantage of adding CT is that the attenuation correction needed for PET can also be derived from the CT data, an advantage not obtainable by integrating PET and magnetic resonance imaging. This makes PET/CT 25%–30% faster than PET alone with standard attenuation-correction methods, leading to higher patient throughput and a more comfortable examination, which typically last 30 minutes or less. Fluorodeoxyglucose (FDG) PET/CT appears to provide relevant information in the staging and therapy monitoring of many tumors, including lung carcinoma, mesothelioma, colorectal cancer, lymphoma, melanoma, and many others, with the notable exception of prostatic cancer. For prostatic cancer, choline derivatives may become useful radiopharmaceuticals. The published literature on the applications of FDG PET/CT in oncology is still limited, but several well-designed studies have demonstrated the benefits of PET/CT.

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Since the first proof-of-concept combined positron emission tomography (PET) and computed tomography (CT) (PET/CT) system started to operate in 1998 and the first worldwide clinical PET/CT scanner came into operation at our institution in March 2001, PET/CT has developed into the fastest growing imaging modality worldwide, according to the industry, with 500–1000 new systems installed in 2004 (1,2). The success of this combined modality is due largely to the fact, that combined PET and CT data acquisition with fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) is highly synergistic in tumor staging and therapy-monitoring applications.

The integration of PET and CT provides, first and foremost, precise localization of the lesions on the FDG PET scans within the anatomic reference frame provided by CT, thereby increasing specificity of the examination: "Hardware-fused" PET/CT images are always available at the end of the examination. Second, the CT data from a PET/CT examination are also used to correct the PET emission images for photonic self-attenuation by the human body (3–5). With conventional PET scanners, attenuation correction is achieved by using data from a radioactive transmission source rotating around the patient, very much like the CT tube during a CT scan, but with a photon flux that is much lower than that of a CT tube. If attenuation correction is performed, quantitative measurements of standardized uptake values in PET images can be obtained routinely. Third, as a consequence the use of the fast CT data acquisition makes PET/CT approximately 25%–30% faster than PET with radioactive-source transmission correction, which, fourth, results in more efficient use of fast-decaying PET radiopharmaceuticals (3): hence, the synergistic nature of the integrated PET/CT examination.

In this article, the emphasis will be on applications of FDG PET/CT in tumor staging, except for brain PET, where software fusion of PET and magnetic resonance (MR) imaging data is probably the best way for an integrated imaging approach. Other applications will be discussed in the last two sections. While the use of PET/CT is increasing rapidly, the number of peer-reviewed publications on the clinical applications is still limited, although many abstracts are being published. Thus, in, this review we also cite some PET-only literature.

General Aspects of PET/CT

Technical Issues

There are some potentially critical technical issues when CT data are used for attenuation correction and as an anatomic reference frame in PET/CT. The measured attenuation maps in PET/CT are the CT images obtained from polychromatic x-rays of around 100 keV. These are transformed to μ maps at the spatial resolution corresponding to the PET images and correspond to attenuation images at 511 keV, which is the photon energy relevant in PET. It turns out that this transformation is relatively simple and can be achieved by using a bilinear lookup table with its inflection point at 0 HU (5). The obtained μ maps are then forward projected and used to correct the emission data obtained from the PET system. Finally, the attenuation-corrected PET data and the CT data are viewed conjointly by using appropriate software. The data thus obtained can also be transmitted to a radiation therapy planning system and can be used there.

The artifacts that can be generated on PET images due to the use of CT data transformed into μ maps are related to the use of concentrated CT contrast agents, CT beam-hardening artifacts due to metallic implants, and physiologic motion. They all can result in alterations of standardized uptake values of lesions or in the appearance of artifactual lesions. Iodine and barium contrast agents used in CT do not attenuate 511-keV photons as much as they do 100-keV photons; thus, errors are introduced when the 511-keV μ maps are calculated. The problem, however, is substantial (approximately >5% change in apparent standardized uptake value) only when concentrated contrast material is used that causes enhancement above around 200 HU (6). Hence, it is currently advised to use imaging protocols in PET/CT that involve dilute oral contrast agents for bowel opacification in PET/CT and not to use CT data obtained with intravenous bolus contrast agents for attenuation correction. Because the latter can be quickly acquired at the end of a PET/CT examination with a state-of-the-art CT scanner, this poses no major limitation to the development "one-stop shopping" imaging protocols in PET/CT (7,8).

Beam hardening in CT images results in erroneous correction of PET emission images in the vicinity of metallic implants, which can lead to the appearance of artificially increased uptake masquerading as a lesion (9,10). Cor-

Essentials

- Currently available data indicate that PET/CT is more sensitive and specific than either of its constituent imaging methods alone and probably more so than images obtained separately from PET and CT and viewed side by side.
- CT data from PET/CT can also be used to correct PET emission images for photonic self-attenuation by the body; thus, the use of fast CT data acquisition makes PET/CT 25%–30% faster than PET with radioactive source transmission correction.
- Published results on the use of PET/CT in oncology are still limited, but several well-designed studies have demonstrated the benefits of PET/CT, especially in staging of non–small cell lung cancer, recurrent colorectal cancer, and malignant lymphoma.

rections cannot be made; thus, a decrease in diagnostic relevance of the imaging data very close to metallic implants may result. However, these artifacts are much less extended than the metallic artifacts noted on MR images.

Artifacts generated by motion can occur at many sites. In PET/CT the major artifacts occur in regions adjacent to the heart and diaphragm. Specifically, PET data are acquired most frequently during free breathing, which corresponds largely to the end-expiratory position of the diaphragm, while CT data are normally acquired at maximum inspiration. This leads to an anatomic mismatch between the two data sets, with the lungs more expanded during CT, and in turn to an apparent photon deficit of the soft tissues just inferior to the diaphragm. Any lesion located in this region will thus also show erroneous standardized uptake values (9,11). An analysis of this problem has shown that with the modern fast CT scanners, it is probably best to acquire the CT data during tidal breathing as well, since the patient's diaphragmatic excursions are usually small and the average position of the diaphragm imaged with PET and the position of the diaphragm during the fast-pass of the CT scanner coincide relatively well. Ideally, CT data are acquired during end expiration, but patient cooperation frequently makes it difficult to achieve this (9).

Figure 1
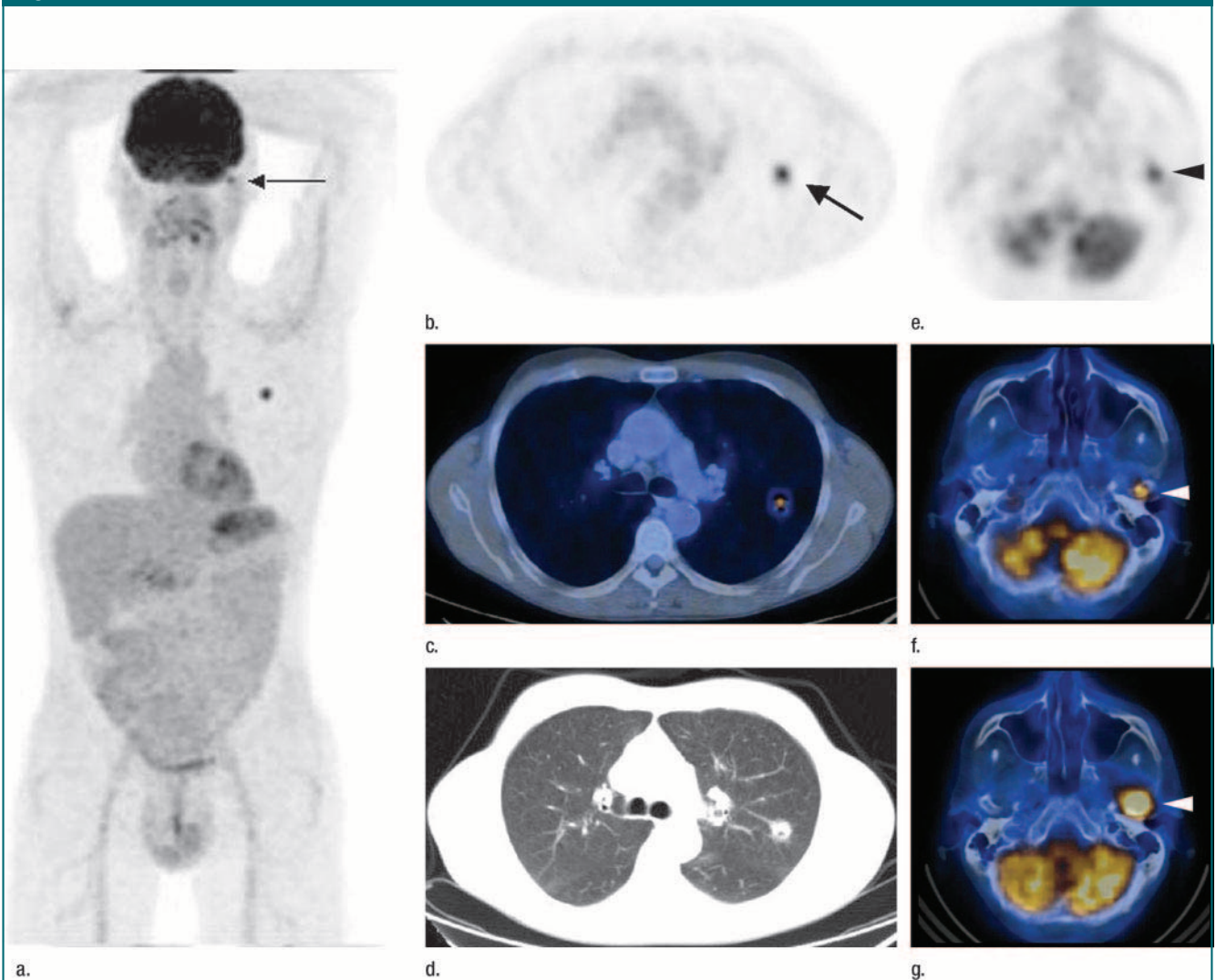
Figure 1: Non–small cell lung cancer (arrow in **b**) in the left upper lobe is shown in **(a)** coronal PET maximum intensity projection (MIP) and **(b)** transverse PET image, **(c)** transverse PET/CT image, and **(d)** transverse CT lung window image. **(e)** Transverse PET image shows small focus at left skull base (arrowhead, arrow in **a**); **(f)** on transverse PET/CT scan, focus appears to be a bone metastasis (arrowhead) in the mandibular condyle, which was not noted at CT alone (not shown). **(g)** This was confirmed with follow-up transverse PET/CT, where interval growth of the lesion (arrowhead) was seen. Osseous metastasis was confirmed at histologic examination.

Issues Relevant to Clinical Imaging Protocols

Clinically, variable diaphragmatic position or any other patient motion between CT and PET data acquisitions leads to errors in image fusion. This is rarely a diagnostic problem, since one has a priori knowledge about how a PET lesion may be displaced on the corresponding CT image (11). It has been shown that the use of CT data for transmission correction does not alter the size of the lesion significantly and that the measured standardized uptake values do not differ substantially from those obtained with radioactive source transmission correction, except when the lesion is in a body region subject to one of the problems discussed earlier (12).

As a result of this basic information, as well as of data showing that PET lesion specification with the aid of CT does not improve when tube current is increased above 20–60 mAs in a normal-sized patient (3), the imaging protocol that we currently recommend is as follows: *(a)* measurement of blood glucose level and injection of rapid-acting insulin if the glucose level is above 8 mmol/L; *(b)* administration of 1 L dilute oral contrast agent approximately 1 hour before and of 10 mCi (370 MBq; approximate dose to patient, 10 mSv) FDG 45–90 minutes before examination; *(c)* bladder voiding just before examination to eliminate renally excreted FDG; *(d)* comfortable head fixation and arm positioning that depend on main diagnostic question (arms down for ear, nose, and throat tumors; arms up for most other indications); *(e)* low-dose CT (20–60 mAs, according to body habitus) with no intravenous contrast agent followed by emission PET starting at pelvic floor and moving cephalad (to minimize pelvic image misregistration due to bladder filling during PET/CT); both PET and CT performed during free breathing; and *(f)* subsequent intravenous contrast agent–enhanced CT tailored for the diagnostic problem at hand (mean whole-body dose of approximately 3 mSv at 40 mAs).

General Clinical Insights from the Use of PET/CT

All currently available data indicate that combined PET/CT is more sensitive and specific than either of its constituent imaging methods alone and probably more so than images obtained from separate PET and CT systems and viewed side by side. Over the past 10 years, many groups have demonstrated PET to be more sensitive than CT (Fig 1) (13). In PET/CT, probably the most relevant additional effect is that CT data frequently add specificity to the FDG PET data (3); Figure 2 is a case demonstrating this.

Figure 2

a.

b.

c.

d.
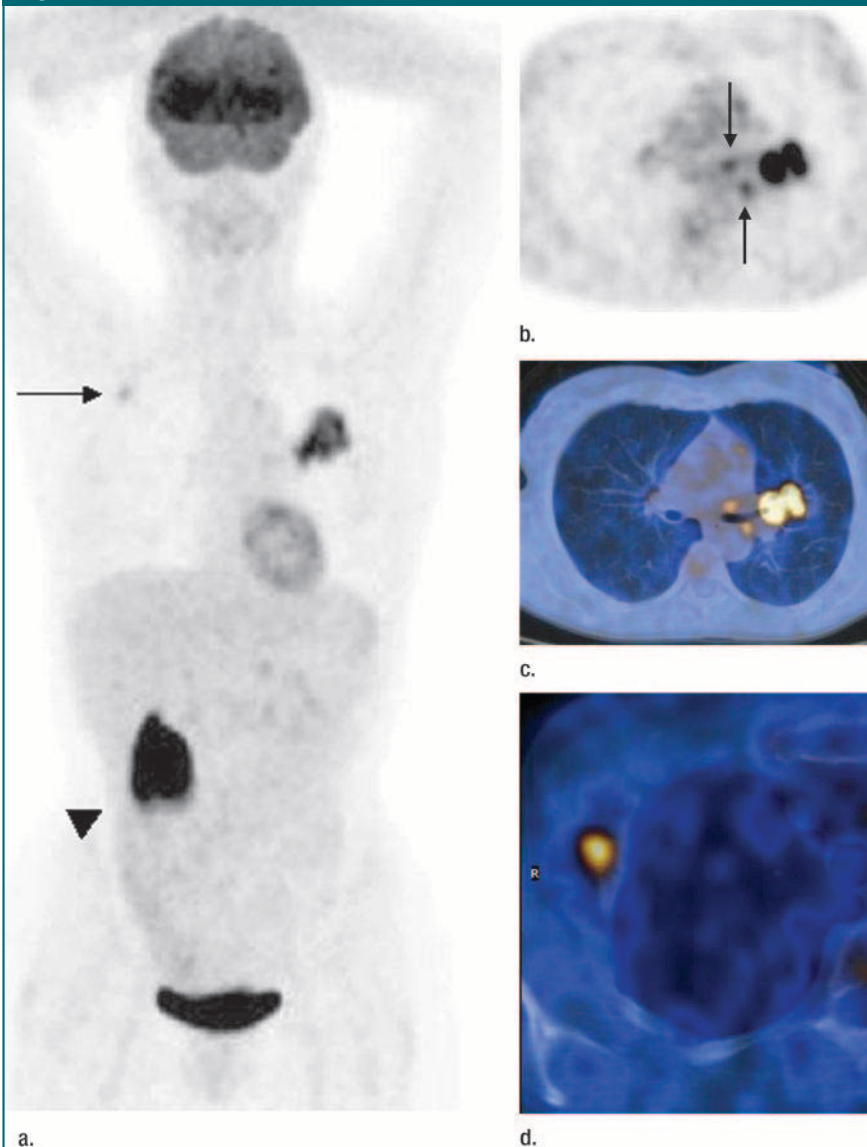
Figure 2: Lung carcinoma of left upper lobe and ipsilateral mediastinal lymph node metastases, which cannot be clearly distinguished on **(a)** coronal PET MIP, but **(b, c)** are clearly discernible (arrows) on transverse **(b)** PET and **(c)** PET/CT images. Also, **a** shows right-sided dilated renal pelvis, which explains increased right midabdominal FDG activity (arrowhead), and right-sided FDG focus (arrow), which appears to be close to the chest wall. **(d)** Transverse PET/CT image shows focus to be superimposed on the lateral aspect of a rib. Bone window CT (not shown) demonstrated callus formation; biopsy showed rib fracture with full medial but not yet full lateral healing.

However, FDG PET data also help to specify CT findings such as lymph nodes with an equivocal appearance (Figs 3, 4). In some situations, such as when disseminated pulmonary metastases are too small to be seen at PET, CT is also able to increase the sensitivity of the PET/CT examination. Thus, there is general consensus that PET/CT is more accurate in tumor staging than PET or CT alone and even more than PET and CT images viewed side by side (14–17). The advantage of conjoint image viewing is such that authors of a recent study (18) have shown that in approximately two-thirds of patients with lesions seen on PET images, CT data are needed to improve the specificity of the findings.

While most PET/CT users consistently give dilute oral CT contrast material for the examination, things are not as clear with intravenous contrast agents. Intravenous contrast material in CT is used for two purposes: lesion characterization and vessel delineation. FDG is frequently much better in characterizing a lesion than is intravenous contrast material for tumor imaging; hence, the main reason for use of intravenous contrast material at the CT examination part is better delineation of vessels (Fig 5). PET/CT in tumor staging is typically performed from the head to the pelvic floor, but the contrast-enhanced CT study may be relevant only in a subregion (eg, in the head and neck in a patient with a head and neck tumor). The use of intravenous contrast material will have to be further explored in the coming years, and protocols have to be specified for the various imaging questions to be answered with PET/CT.

Once PET/CT data have been obtained, lesions identified at PET are localized in the anatomic CT reference frame. It is then a simple task to mentally coregister anatomic imaging studies performed during a different session to the PET/CT study because of the anatomic details available on the latter.

PET/CT in Chest Tumors

In lung cancer, whole-body FDG PET plays an important role in the evaluation of solitary lung nodules, in preoperative

Figure 3
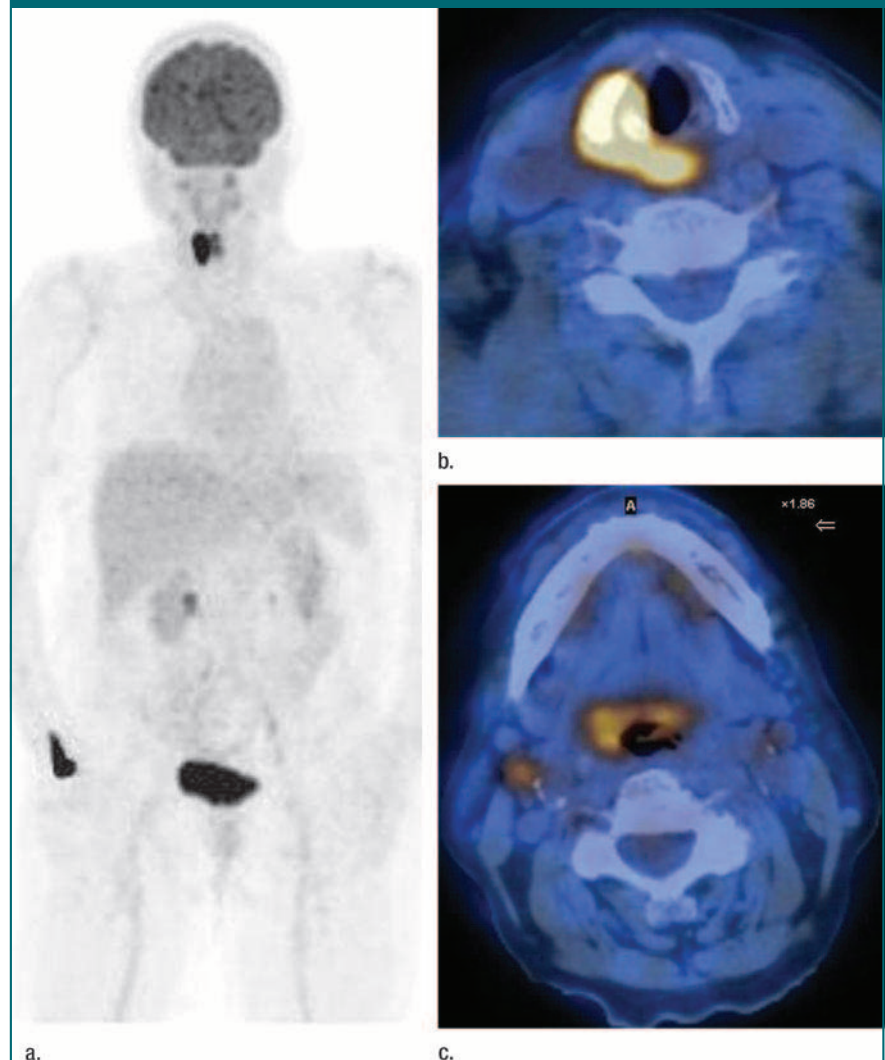
Figure 3: **(a)** Coronal PET MIP shows carcinoma of right hypopharynx with infiltration of piriform sinus, posterior wall of hypopharynx, and aryepiglottic plica with extension to the contralateral side. **(b)** Transverse PET/CT image is suspicious for infiltration of right thyroid cartilage. **(c)** Transverse PET/CT image shows lymph node metastasis to normal-sized left-sided level II lymph node but no signs of distant metastases **(a)**.

staging, in the diagnosis of recurrent disease, and in planning radiation treatment. Integrated PET/CT adds important clinical information in comparison to PET alone, CT alone, or separate comparison of PET and CT images, owing to better lesion identification and localization and fewer overlooked lesions in tumors that do not consistently accumulate FDG (14,16,19). In carcinoid tumors, bronchioloalveolar lung carcinoma, and malignant effusions, diagnosis can sometimes only be based on the CT findings.

The advantage of PET/CT over PET in characterizing pulmonary nodules has not yet been defined. Conventional PET is unsuitable for tumor staging (T staging), because it cannot help anatomically define the tumor confines. Matters with PET/CT are somewhat different. Recently, it has been shown that in tumor staging of patients with lung cancer, analysis of integrated PET/CT images is superior to that of CT images alone, PET images alone, and PET and CT images viewed side by side (14).

Owing to the exact correlation between the extent of FDG uptake and anatomy, focal chest wall infiltration, mediastinal invasion, and differentiation of tumor from atelectasis are improved (Fig 6). The latter is particularly important for the planning of radiation therapy in patients with lung cancer associated with atelectasis (20). However, PET/CT with unenhanced CT is unable to help distinguish contiguity of tumor and mediastinum from the direct invasion of the walls of mediastinal structures, and one still must rely on contrast-enhanced CT to help define mediastinal vascular invasion (Fig 6).

PET has proved to be very effective for mediastinal nodal staging. Nevertheless, mediastinoscopy remains the standard for mediastinal staging, even if not all mediastinal lymph nodes can be accessed with mediastinoscopy, particularly in the paraaortic region and the aortopulmonary window. At most centers, mediastinoscopy will still be performed if a lymph node is identified on PET or PET/CT images as pathologic, which would preclude a surgical approach. In patients with bulky mediastinal disease or multilevel nodal involvement, N staging (nodal staging) is easy. However, exact localization of a solitary lymph node metastasis in the hilum, and thus classification as N1 or N2 disease, is difficult but important (21). The anatomic information of CT in PET/CT may be useful in these cases. In patients with a mediastinal shift due to atelectasis or anatomic variants, the localization of small single nodes with PET can be misleading. In these cases, CT information is essential for precise localization of lymph node metastases.

Whole-body FDG PET is an excellent method to screen for extrathoracic metastases. The advantage of integrated PET/CT imaging is the exact localization of a focal abnormality on PET images. This was the case in 20% of all patients with extrathoracic metastases in our study on the value of integrated PET/CT (14).

FDG PET has been shown to be clinically useful in the evaluation of suspected lung cancer recurrence (Fig 7). Although FDG PET is a sensitive metabolic imaging modality, it lacks specificity after therapy because of FDG accumulation in irradiated tissues and postsurgical inflammatory changes (Fig 7). PET/CT enables the exact localization of FDG accumulation in normal-sized lymph node metastases and helps determines the precise relationship between malignant lesions and surrounding tissue. Especially in complex treatment-related distorted anatomy, PET/CT is extremely useful (16).

Similar to lung cancer, excellent FDG uptake in malignant pleural mesothelioma has been described. The role of PET/CT is to help *(a)* document the extent of pleural disease, *(b)* establish mediastinal lymph node involvement, *(c)* evaluate tumor invasion into the lung and thoracic wall, *(d)* diagnose extrathoracic metastases and *(e)* assess the treatment response to chemotherapy (22). PET/CT also plays an important role in the planning of radiation treatment, as will be discussed later.

Figure 4
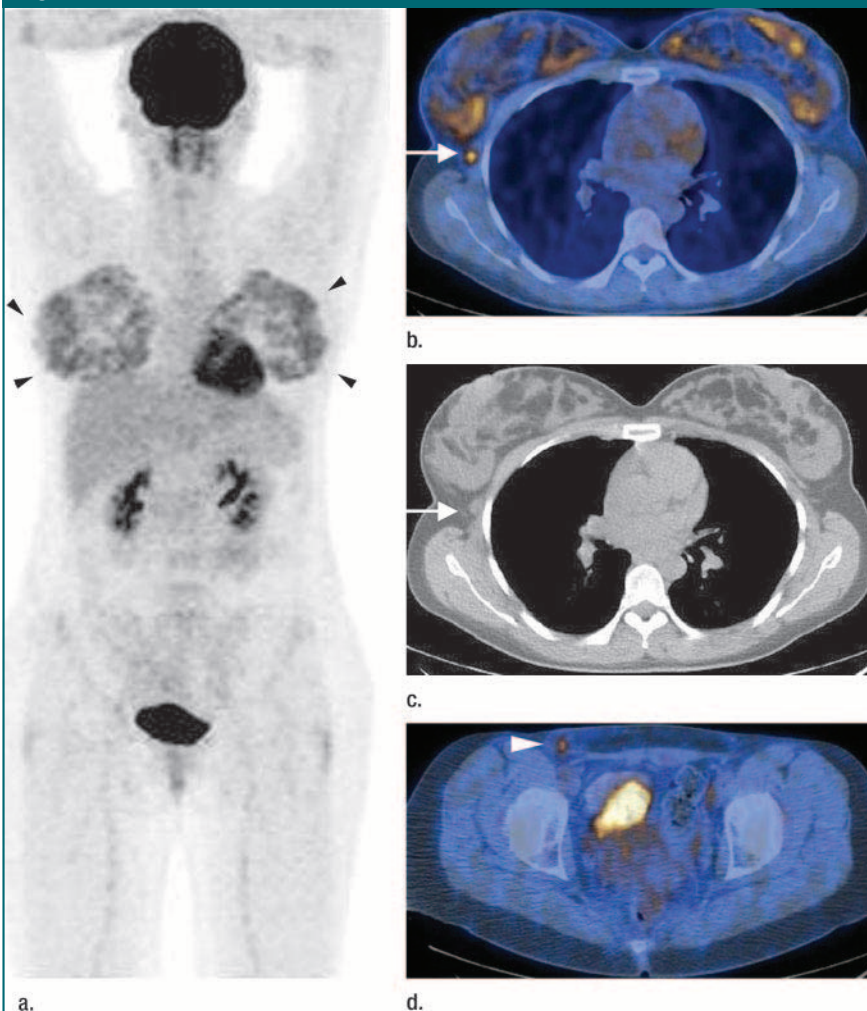
Figure 4: Metastasizing melanoma in a young lactating woman. **(a)** Coronal PET MIP shows increased FDG uptake into breast tissue (arrowheads). Inguinal lymph node with increased FDG uptake is barely notable. Transverse **(b)** PET/CT and **(c)** CT images show additional right axillary metastasis (arrow), which probably would have gone unnoted on **c** alone. **(d)** Transverse pelvic PET/CT image confirms right inguinal metastasis (arrowhead).

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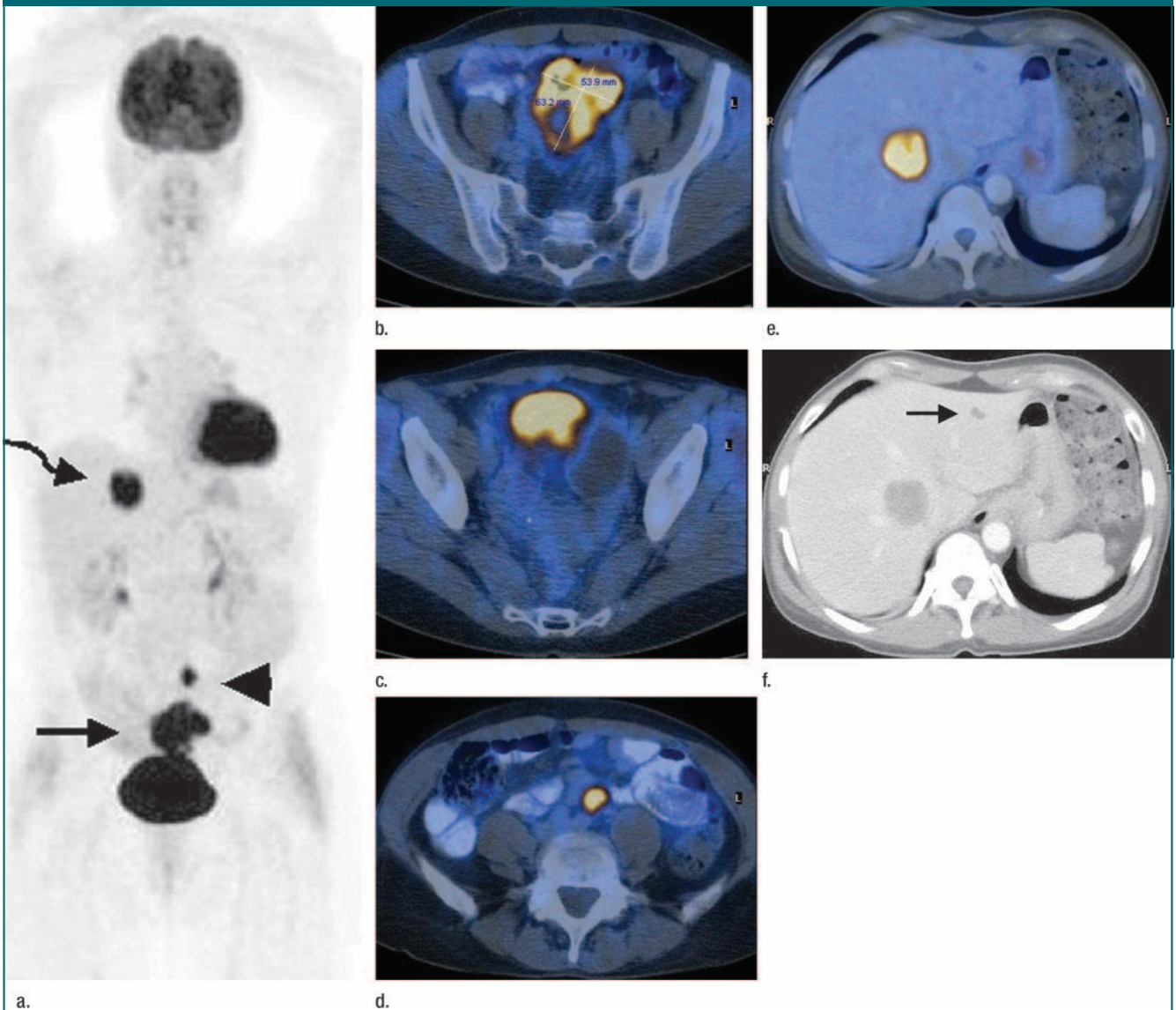
Figure 5

Figure 5: Patient with stenosing colorectal carcinoma was referred for intravenous contrast-enhanced PET/CT before surgery. **(a)** Coronal PET MIP shows primary tumor (straight arrow) above the bladder, retroperitoneal lymph node metastasis (arrowhead), and liver metastasis (curved arrow). **(b–d)** Transverse PET/CT images show **(b)** primary tumor; **(c)** cystic structure corresponding to left ovary with medially thickened wall, raising suspicion of infiltration, which was surgically confirmed; and **(d)** 18-mm retroperitoneal lymph node. **(e, f)** Transverse **(e)** PET/CT and **(f)** contrast-enhanced CT images show single liver metastasis in segment VIII; a second small lesion in segment II seen on **f** (arrow) is negative on **e.**

PET/CT in Colorectal Cancer and Other Abdominal Tumors

Colorectal carcinoma is, after lung carcinoma, the most important cause of death due to cancer in the Western world (23). About 70% of patients have curable resectable tumor at the time of initial diagnosis and are treated with cur-ative intent. Approximately 50% of colon cancer patients will have hepatic metasta-ses, either at the time of initial diagnosis or as a result of recurrence (24).

Initial Staging

The effectiveness of FDG PET/CT at ini-tial diagnosis has not been evaluated to date, but the value of PET suggests that its use is indicated. Two studies (25,26) in which FDG PET alone was used for initial staging have demonstrated high sensitivity for the detection of the pri-mary tumor (100% and 96%) and of distant metastases (87% and 78%) and a low sensitivity (29% and 29%) for lymph node staging. The combination of FDG PET/CT in conjunction with a ded-

icated contrast-enhanced CT protocol could be of interest as a possible single-step staging procedure (Figs 5, 8).

Recurrent Disease

The standard work-up for the detection of recurrence and metastases in colorectal cancer include regular clinical ex-aminations, CT scans, colonoscopy, and, usually, measurement of tumor markers such as carcinoembryonic antigen. However, this approach lacks specificity and may result in diagnostic and therapeutic delays. Serologic tumor markers are useful, although it has been shown that carcinoembryonic antigen level has only 60%–70% sensitivity for the detection of colorectal cancer recurrence (27). The morphologic information from CT does not permit distinction between postsurgical changes and tumor recurrence, nor can it help detect tumor involvement of normal-sized lymph nodes (28). Colonoscopy is useful only in the detection of local recurrence.

Figure 6

a.

b.

c.

d.
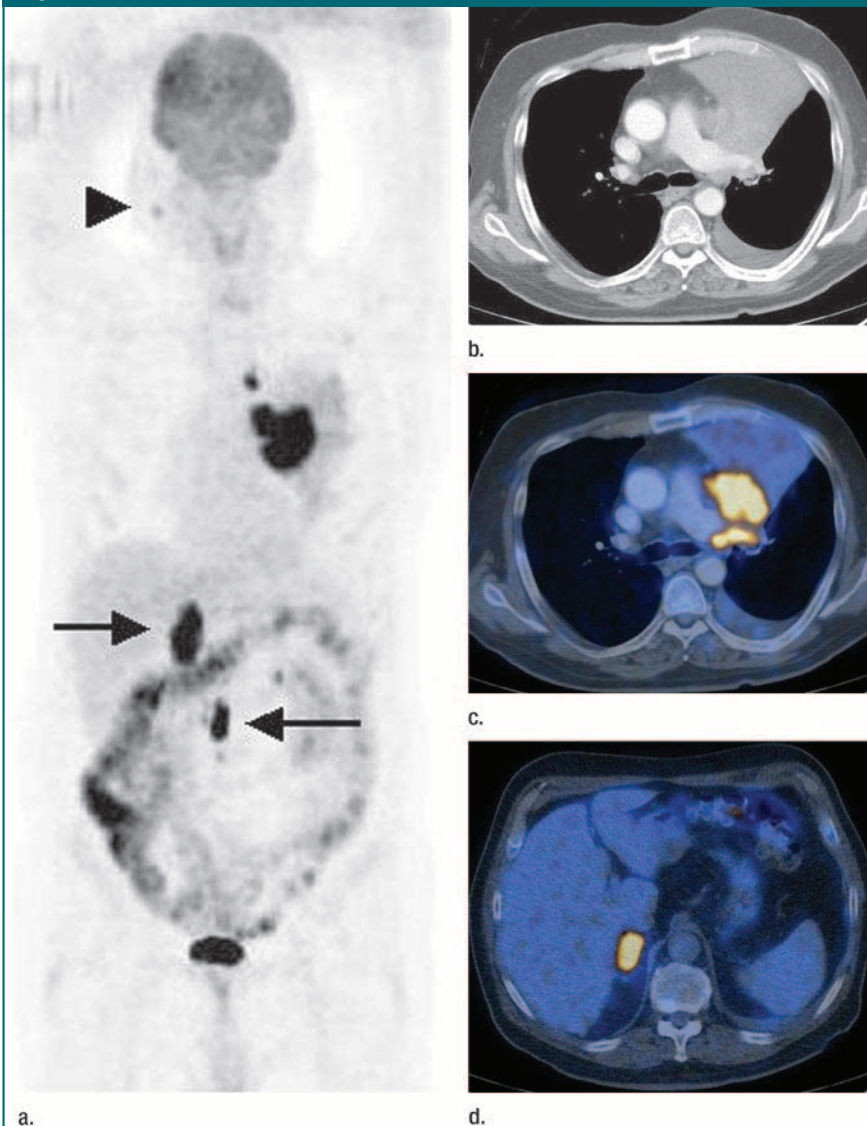
Figure 6: **(a)** Coronal PET MIP and transverse **(b)** contrast-enhanced CT and **(c, d)** PET/CT images in patient with non–small cell lung cancer show left central tumor with ipsilateral mediastinal lymph node metastasis and right adrenal (upper arrow in **a;** also seen in **d**) and retroperitoneal metastases (lower arrow). **(b, c)** Tumor is associated with distal atelectasis on **b;** on corresponding PET/CT image (**c**), distinction of tumor from atelectasis is easy. Infiltration of tumor into left pulmonary artery is shown on **b** and corroborated on **c.** Focus in the right neck (arrowhead, **a**) corresponds to a relatively common benign lesion (Warthin tumor) with FDG uptake.

Figure 7

a.

b.
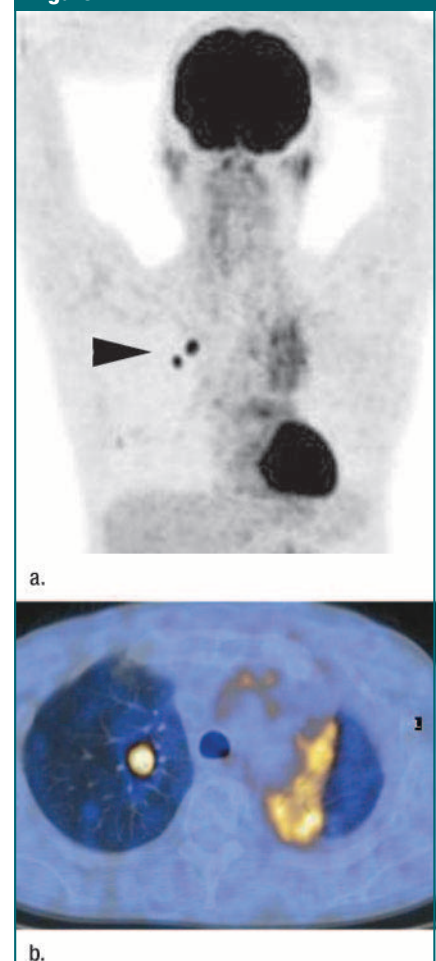
Figure 7: Recurrence of lung carcinoma in right upper lobe. **(a)** Coronal FDG PET MIP shows avid foci (arrowhead), with moderate FDG uptake in left upper lobe, paramediastinal area, and anterior mediastinum. **(b)** Transverse PET/CT image. Activity seen in **a** coincides with the atelectatic and/or fibrous changes resulting from radiation therapy for lung cancer, which ended approximately 4 months before this examination was performed. This represents sterile inflammatory postirradiation changes.

The suitability of FDG PET in helping detect recurrence and metastases has been shown in several studies (29–31). Tumor metastases can be identified even in morphologically normal-sized structures. Owing to the lack of anatomic landmarks on the image, even organ borders sometimes cannot be delineated; as an example, liver involvement versus extrahepatic localization of tumor burden represents important information when choosing a treatment (28). This limitation is largely overcome by PET/CT. In a study by Cohade et al (32), a direct comparison of PET and nonenhanced PET/CT in 45 patients with known colorectal cancer demonstrated an improvement in diagnostic accuracy from 78% to 89% when PET/CT was used compared with when PET alone was used. PET/CT improved not only the localization of lesions but also the certainty in interpretation of lesions as normal or definitively abnormal. Considerable limitations of that study were the retrospective analysis and the missing comparison with contrast-enhanced CT studies.

Postsurgical and radiation therapy changes in the small pelvis are challenging for morphologic imaging in patients with recurrent rectal cancer, since tumor recurrence cannot be differentiated from benign scar tissue. In a study by Even-Sapir et al (33), PET/CT was used to distinguish benign and malignant presacral abnormalities with a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 96%, 88%, and 100%, respectively, and PET/CT findings were clinically relevant in 47% of 62 patients. A comparison with other "conventional" imaging studies was not performed.

In our own study by Selzner et al (34), the diagnostic value of contrast-enhanced CT and nonenhanced PET/CT were prospectively evaluated against each other in 76 patients who had been referred for preoperative evaluation for liver resection for metastatic colorectal cancer. Detection of intrahepatic tumor load, extra- and intrahepatic metastases, and local recurrence at the colorectal site were evaluated. The main endpoint of the study was the assessment of

Figure 8
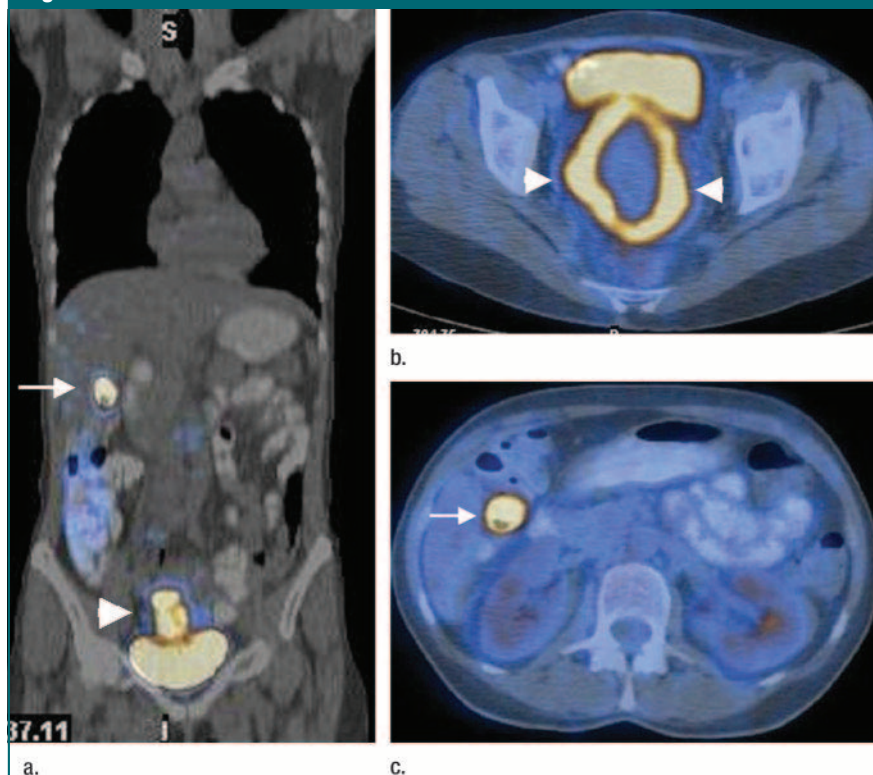
Figure 8: **(a)** Coronal and **(b)** transverse PET/CT images in a patient with cervical carcinoma (not shown) and associated pyometrium (arrowheads). Strongly avid focus of FDG uptake (arrow) is seen in left upper abdominal quadrant on **a,** which appears to be localized in the liver, suggesting liver metastasis. **(c)** Transverse PET/CT image shows that lesion (arrow) is located in right colonic flexure, thus representing focal bowel lesion. Histologic examination demonstrated a large polyp.

the effect of PET/CT findings on therapeutic strategy. Contrast-enhanced CT and PET/CT provided comparable findings for the detection of intrahepatic metastases, with sensitivities of 95% and 91%, respectively. However, PET/CT was superior in helping establish the diagnosis of intrahepatic recurrence in patients who had undergone prior hepatectomy (specificity, 50% vs 100%, $P = .04$). Local recurrences at the primary colorectal resection site were detected with the aid of contrast-enhanced CT and PET/CT with sensitivities of 53% and 93%, respectively ($P = .03$). Extrahepatic disease was missed at CT in one-third of the cases (sensitivity, 64%), while PET/CT failed to demonstrate extrahepatic lesions in only 11% of the cases (sensitivity, 89%) ($P = .02$). New PET/CT findings resulted in a change in therapeutic strategy in 21% of

patients. This study also demonstrated the well-known limitation in spatial resolution of around 4–6 mm for PET, since small tumors (<5 mm) were often not detected. Also, the use of chemotherapy in the month prior to PET/CT resulted in a high incidence of false-negative results. On the other hand, this effect might be used as a predictor of success in neoadjuvant chemotherapy before resection.

The results from the above-mentioned studies clearly demonstrate the advantages of PET/CT for colorectal cancer. As with any high-cost imaging modality (35), the use of PET/CT has to be carefully justified.

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors are mesenchymal tumors that, in approximately 90% of cases, originate in the

stomach and small intestine. Unlike contrast-enhanced CT, FDG PET is able to show early effects in patients undergoing treatment with imatinib mesylate (Gleevec; Novartis, Basel, Switzerland) (36).

In two recent studies (37,38), it was shown that patients without FDG uptake after the start of treatment had a better prognosis than patients with residual activity, which is not demonstrated with contrast-enhanced CT. Furthermore, lesions were better defined on PET/CT images than on PET and CT images compared side by side. This is relevant information for clinical decision making.

Figure 9

Figure 9: Non-Hodgkin lymphoma with involvement of the nerve sheet (neurolymphomatosis). **(a)** Coronal PET MIP and **(b, c)** sagittal PET/CT images show tumor involving several medial lymph nodes of the left thigh (**b**) and extending along the nerve sheet from left midthigh to subcalcaneal soft tissues of the foot (**c**).

PET/CT in Lymphoma

Hodgkin lymphoma accounts for fewer than 1% of all cases of cancer. More than 70% of all patients with newly diagnosed Hodgkin lymphoma can be cured with combination chemotherapy and/or radiation therapy. Careful staging and treatment planning are required to determine the optimal treatment. Non-Hodgkin lymphoma accounts for about 5% of all cases of cancer. Non-Hodgkin lymphoma is less predictable than Hodgkin lymphoma and has a greater predilection to disseminate to extranodal sites. Non-Hodgkin lymphoma is divided into two prognostic groups: low grade and aggressive. In general, with modern treatment protocols for patients with non-Hodgkin lymphoma, overall survival at 5 years is approximately 50%–60%.

Hodgkin and Non-Hodgkin lymphoma usually show avid FDG uptake at initial staging (Fig 9) (39–41). In most studies in which PET was used, both diseases have been studied as one group. In comparison to morphologic imaging with contrast-enhanced CT, metabolic imaging with FDG PET showed a higher specificity for disease staging (40). A major indication for FDG PET is evaluation of treatment response after completion of therapy, especially in patients with residual masses, where it is unclear whether these masses represent tumor persistence (42,43). Compared with other nuclear medicine methods, FDG PET has significantly higher site and patient sensitivity than does gallium 67 scintigraphy in both staging and early therapy evaluation (44,45).

To date, results regarding the use of FDG PET/CT in staging and restaging Hodgkin and non-Hodgkin lymphoma are limited (46,47). Our own initial results suggest that PET/CT performed with nonenhanced CT is more sensitive and specific than contrast-enhanced CT alone for the evaluation of lymph node and organ involvement in patients with Hodgkin lymphoma or aggressive non-Hodgkin lymphoma (47). Lymph node involvement was demonstrated with a sensitivity of 94% for PET/CT and 88%

for contrast-enhanced CT; the specificities were 100% and 86%, respectively. With regard to organ involvement, the sensitivities of PET/CT and contrast-enhanced CT, respectively, were 88% and 50%, and the specificities were 100% and 90%. With regard to exclusion of disease, PET/CT performed significantly better than did contrast-enhanced CT ($P < .05$, McNemar test). That study was retrospective, the number of patients was small, and the patient population was substantially heterogeneous. Histologic verification of the specific suspected pathologic findings was available in only a few patients. Further prospective studies are needed to define more clearly the role of PET/CT versus separate PET and CT in this disease.

PET/CT in Head and Neck Tumors

PET provides improved staging information when compared with CT and MR (48). The limitations of CT and MR are due mainly to equivocal findings, such as lymph nodes of normal or questionable size, which cannot be classified as either normal or pathologic. PET itself poses some image-interpretation issues, as there are a number of situations where FDG accumulates in normal structures, which can be classified as such only with an anatomic reference. Early results suggest that PET/CT is useful in head and neck tumors for local-regional staging, identification of distant metastases, and therapy monitoring (49).

Physiologic or artifactual FDG accumulations in the head and neck, which can be mistaken as pathologic, occur in lymphatic tissues, salivary glands, muscles, and brown fat and near metallic dental work. All tonsillar tissue in the naso- and oropharynx and in the salivary glands can show moderate to relatively intense FDG uptake (Fig 7a) (2). Muscles in the head and neck region, such as the sternocleidomastoid and the longus colli, frequently show uptake, as do the accessory muscles of respiration in patients with respiratory insufficiency. The genioglossus muscles in the floor of the mouth accumulate FDG if

the patient is supine during the uptake phase. With the fused CT information of PET/CT, such accumulations can readily be classified as normal. Unilateral accumulation of FDG in the globular posterior cricoarytenoid muscle masquerading as a scalene lymph node is due to strain on the muscle contralateral to the side where a recurrent laryngeal nerve palsy is present. This is found, for example, in patients with tumor infiltration into the aortopulmonary window, a unilateral nerve lesion after thyroid surgery, and after radiation therapy (50). Furthermore, there can be a substantial accumulation of FDG in brown adipose tissue, which is found mainly in the head and neck region. Again, the anatomic reference provided by CT helps to diagnose this condition unequivocally (51). Artifacts mimicking FDG uptake around dental metal can also generally be classified properly by using PET/CT (10).

Local-Regional Staging

The literature on the use of PET/CT in local-regional staging of head and neck tumors is still sparse, but the easier differentiation of normal from abnormal FDG accumulations and the identification of tumor-involved lymph nodes of normal size appear to be the major advantages (Fig 3). In a recent study (49) of 68 patients with 168 foci of abnormal FDG uptake, PET/CT was found to be relevant in the determination of the exact location in 74% of the lesions in patients who had undergone prior surgery and in 58% of lesions in untreated areas. The number of lesions whose pathologic relevance was equivocal on PET images was 39; on PET/CT images, this number decreased to 18. PET/CT affected care in 18% of patients.

Distant Metastases

PET is the best imaging modality for finding distant metastases in many cases of malignant tumors (Figs 1, 5, 6). Because PET and PET/CT are typically used to survey the body from the head to the pelvic floor, few metastases escape depiction. While such metastases are relatively infrequent in head and neck tumors, the information is relevant

in view of the fact that the major therapeutic approaches to head and neck tumors are surgery and radiation therapy. Obviously, finding a distant metastasis precludes a curative approach. In addition to metastases, PET also is able to demonstrate synchronous or metachronous tumors (52). Relevant tumors include lung and esophageal carcinoma. Furthermore, there is a small but relevant prevalence of precancerous and cancerous lesions in the large bowel that are more readily defined by using PET/CT than by using PET alone, because on PET/CT images these lesions can be easily identified as large-bowel lesions.

Detection of Recurrence

Detection of recurrence of head and neck tumors with CT and MR imaging is notoriously difficult because of the frequent alteration of anatomy due to extensive surgery and persistent contrast enhancement of nonmalignant tissue. PET has been found to have a high specificity because it is excellent in excluding recurrence. However, sensitivity is only moderate (53,54) owing to persistent FDG accumulation in areas of sterile inflammation, which are known to persist long after the end of radiation therapy (55). PET/CT has the same problem, but the anatomic correlation can help to identify a biopsy site, if biopsy is deemed to be necessary for definitive exclusion of tumor recurrence. Issues regarding PET/CT in radiation oncology will be discussed later.

Other Indications

PET/CT is, by definition, useful in all tumor imaging where PET has been shown to be useful. Good indications for PET other than those discussed above are its use in the staging of thyroid carcinoma that does not respond to iodine therapy, pancreatic carcinoma, cholangiocarcinoma, gynecologic tumors, malignant bone tumors, breast cancer staging in patients suspected of having extended disease, and melanoma. PET/CT may play an important role in radiation therapy. PET/CT indications for the use of radiopharmaceuticals other than

FDG and FDG PET for inflammation are discussed in later in the section on Other Radiopharmaceuticals for PET and PET/CT of Tumors.

Thyroid Carcinoma

Differentiated thyroid cancer commonly is diagnosed and treated with iodine 131 if the thyroglobulin level is elevated. In cases of dedifferentiation of papillary or follicular cancer, tumor cells lose their ability to accumulate iodine, and Hürthle cell carcinoma does not take up iodine in the first place. If thyroid cancer is iodine negative, other imaging methods are needed for staging and restaging. It has been shown that FDG PET is a valuable imaging modality in patients with negative radioiodine scans. The advantage of PET/CT is accurate anatomic-functional image coregistration. Exact localization of metastases and the differentiation of scar tissue from tumor issue is needed before surgery. Pitfalls such as FDG accumulation in the contralateral posterior arytenoid muscle in patients with recurrent nerve palsy can be excluded with PET/CT, and Teflon-induced granuloma formation is readily identified (50,56). Integrated PET/CT allows precise diagnosis and prevents unnecessary interventions.

Primary Liver Tumors and Pancreatic Carcinoma

Imaging of primary solid liver tumors and differentiation from other liver lesions is the domain of morphologic imaging with ultrasonography (US), CT, and MR imaging. Well-differentiated hepatocellular carcinomas and all benign solid liver tumors rarely show increased FDG uptake. On the other hand, in patients with known moderately to poorly differentiated hepatocellular carcinoma or cholangiocarcinoma, PET has been shown to be useful, particularly in the detection of distant metastases and for follow-up after treatment (57,58). Imaging of the pancreas with CT and MR imaging is the cornerstone for the diagnosis and staging of pancreatic disease owing to the ability of these imaging modalities to exactly delineate the pancreas from vascular and adjacent structures.

Differentiation of pancreatic masses as chronic pancreatitis or pancreatic carcinoma, however, remains difficult with all imaging modalities. In a study by Heinrich et al (59), 59 patients suspected of having pancreatic cancer underwent staging with abdominal CT, chest radiography, assay for the cancer antigen CA 19-9, and FDG PET/CT; findings from these tests were confirmed at histologic examination. A cost-benefit analysis was performed on the basis of charged costs of PET/CT and pancreatic resection. The positive and negative predictive values for pancreatic cancer were 91% and 64%, respectively. False-positive results were due to inflammatory pseudotumor, pancreatic tuberculosis, chronic pancreatitis, and focal high-grade dysplasia, which was suspicious for malignancy at brush cytologic evaluation. PET/CT demonstrated additional distant metastases in five patients and synchronous rectal cancer in two. PET/CT findings changed patient care in 16% of patients with pancreatic cancer deemed resectable after routine staging ($P = .031$). In total, PET/CT reduced costs by $74 925 ($1270 per patient). Despite its effect on the staging of pancreatic cancer, neither PET nor PET/CT can replace contrast-enhanced CT and endoscopic US.

Gynecologic Tumors

Epithelial carcinoma of the ovary is the fifth most frequent cause of cancer death in women, with half of all cases occurring in women over the age of 65 years (60). Owing to its late diagnosis and poor prognosis, ovarian cancer is the leading cause of death due to gynecologic tumors. To date, only two studies in which PET/CT was used for restaging ovarian cancer are available (61,62). In the study by Sironi et al (61), 31 women with ovarian carcinoma were treated with primary cytoreductive surgery. In all patients, histologic examination after second-look surgery was used to determine the diagnostic accuracy of PET/CT in the evaluation of disease status. The overall lesion-based sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT were 78%, 75%, 77%, 89%,

and 57%, respectively. In the detection of a tumor, a size threshold could be set at 5 mm, as this was the largest diameter of a lesion missed at PET/CT. The use of nonenhanced PET/CT improved the diagnostic accuracy compared with PET alone but was not as effective as fusion of contrast-enhanced CT images and FDG PET images, as demonstrated in other studies (63). Therefore, it is possible that PET/CT with intravenous contrast enhancement may become the technique of choice in staging of recurrent ovarian cancer.

Worldwide, cervical cancer is the second most common cancer among women. One of the major factors in survival is local extent of the disease (64). Even though the presence of lymph node metastases in the pelvic or paraaortic regions does not change the stage, it does lead to changes in therapy, particularly changes in the radiation treatment plan. When using conventional radiologic procedures like US and CT, the sensitivity for detection of paraaortic lymph node metastases is low (20%–40%) (65). In a study by Grigsby et al (66), determination of tumor involvement of paraaortic lymph nodes by using FDG PET alone was better than that with standard CT. More important, PET findings were a better predictor of survival than were CT findings.

To date, in only two studies (67) with small and heterogeneous patient populations, PET/CT was used in the evaluation of gynecologic malignancies, primarily endometrial and cervical cancer. In the study by Grisaru et al (67,68), 53 patients with various gynecologic tumors were evaluated for staging or restaging purposes by using PET/CT. Results were compared with those of conventional imaging studies including CT and MR imaging. All values for sensitivity, specificity, and positive and negative predictive values were greater than 93%, whereas sensitivity and specificity for conventional imaging studies were 40% and 64%, respectively. A more elaborate study by the same group of investigators (68) demonstrated the usefulness of PET/CT in the localization of FDG uptake in the uterus and in the

differentiation of physiologic from pathologic uptake in the uterus and ovaries. Of the most interest, increased uptake in the endometrium adjacent to a cervical tumor did not necessarily reflect endometrial tumor invasion. In addition, increased ovarian uptake in postmenopausal women was associated with malignancy, whereas increased ovarian uptake may be functional in premenopausal patients.

Breast Cancer

Breast cancer is often curable when diagnosed at an early stage. The sensitivity of PET for the detection of small lesions is limited, restricting its use in the evaluation of primary breast cancer and axillary nodal spread. In addition, PET is affected by the histologic characteristics of the tumor. FDG PET can fail to demonstrate a growing cancer such as tubular carcinoma or a noninvasive cancer such as ductal or lobular carcinoma in situ. At present, the major clinical application of whole-body FDG PET is the assessment of systemic metastatic disease. We must caution that some osteoblastic metastases can be false-negative; however, no conclusive data are available.

The clinical value and the advantages of integrated PET/CT compared with PET alone are not yet clearly defined. Integrated PET/CT may play an important role in radiation therapy planning by providing an accurate estimate of the tumor extent (69).

Melanoma

Malignant melanoma can metastasize to any part in the body, including the brain, the gastrointestinal tract, and the myocardium. It is well known that malignant melanoma is one of the most avidly FDG-accumulating tumors (Fig 4). With exception of the brain, whole-body FDG PET is a very sensitive and effective imaging modality for staging in patients with a high likelihood of metastases (Breslow thickness ≥ 2 mm, known metastases). Surgical resection is the treatment of choice for regional lymph node metastases or a single distant metastasis. If multiple metastases are present, only palliative symptomatic

therapy is indicated. In patients in whom surgery is planned, whole-body PET should be performed to exclude occult metastases. At our institution, combined PET/CT is important for planning minimally invasive surgery for small lesions. Integrated PET/CT it is more patient friendly because patients need only one imaging appointment.

Radiation Therapy

With regard to radiation therapy, PET/CT may be particularly useful because, in addition to the typically excellent staging afforded by PET/CT before treatment, the CT data from a PET/CT examination can be used for radiation therapy planning, provided the CT data are properly acquired. As reported in the literature (70,71), PET has a considerable effect on the decision-making process prior to radiation therapy, and treatment changes occur in around 25% of patients. These treatment changes include prevention of inappropriate radiation therapy and changes in the intent regarding curative versus palliative radiation therapy, the radiation dose, or the planning target volume (70).

When PET data are used in addition to CT data for planning, there is much better agreement among observers on how to delineate gross tumor volume (20). However, the effect of better delineation of gross tumor volume on planning therapy volume is frequently irrelevant. The latter volume includes known regions of micrometastatic spread and a safety margin and is, therefore, frequently considerably larger than gross tumor volume. As a result, the direct effect of PET/CT on therapy planning is typically limited in pelvic tumors, unless local-regional metastases are found. The effect of PET for radiation therapy planning on the definition of the planning therapy volume may be more relevant in lung tumors, where it is notoriously difficult to distinguish tumor involvement from atelectasis, and in head and neck tumors, where an optimized definition of the planning treatment volume is critical to avoidance of substantial sequelae to radiation therapy (71).

The key questions of the effect of PET/CT in radiation therapy planning

can only be answered by means of outcomes studies. The first question is whether the reduction of the planning treatment volume due to PET/CT information will not result in an increase in early recurrences. The second question is whether extension of the planning treatment volume on the basis of PET data will improve patient survival. These data are currently not available. We have already mentioned that sterile inflammatory changes can persist for several months after radiation therapy (Fig 7).

Future Perspectives

The future of PET/CT looks bright. Developments in systems technology and radiopharmaceuticals promise to make PET/CT much more useful and versatile in the future.

Systems Performance

Improvements in systems performance are underway on both the PET and the CT sides. More efficient PET components with different detector materials and newer electronic designs are appearing on the market or are under development by manufacturers. The promises are faster image acquisition or, alternatively, higher spatial resolution. Recently announced systems have detector subunit sizes of 4 mm at high sensitivity, which should result in nearly 4-mm spatial resolution over a sizable field of view. While increased imaging speed is desirable, current PET/CT scanners acquire data from extended body fields of view in less than 30 minutes, which is both generally acceptable to patients and economically viable. On the CT side, 64-section scanners are being introduced and will likely be integrated into PET/CT systems in the foreseeable future. An increase to 256-section CT is conceivable, which then would lead to PET/CT scanners in which both systems can image the entire brain or heart without table movement, an interesting notion.

It should be noted that it is currently by no means clear how many CT capabilities have to be built into a PET/CT system for best results. For tumor stag-

ing, current systems are quite adequate, and the major limitation in systems performance is the data-acquisition speed of PET. On the other hand, when conceiving a cardiac "one-stop shopping" PET examination, CT is the limiting component. Initial clinical results on cardiac one-stop shopping PET/CT are promising and are being published, but the technology to perform such examinations is not yet mature (72) (Fig 10). Thus, it is likely that PET/CT systems will appear on the market that are tailored to specific applications.

Other Indications for FDG PET/CT of Tumors

There are several less common tumors for which FDG PET and PET/CT appear to be useful; these include testicular cancer, sarcomas, and multiple myeloma. The major application where FDG PET appears of limited value is prostate cancer. It is known that FDG will accumulate in aggressive prostate

cancers, but at that stage of the disease imaging is probably not very useful (73).

Other Radiopharmaceuticals for PET and PET/CT of Tumors

Recently, various derivatives of choline, as well as carbon 11 (^{11}C) acetate, have been shown to accumulate in prostate cancer. While ^{11}C radiopharmaceuticals will probably not go into widespread use in the foreseeable future because of the difficulties in utilizing the short-lived ^{11}C-based substance (half-life of 20 minutes), ^{18}F choline and ^{18}F ethylcholine are compounds whose clinical utility is currently being explored in

prostate carcinoma. The major questions to be answered in prostate cancer are related to the exclusion of lymph node involvement in primary staging and the identification of tumor in patients who show a biochemical recurrence with an increasing prostate-specific antigen level. Early results show some promise for staging, while the data suggest that ^{18}F-choline PET is unable to help distinguish prostate cancer from benign prostatic hypertrophy (Fig 11) (74,75).

Other promising tracers include various amino acids such as ^{11}C methionine, again of limited clinical utility be-

Figure 10
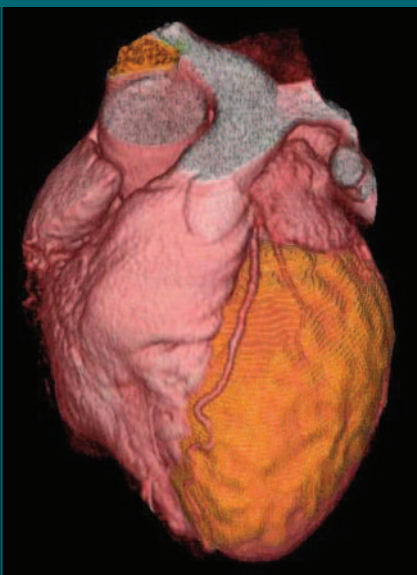
Figure 10: Early results of cardiac PET/CT examination. Gray-scale image represents CT anatomic data showing, in this case, intact left anterior descending artery and diagonal branch. Red color spread over surface of the left ventricular free wall corresponds to PET ammonia stress perfusion data, which show absence of perfusion defects.

Figure 11

a.   d.
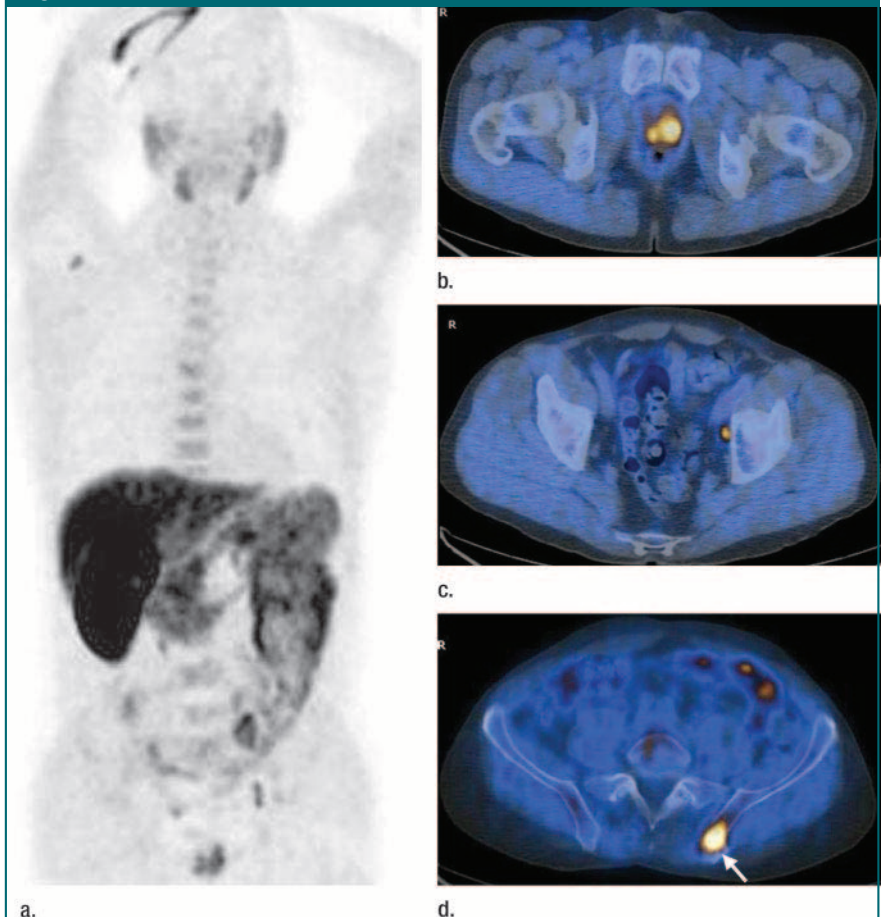
Figure 11: ^{18}F choline PET in a patient with prostate cancer. **(a)** Coronal PET MIP shows typical appearance of ^{18}F choline PET scan: no activity in brain and high activity in liver, spleen, and parts of gastrointestinal tract. **(b, c)** Transverse PET/CT images also show activity in prostate, corresponding to cancer and pelvic lymph nodes. It would be difficult to definitively determine this lymph node to be positive on the basis of CT images alone. **(d)** Furthermore, transverse ^{18}F choline PET/CT images shows sclerosing bone metastasis (arrow) at posterior iliac spine on the left.

cause of the label, and ^{18}F ethyltyrosine, ^{18}F thymidine, and some receptor-specific markers. The amino acids are of interest because, unlike FDG, they seem not to accumulate in inflammatory processes and could thus potentially provide a more specific tumor label (76). Unfortunately, they are also less sensitive than FDG for tumor staging. It is likely that they will continue to play a role in brain tumor imaging because, unlike FDG, they do not accumulate much in normal brain tissue. ^{18}F thymidine has been evaluated as a marker for cellular proliferation, with mixed results. Many other PET radiopharmaceuticals are currently under investigation in small trials and include octreotide derivatives and ^{18}F-DOPA for the detection of endocrine-active tumors and various markers for cellular hypoxia (77). No alternative for PET has yet been found that could match or surpass FDG; so, in a clinical setting FDG is likely to be the dominant tracer for PET and PET/CT in the next decade.

FDG PET/CT Imaging for Inflammation

The marked accumulation of FDG not only in many tumors but also in activated macrophages and granulocytes may make FDG PET useful in imaging patients with inflammatory disease. There are not many substantial data on the use of PET/CT in this setting at this time. However, localization of inflammatory foci in the appropriate soft-tissue or bone structures and the additional information provided by CT will likely be very useful, which thus suggests that future of PET/CT for inflammation will be as successful as that for tumor imaging.

The disease entities involving inflammation, where data suggest that FDG PET is useful, are as follows: *(a)* fever of unknown origin, where infectious foci or sterile inflammatory processes (eg, vasculitis) can be demonstrated (Fig 12) (78); *(b)* widespread soft-tissue infections, where the search for the focus is relevant; *(c)* suspected chronic osteomyelitis, where the focus needs to be identified and other imaging modalities cannot help in this task (79,80); and *(d)* osteosynthetic im-

Figure 12

a.

c.
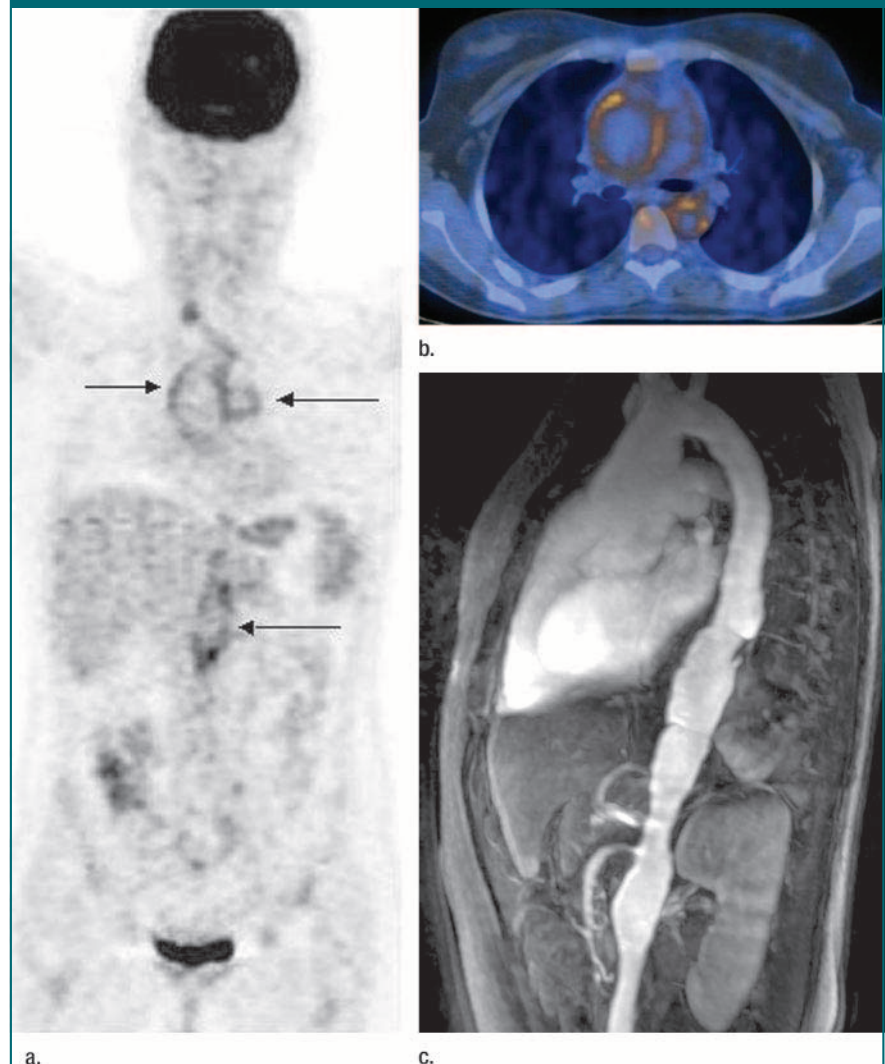
Figure 12: Fever of unknown origin in a 20-year-old patient in whom arteritis was diagnosed on the basis of PET/CT findings. **(a)** Coronal PET MIP shows inflamed aortic (upper left arrow, lower arrow) and pulmonary arterial walls (upper right arrow). **(b)** Transverse PET/CT image shows circular activity that is confined to aortic and pulmonary arterial walls. **(c)** Corresponding sagittal contrast-enhanced MR angiogram shows irregular wall of entire descending aorta.

plants, where the suspicion of an infection has arisen (81).

With regard to the last indication, it should be noted that in hip prostheses, differentiation of loosening from infection is a poor indication for PET. Hip prostheses will frequently exhibit physiologic formation of granulation tissue in the region of the prosthetic head and periprosthetic artificial FDG accumulations, which make it impossible to differentiate chronic sterile inflammation,

infection, and loosening from each other (82).

Conclusion

The use of PET/CT is currently showing rapid worldwide growth. This is due to the fact that PET and CT complement each other's strengths. Currently available data in tumor imaging with PET/CT indicate that, when available, PET/CT will be used as a primary staging tool in

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many patients with tumors. Interesting developments are occurring with regard to new radiopharmaceuticals, imaging technology, and other applications of PET/CT (eg, for infection), which appear to be clinically relevant.

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