5 Review of PET/CT Images in Melanoma and Sarcoma: False Positives, False Negatives, and Pitfalls

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While FDG-PET is a powerful modality for staging, restaging, response assessment, and surveillance of both melanoma and sarcoma, it is prone to a few pitfalls that the reader must be aware of. Both false positives and false negatives have been known to occur.

False Positives

The most common cause of false-positive FDG-PET is inflammation [1]. White blood cells, in particular macrophages, accumulate glucose and thus its analog FDG, resulting in increased uptake in the local region which can be confused with presence of tumor [2]. This is known to be a problem with a variety of tumors, and melanoma is no different. This is somewhat different from the case with MR and CT where increased vascularity leads to increased contrast enhancement, though both cases may sometimes be seen. The effect is well-known enough FDG-PET has been used to look for foci of occult infection in fever of unknown origin.

As benign inflammation tends to decrease in uptake over time whereas malignancy tends to continue to accumulate glucose, some have advocated dual time-point imaging to distinguish between inflammation and malignancy. The effect is not reliable enough to be useful, however [3], and dual time-point imaging has generally not proved sensitive or specific enough to be useful, however.

In general, benign inflammation can be due to iatrogenic causes or to actual inflammation or infection (Figs. 5.1 and 5.2).

Recent Therapy

One of the most difficult causes to disentangle from malignancy is recent local therapy. Surgery or radiation will produce inflammation and hence uptake. It is for this reason that an inspection of the recent history of surgery, radiation, and chemotherapy the patient has had is important when interpreting examinations.

Surgery in particular can produce local inflammation persisting for months afterward (Fig. 5.3) [4]. The degree and duration are heavily dependent on the type of surgery, with larger procedures producing more uptake and larger amounts of uptake. Linear uptake is usually recognizable as surgical, and changes in local anatomy (e.g., from a cystectomy with neobladder—Fig. 5.4) may provide evidence of a recent procedure. In addition, the presence of surgical clips should be noted. (This is one reason to inspect a site using

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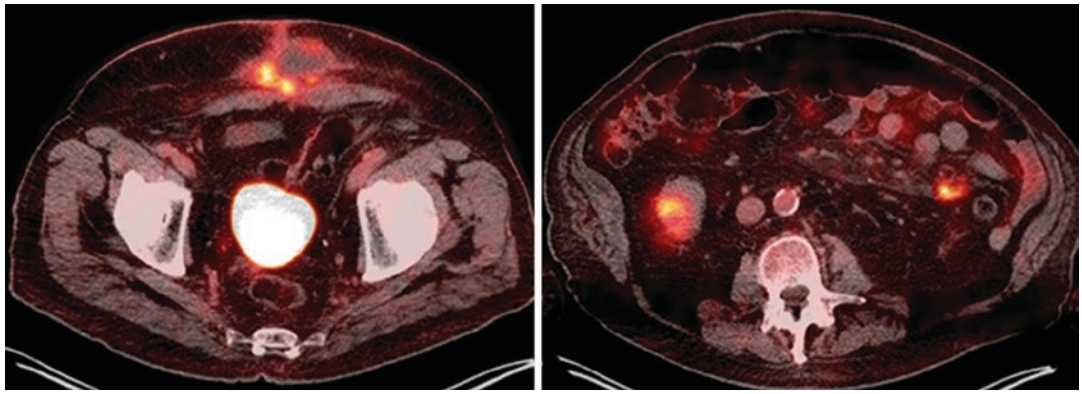

Fig. 5.1 Peripheral uptake and uptake in draining lymph nodes from large abdominal wall abscess

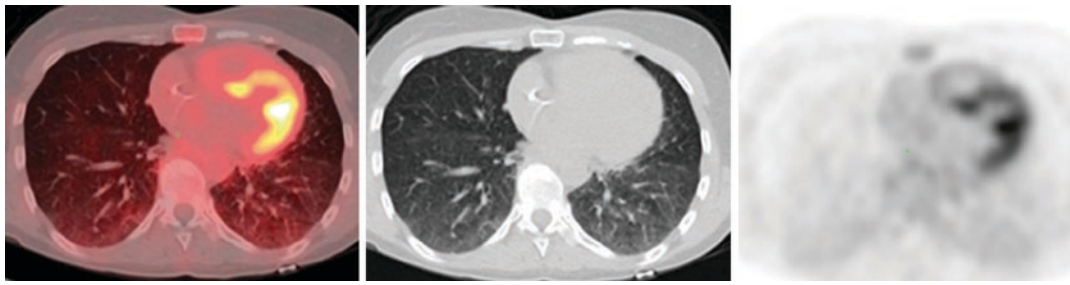

Fig. 5.2 Diffuse lung inflammation, with mild ground-glass opacities on CT and uptake on PET

at least one sequence other than fused images, as surgical clips may be obscured by intense uptake on fused images—Fig. 5.5.) In some cases, there may be no recourse other than to simply say "recommend attention on follow-up," but usually the localization and specific pattern of surgical uptake can give the answer.

Radiation can produce a great deal of uptake, and radiation fibrosis can make reading the scan challenging. Fibrosis in the lungs can appear as a secondary mass, whereas radiation changes in the soft tissue, while generally not confused with malignancy, can make mass lesions hard to see. One useful property of radiation changes is their limitation to the area of the radiation port—they will have sharp geometric borders unlike any physiologic or other pathologic process [4].

The bone marrow (and often the spleen) will often show increased uptake after either chemotherapy or the growth factors such as Neulasta given with it. This can decrease sensitivity for metastases to these areas. Conversely, an incidental finding that can sometimes indicate the presence of prior radiation if missing from the provided history is decreased uptake in multiple contiguous vertebral bodies (from local myelofibrosis) (Fig. 5.6).

In general, the precise duration to wait after any sort of therapy is unclear. Chemotherapy usually cannot be stopped, so the scan is done before the initiation of the next cycle. Postsurgical uptake is quite variable, but a few weeks are usually sufficient to at least figure out what is actually recurrence. Uptake from radiation can last a long time. Unlike the timing of the wait from other types of treatment, this has been heavily studied, with the head and neck squamous cell carcinoma literature finding a good negative predictive value for radiation done 3 months after (whereas 1 month after is generally not sufficient). While the American Society of Nuclear Medicine and Molecular Imaging does not have specific guidelines for how long to wait, the European Association of Nuclear Medicine's

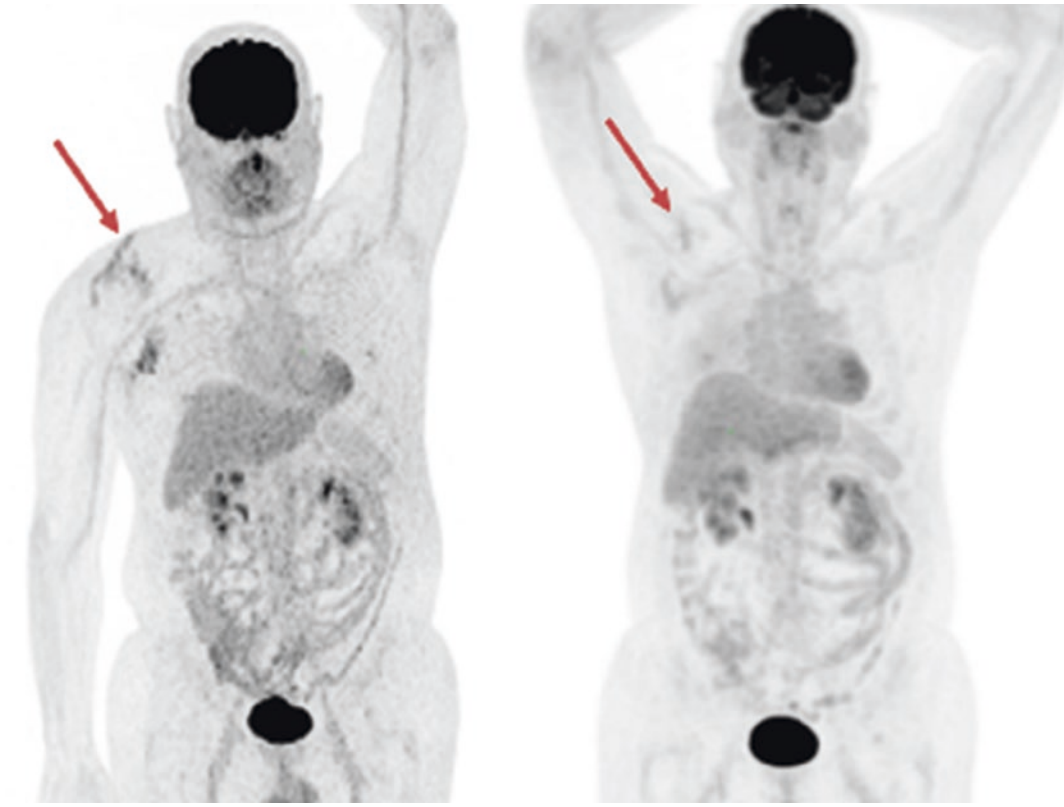

Fig. 5.3 Right shoulder melanoma surgical site shortly after resection and approximately 1 year later (arrows). Most of the immediate uptake has died down, but vague postsurgical changes have still died down

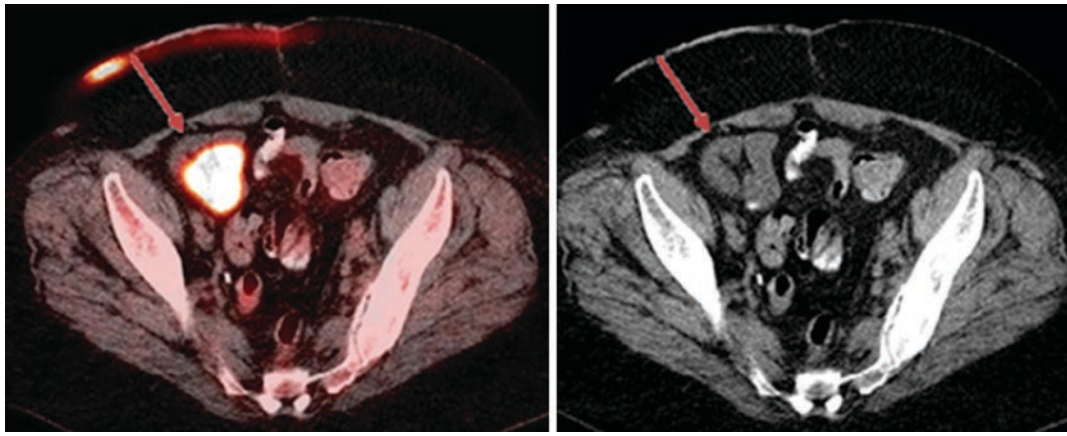

Fig. 5.4 Intense uptake in neobladder after cystectomy (arrows); the CT appearance is of loops of bowel filled with low-attenuation fluid (urine), which is extremely FDG-avid (as the tracer is excreted in the urine)

guidelines does suggest 10 days for chemotherapy, 2 weeks for growth factors such as G-CSF and GM-CSF, 6 weeks for surgery, and 2–3 months for radiation [5].

Many of the newer immunotherapy drugs such as ipilimumab and pembrolizumab may produce false positives due to inflammation from immune-related adverse events, such as arthritis

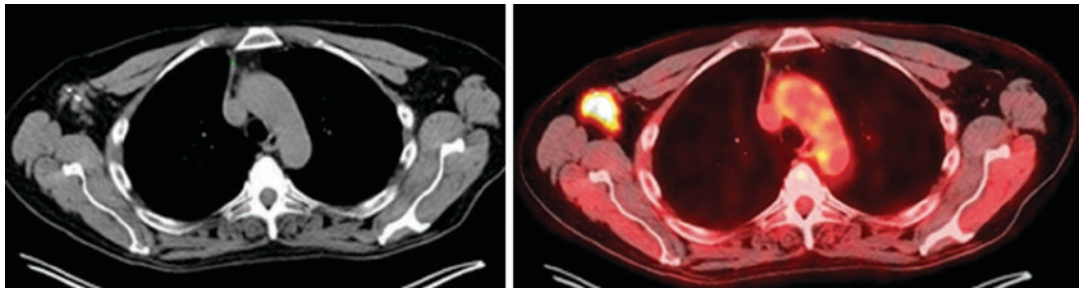

Fig. 5.5 Axillary surgical clips are obscured by intense uptake from recurrence; suppression of PET from fused image reveals them

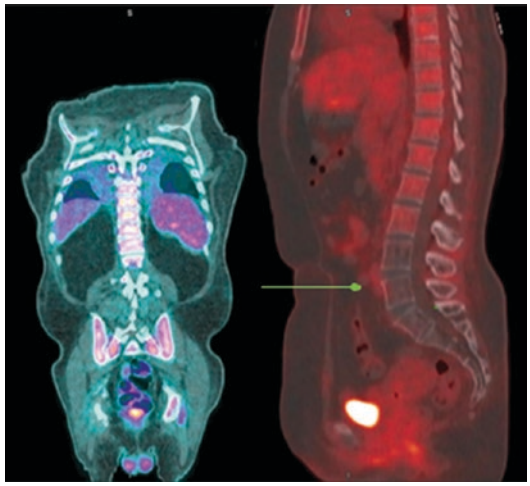

Fig. 5.6 Diffuse spine uptake and spleen greater than bone marrow liver uptake typical of Neulasta. A lack of uptake in the lower L-spine (arrow) suggests prior radiation therapy to this area

and colitis [6] and a sarcoid-like mediastinal and hilar lymphadenopathy [7] or thyroiditis [8]; this has been described in a variety of cancers, but melanoma is no exception. While the false positives may be confusing, the presence of these findings may actually correlate positively with progression-free survival [6, 7] or early response [8], although the relationship of colitis has been questioned [9]. A few different response criteria such as IPERCIST [10] and IMPERCIST5 [11] have been formulated, but presently the most widely used is presently iRECIST [12], which has a category of "immune unconfirmed progressive disease" where progression must be confirmed on a follow-up scan. Given the wide variety of protocols, it can be difficult to determine what exactly the benchmark in a research trial is unless this is communicated directly from the referring clinician, so the safest approach is to refrain from definitively calling "progression" in the presence of new lesions on immunotherapy and to simply note the presence of new lesions in patients on these drugs.

Inflammation/Infection

Inflammation and infection will also show increased uptake—thus bacterial infections will show locally increased uptake, whereas viral infections, being more systemic normally, will tend to show increased uptake in multiple nodes around the body. HIV quite notably can cause low-grade uptake in axillary and inguinal nodes (Fig. 5.7). This tends to be bilaterally symmetric, unlike a local infection or local spread of disease.

Granulomatous inflammation such as that in tuberculosis, mycobacteria, or fungi, as well as inflammatory diseases such as sarcoid, is a well-known cause of false positives on FDG-PET for a variety of tumors (Fig. 5.8) [2]. The nodular nature of granulomatous inflammation is particularly confusing as it can look like a spherical metastasis. Granulomatous inflammation tends to be in a more symmetric or systemic pattern, but this is often difficult to tell. A history of exposure to TB or fungi may be of use.

A related pattern is the often-seen low-grade mediastinal and bilateral hilar nodal uptake seen in many patients on FDG-PET (Fig. 5.9). This may be related to granulomatous inflammation (as described above) or may have to do with other low-grade inflammatory processes. Nonetheless, it tends to be rather diffuse, low-grade, and sym-

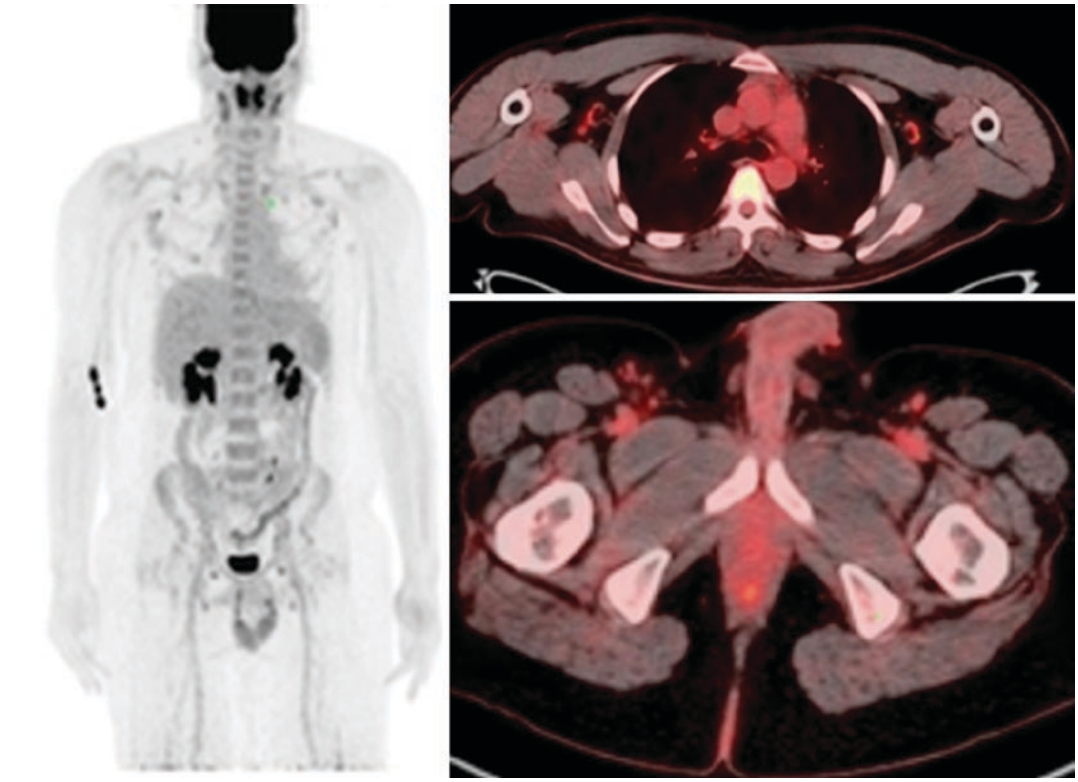

Fig. 5.7 Low-grade uptake in axillary and inguinal nodes from HIV

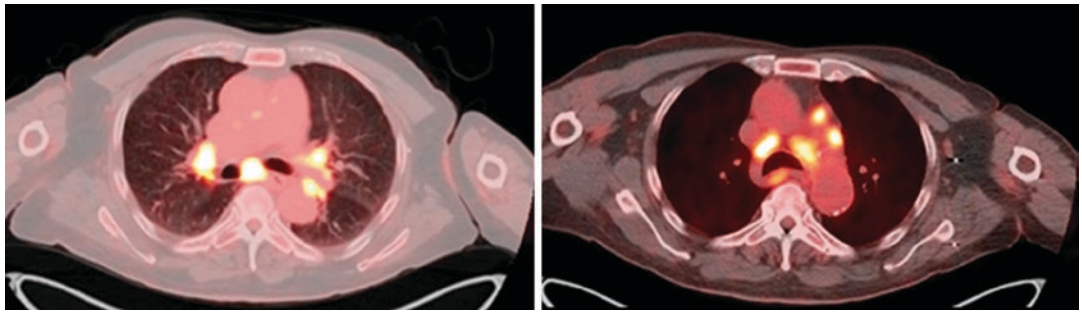

Fig. 5.8 Bilateral mediastinal and hilar nodal uptake typical of sarcoid or other inflammatory reactions

metric, and melanoma, as a cutaneous tumor, will tend to spread to axillary and inguinal nodes before reaching the mediastinum. Of course, if there are many focal nodes on one hilum, a primary lung tumor may be responsible.

Degenerative change is another common source of abnormal uptake. While this is more of a common problem with bone scintigraphy, mildly increased activity can be seen at the site of degenerative changes in many cases (possibly as a result of accompanying inflammation). Generally localization is sufficient to identify change as degenerative (metastases to osteophytes do occur but are rare). Once in a while an insufficiency fracture in a site affected by radiation may occur.

With all the questions about inflammation, one can wonder if simply waiting for the resolution of the infection (or treatment of the autoimmune disease) may help in imaging. In fact we do recommend not imaging patients, particularly in non-urgent setting such as surveillance, until any

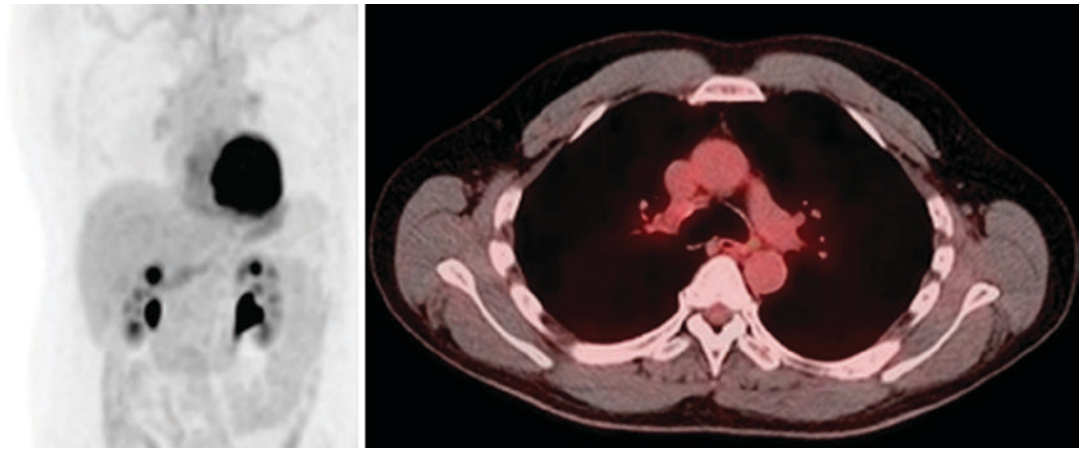

Fig. 5.9 Low-grade mediastinal and bilateral hilar uptake. Sometimes a visible site of infection is visible, more often not. If the uptake is mild and symmetric enough, this is often ruled benign

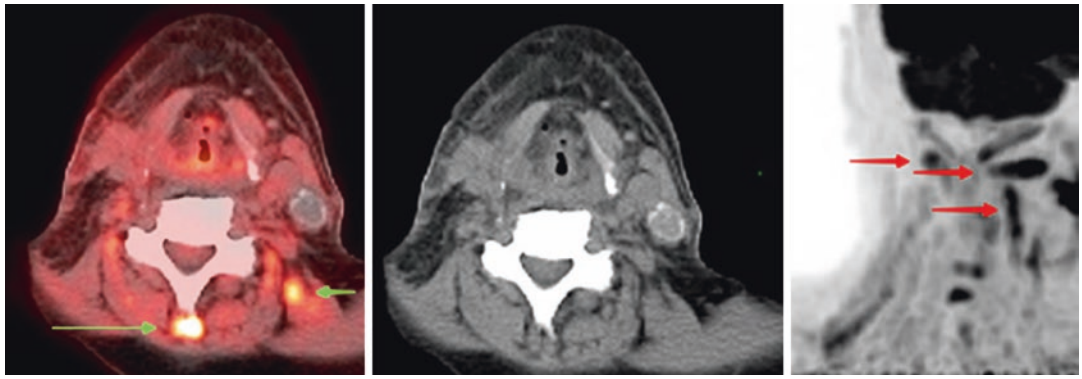

Fig. 5.10 Intense uptake in numerous small muscles of the head and neck (arrows) can be confused for nodal metastatic disease. (A non-avid calcified node is, in fact, visible anteriorly)

known existing inflammatory diseases have resolved. However, this may not always be an option if imminent treatment is necessary or the patient has a chronic inflammatory disease that is unlikely resolve completely.

Another cause of abnormal uptake apart from inflammation is extravasation [4]. In addition to reflecting sites of actual physiologic uptake by glucose-using processes, FDG is a physical substance that has to be injected. In cases of extravasation, it will be picked up by macrophages and brought to the draining lymph node. As the patient is imaged at 1 hour, the initial extravasation may not be visible if small (though it often is). The relevance is that uptake may be seen in a draining axillary node on the side of the injection and mistaken for the spread of tumor. The node will, of course, appear normal. Noting that the abnormal uptake is on the same side as the site of injection is usually sufficient to exclude metastasis. It is for this reason that one notes the side and site of injection and injects opposite to the side of any lesion. Right axillary uptake in a patient with a right upper extremity melanoma injected in the right antecubital fossa could represent either extravasation or spread of tumor, but if the same patient were injected on the left, one could be fairly sure the uptake was related to spread of malignancy.

Physiologic uptake in muscles is usually distinguishable by its diffuse intensity and linear, rather than nodular, contour. However, the small muscles of the neck may occasionally be confusing, particularly if activated unilaterally due to prior surgery in this region (Fig. 5.10).

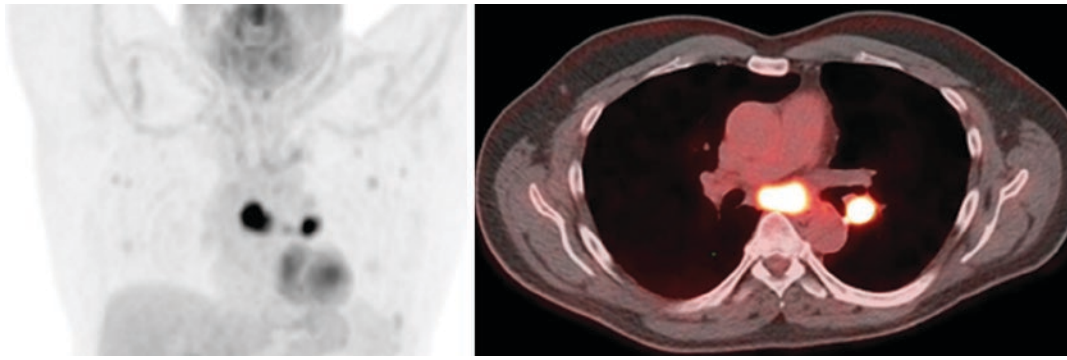

Fig. 5.11 Unilateral hilar and mediastinal nodes, more typical of a primary lung tumor (resected) than metastases

Finally, other tumors will of course take up FDG, and one may find a tumor one was not expecting. The various incidental hot spots that may be either benign or malignant are discussed below, but malignant-appearing lesions (classically a spiculated lesion in the lung, but other common sites of malignancy such as the breast or kidney are also possible) may be seen in a variety of places (Fig. 5.11). Whether this truly represents a *false* positive is a matter of semantic debate, but they are nonetheless serious health problems to be dealt with like any other tumor.

False Negatives

High Background Organs

The brain is famously high in background uptake on FDG scans, which greatly decreases sensitivity for metastases [4]. Even melanoma, which is quite FDG-avid, can be difficult to see over the high background brain uptake. In some cases, large metastases may be seen as cold spots. In general, while it is worth inspecting the brain for "hot" areas that may be metastatic, brain MRI is a much more sensitive test for brain metastases. (CT, even with contrast, is a poor substitute.)

Bone marrow usually displays at least some uptake, although this is increased (as described above) after the use of growth factors which stimulate blood cell formation [4]. The diffuse bone marrow uptake of active bone marrow is usually easy to distinguish from the multifocal, many-small-intense areas uptake of bone metastases. Even when the number of metastases is very large, it is usually easy to distinguish from diffuse bone marrow activation. The major concern is decreased sensitivity for metastases; for this reason the bone should be inspected on bone window at least once to look for non-avid lytic or blastic lesions.

Muscle metastases often have no CT correlate as the soft tissue density of metastases is similar to that of lung (contrast this with lung or bone). Muscle may also show physiologic uptake if the patient has moved during the uptake period (something difficult to completely prevent as people find it difficult to stay 1 hour without moving at all), but given the diffuse distribution in commonly used muscles this is usually easy to distinguish. Postsurgical changes may cause intense muscle uptake if muscles have to compensate for resected muscles on the other side (this is most commonly a problem in head and neck lesions where small muscles may be confused with nodal metastases) [4]. In this case it is often more obvious the uptake is muscular in nature on maximum intensity projection images.

The kidneys are a particularly perplexing case as cortical uptake is relatively mild but uptake in the collecting system (which holds urine full of excreted FDG) may be quite high. Renal metastases (a possibility with melanoma) may be confused with uptake in the collecting system. If the study can be done with intravenous contrast, renal metastases (or primary renal tumors) may be easier to detect.

In general, bladder metastases are impossible to detect on PET. A round lesion may be visible on CT, particularly if intravenous contrast has been administered, but any uptake will be drowned out by the intense, contiguous uptake of the urine in the bladder. Tumors contacting the bladder may occasionally be seen as a cold spot, but the PET is of no use in finding metastases to the bladder.

Brown fat is sometimes seen if the patient has been cold before the scan, particularly in younger patients and women [4]. This is one area where fused images are most useful as the intense uptake in the fat can be localized to the fat rather than a node (Figs. 5.12 and 5.13); of course, the neck is also a commonplace for nodes to be found [2].

Too Small to Characterize

PET is not reliable for *characterizing* lesions below about 1 cm (Fig. 5.14). Due to the relatively high distance gamma photons travel within the crystals that detect them, spatial resolution for nuclear modalities is relatively poor and partial volume effects (where the uptake from a single voxel affects neighboring voxels) are prominent. Uptake in a single imaging voxel will also increase uptake in neighboring voxels, and a very intense lesion will appear larger than a less intense lesion of the same size on the PET. This is where the CT becomes useful, as the actual size of the lesion can often be determined from the CT. In addition, if a lesion is small enough, it may not accumulate enough tracer to be visible above background (which is usually nonzero) (this has been a problem in the use of SUVmax to characterize tumors as benign or malignant, as maximum voxel intensity will be affected by size up to a size of about 3 cm) [13].

However, it has been known to *detect* lesions below 1 cm (Fig. 5.15). The reason for this conundrum is that small metastases from very avid tumors (and melanoma is one such tumor) can successfully take up enough tracer to be significantly avid above background. A 4 mm, strongly avid, spherical lung nodule or axillary node is quite concerning for metastasis, particularly if multiple. This is particularly useful in low-background organs such as lung and fat

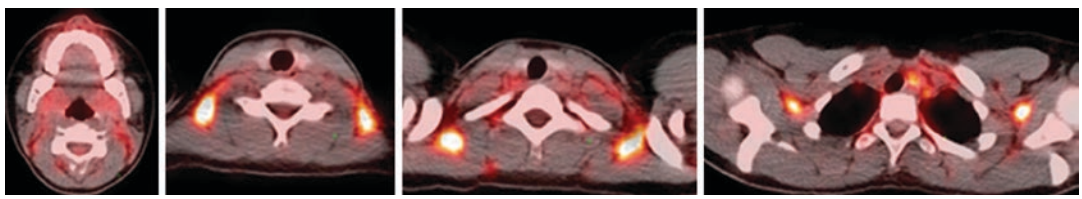

Fig. 5.12 Brown fat in standard locations—posterior neck fat and (less often) posterior mediastinal uptake

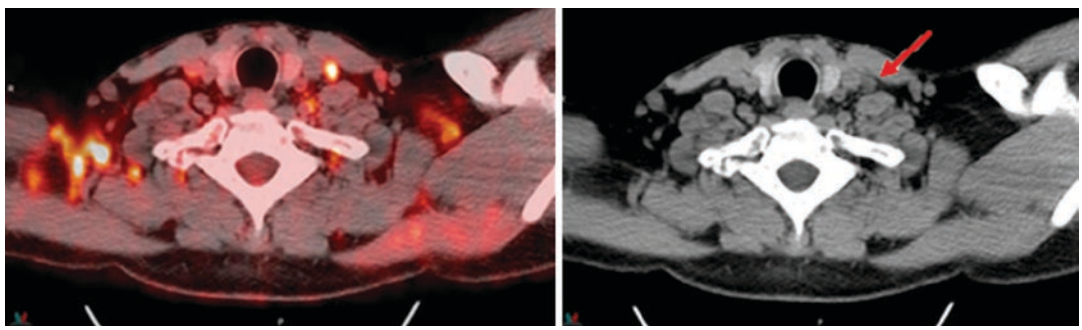

Fig. 5.13 Numerous foci of uptake localize to fat and likely represent brown fat. A single focus of uptake adjacent to the carotid on the left may represent an actual metastatic node

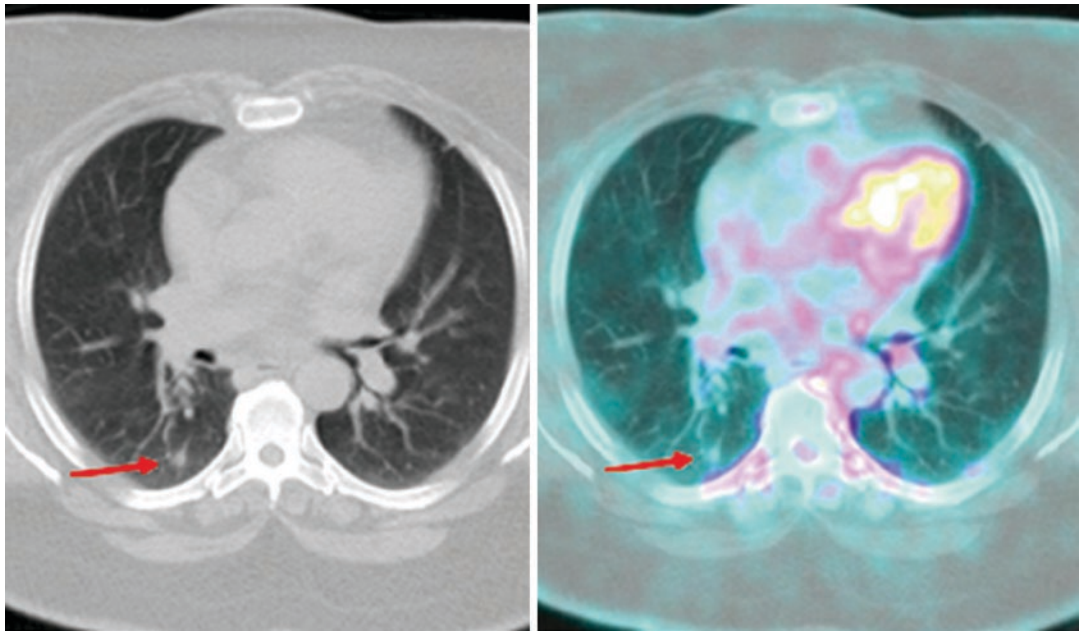

Fig. 5.14 Pulmonary nodules under about 1 cm (arrow) may be too small to characterize. As benign pulmonary nodules are common, they can usually be followed by CT as per Fleischner Society guidelines

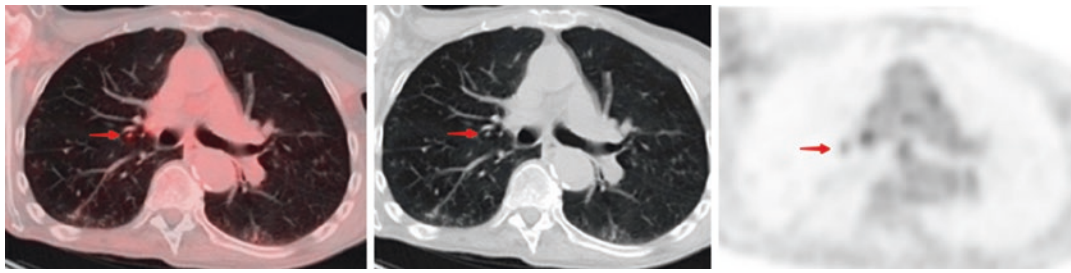

Fig. 5.15 Nodules as small as 2 mm may show visible uptake if intense enough, as in the case of this right perihilar nodule. While the negative predictive value at this size is poor, if there is reasonable suspicion for metastasis, the finding is at least concerning

(which nodes are usually surrounded by). Nonetheless, sensitivity decreases with smaller lesions, and in high-background areas such as the brain, a lesion must be a few centimeters in size to be visible at all on PET.

Too Superficial to Detect

A problem with superficial lesions is that, being spread out in two dimensions, they do not accumulate all their uptake in a single three-dimensional voxel the way a round metastasis does and hence have lower measured uptake. The attenuation correction algorithm also decreases counts from skin lesions (which being on the surface are not attenuated), and so at least a cursory look at non-attenuation-corrected (or NAC) images is in order. Usually superficial lesions are easy to detect, being right on the skin on the MIP. As non-malignant infections of the skin or minor injuries are avid and common, usually calling attention to the location and recommending correlation with physical examination is sufficient.

Involuntary (Breathing) and Voluntary Patient Motion

Patient motion has a number of problems. First of all, as the moving part of the body may occupy multiple positions in space during the imaging time, uptake will be decreased and "smeared" out over the multiple locations. This can decrease sensitivity and be quite confusing. Alternatively, the patient may be still during both PET and CT but move between the scans, causing the body part to be in different positions in the two different scans. In this case, the CT and PET should be viewed separately in the area of concern, and NAC images consulted as attenuation correction is often affected. Second, because modern attenuation correction algorithms use CT images to calculate attenuation, a part of the body may appear too hot or too cold on PET, possibly leading to either false negatives or false positives. NAC images may again be of use here. Third, there is the problem of misregistration. If fused images are used, the area of uptake may appear to be in a different location than it actually is.

This is most prominent with breathing. The diaphragm moves up and down during breathing and separates the lung from the liver on the right, both of which are common sites of metastasis. An added complication is that CT images take only a few seconds, whereas a PET bed position takes several minutes. The patient can hold their breath for CT, but not for PET; thus to have the two areas registered well requires the CT to be performed using shallow breathing, which is a change from usual CT protocol, where the images are acquired in deep inspiration to maximize lung expansion. Should the patient take a deep breath (if instructed by a technologist who usually does only CT) or breathe out of anxiety during CT acquisition, liver lesions may be projected over lung or vice versa. Usually lung lesions have a clear CT correlate, but liver lesions (particularly in a nonenhanced scan) may be difficult to confirm. In this case, the CT and PET should be viewed separately; lesions can often be seen to be clearly in the lung or in the liver on PET (Fig. 5.16). In addition, NAC images may be useful if attenuation correction is affected.

Physiologic bowel motion can often be problematic as well, placing bowel metastases in the mesentery or vice versa (Fig. 5.17), although this is difficult to prevent. (Some centers give glucagon before scans.) While looking at CT and PET image separately may still be of use, normal variation in physiologic bowel uptake decreases the utility of this somewhat. The CT images should be carefully inspected for presence of mesenteric nodules or nodules adjacent to or in bowel, but the relative low prominence of bowel metastases on CT (particularly without intravenous contrast) can lower the utility of this as well. If it affects management, a separate contrast-enhanced CT of the abdomen and pelvis may be necessary.

Finally, a patient may move their extremities. Given the relative lack of importance of extremity metastases (usually important only if the primary was an extremity lesion as by the time extremity metastases are present the trunk is usually affected), this may be less of an issue. However, if solitary metastases are suspected and will change management if present, the patient can be referred for physical examination, radiography, or MRI, depending on the precise location.

Adjacent to Nearby Uptake (Within the Surgical Bed)

Local metastases within the surgical bed may be confusing as they can be hard to distinguish from postsurgical changes. Careful reading of the history can be useful. If enough time has elapsed, an operative note may be available. However, in cases where scarring is genuinely difficult to distinguish from local recurrence, only reimaging in a few weeks may be useful.

Low-Grade Tumors

This is usually only a problem with sarcoma—melanoma is usually intensely FDG-avid and can be seen even at relatively small sizes. Low-grade tumors are usually better-differentiated and have less affinity for glucose and, as a result,

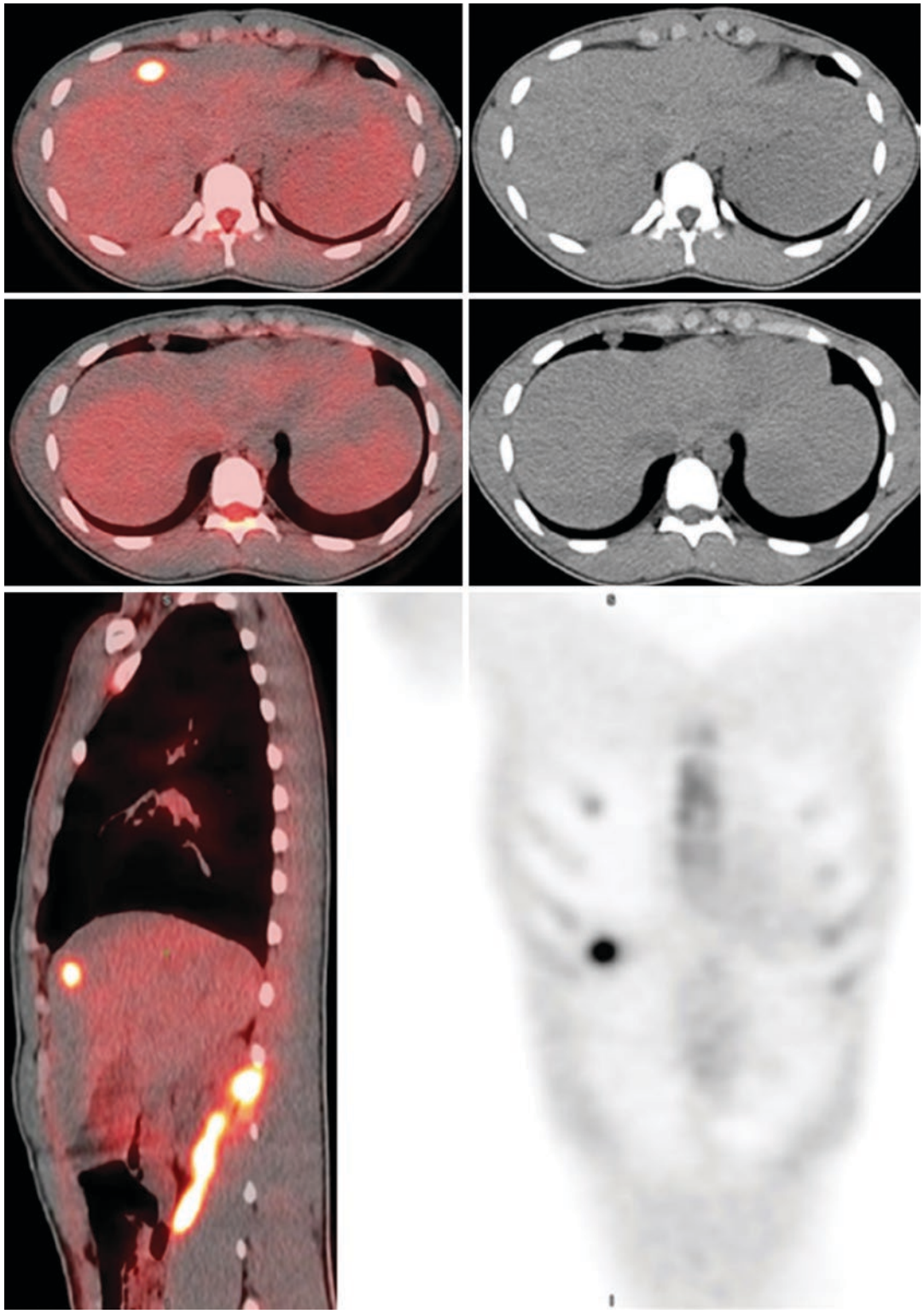

Fig. 5.16 At first glance, it would appear there is a liver metastasis and a non-avid lung metastasis, but cross-correlation with sagittal and coronal images makes clear there is in fact a single avid lung metastasis. Contrast-enhanced CT and/or MR of the liver might still be indicated

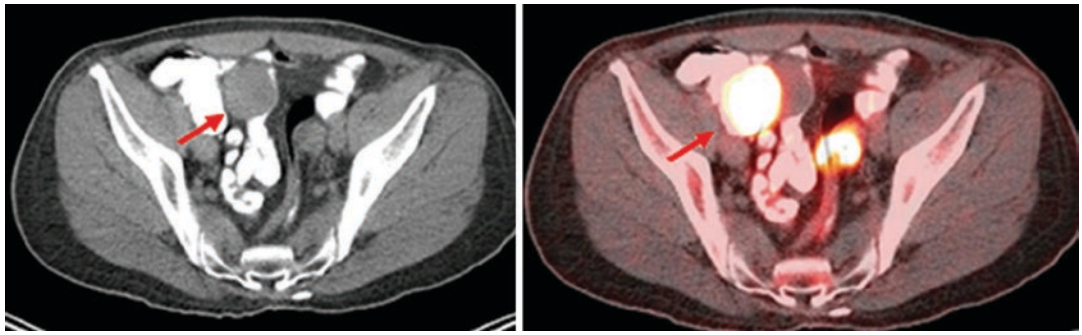

Fig. 5.17 While the metastases are localizable to the bowel, the CT and PET are clearly in different locations in front (arrow)

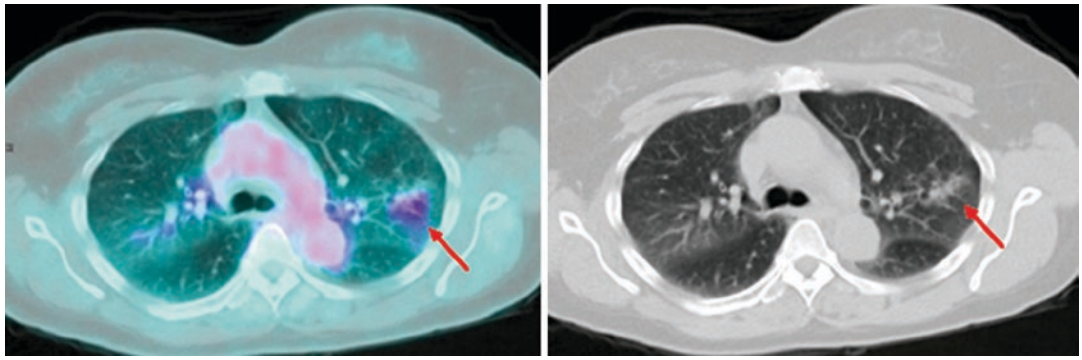

Fig. 5.18 Adenocarcinoma of the lung (arrows), well-known as an example of a malignancy often not (very) avid on PET

may take up relatively little FDG, decreasing the sensitivity of the test for metastatic disease. A variety of incidentally found tumors may have low FDG uptake, including renal, prostate, low-grade lymphoma, carcinoid or neuroendocrine, adenocarcinoma of the lung (Fig. 5.18), lobular carcinoma of the breast, and mucinous tumors of any organ [2].

Pitfalls

Unusual Metastasis Sites (but Not in Melanoma)

Melanoma is notorious for sending metastases to sites other tumors do not. While these are in many cases not particularly difficult to see if one is looking for them, sites that are usually benign in other tumors may not be so in melanoma.

Melanoma may send metastases to the viscera. While the liver and adrenal glands are common sites for metastases from various other tumors, other organs may become targets such as the spleen, pancreas, kidneys, heart, or even less common sites such as the gallbladder. In general, it is sufficient to simply remember to look closely at these organs as well. In some cases, such as the pancreas, it is not clear if there is a metastasis to a node near the organ or the organ itself. In many cases this is not important as systemic disease is present, but if it is crucial in any particular case, a contrast-enhanced CT (or MRI) can be used as follow-up.

A word on bowel metastases is warranted. The bowel moves involuntarily due to peristalsis, has

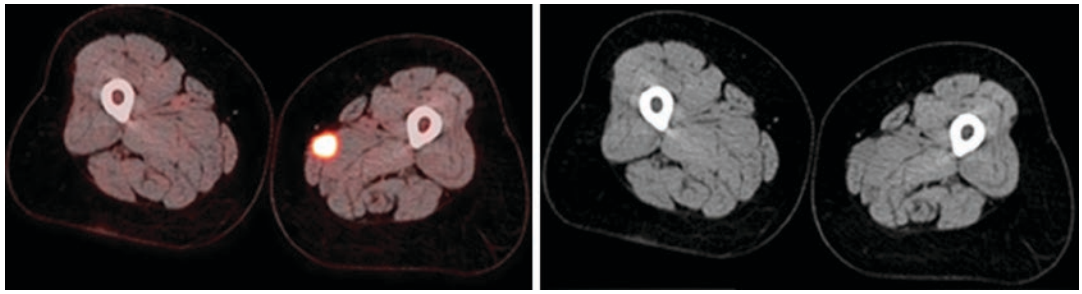

Fig. 5.19 Metastasis to thigh muscle from melanoma. The metastasis may be difficult to see on CT, which is where the typical high avidity of melanoma becomes useful

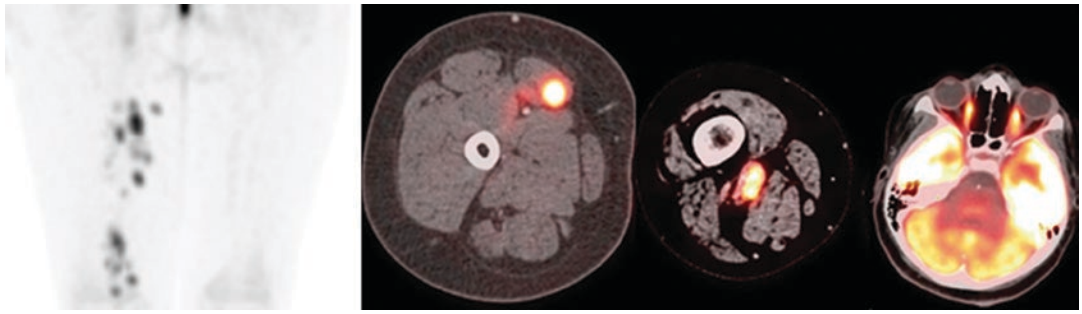

Fig. 5.20 This rhabdomyosarcoma sends multiple metastases to thigh muscles (and nodes). There is even a distant metastasis to a rectus muscle in the left orbit

variable uptake physiologically, and is prone to developing its own primary tumors which are FDG-avid. For this reason the bowel can be a very confusing site. For this reason careful attention to the bowel is warranted. Again, a contrast-enhanced CT may be useful. As described below, focal areas of uptake that appear roughly spherical in contour should be investigated by colonoscopy.

Muscle is a site of metastasis that is relatively specific to melanoma (Fig. 5.19). As such the muscles, including in the extremities, should be examined, particularly if the primary tumor is in the extremity itself. (A sarcoma may also spread locally from the extremities—Fig. 5.20.) If there is high physiologic uptake due to muscle activity, as described above, the CT should be examined carefully for abnormal lesions. In patients who have taken insulin or eaten shortly before the scan, there may be diffuse muscle uptake; this is why one should carefully interview patients and reschedule (if possible) if these things have occurred [2].

Cutaneous metastases are not unheard of, particularly with melanoma. As described previously, a careful look at the skin, particularly using MIP images and NAC images, should help to detect any lesions large enough to be visible on PET [4]. Physical examination correlation is advised as these lesions are usually fairly obvious.

Sites at Border of Image Field

Due to technical factors (fewer detectors are involved), noise rises as one approaches the border of the image field, and the last and first images are usually quite noisy. This can produce either false negatives or false positives. If a suspicious area is caught before the patient leaves, the area can be reimaged, this time in the center of the field of view. Additionally, it is important to pay close attention to protocolling in this situation; a skull base to mid-thigh protocol is particularly inappropriate for a scalp lesion (and some

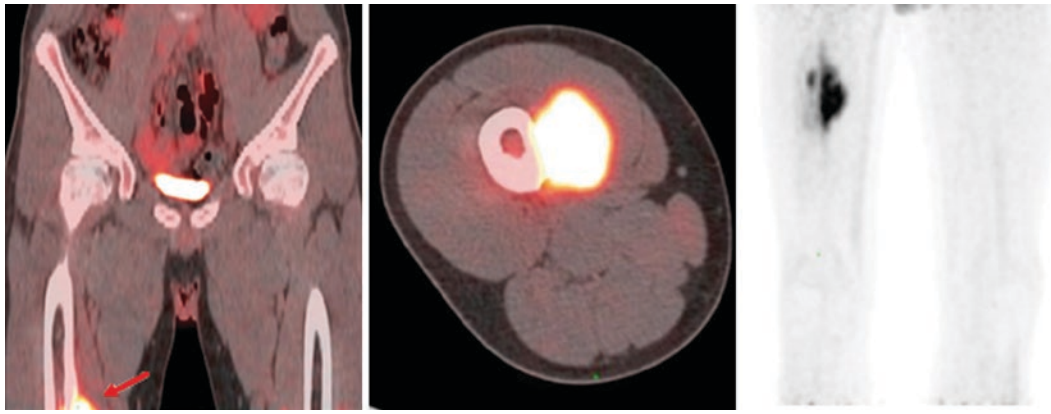

Fig. 5.21 This patient had a thigh sarcoma (arrow) that was nearly missed due to using a standard skull-base-to-mid-thigh protocol. The patient was brought back and the proximal lower extremities scanned to properly visualize the lesion itself

additional "air space" can be included even with a vertex to toe image) or thigh lesion (Fig. 5.21).

Obscured by Intense Nearby Uptake

In addition to high background uptake obscuring metastases to the brain itself, the high physiologic brain uptake obscures uptake in nearby areas such as the skull base due to partial volume effects. While difficult to work around, a careful look at the CT, particularly in often-missed areas of metastasis such as the clivus, can be of great use.

Uptake in the heart is quite variable, to the point where myocardial metastases, though described in many series, are difficult to detect by PET. In addition to the difficulty discovering metastases to the myocardium, uptake in cardiophrenic nodes may be obscured. Occasionally a nearby pulmonary metastasis may be missed as well; however, it is usually detectable on CT.

Uptake in the blood pool is not exceptionally high. However, a common problem is that retroperitoneal nodes (particularly in the aortocaval region) may be projected over the blood pool and mild uptake in retroperitoneal nodes may be difficult to distinguish from blood pool. Since it is only mild uptake that presents this problem (intense uptake in a retroperitoneal node will clearly be seen), an admonition to pay attention on follow-up exams may be sufficient. Alternatively, mild uptake in the retroperitoneal nodes may be confused with blood pool. In this case it is usually sufficient to be vigilant for enlarged nodes in this region. Viewing the CT and PET separately may be useful here.

Intense uptake in the bowel may be confused with mesenteric nodes (or vice versa), as described above. Another problem is that diffuse intense bowel uptake (Fig. 5.22), most commonly with use of metformin, a common oral hypoglycemic, may obscure the presence of nearby intense mesenteric nodes or omental metastases, producing a false negative. In this case, with intense bowel uptake, it is important to look carefully at the CT to see if there are any extra nodules within the abdominopelvic cavity. (One should also ensure the patient is actually *on* metformin, of course; if not the possibility of bowel inflammation should be investigated.)

New reconstruction algorithms have removed the prior problems with low-intensity areas surrounding the very intense bladder and obscuring nodes. Looking carefully for pelvic nodes nearby on CT can help deal with the problem of pelvic nodes becoming inconspicuous due to the proximity of the bladder. If these problems are still noted, repeating the reconstruction without scatter correction may be of use.

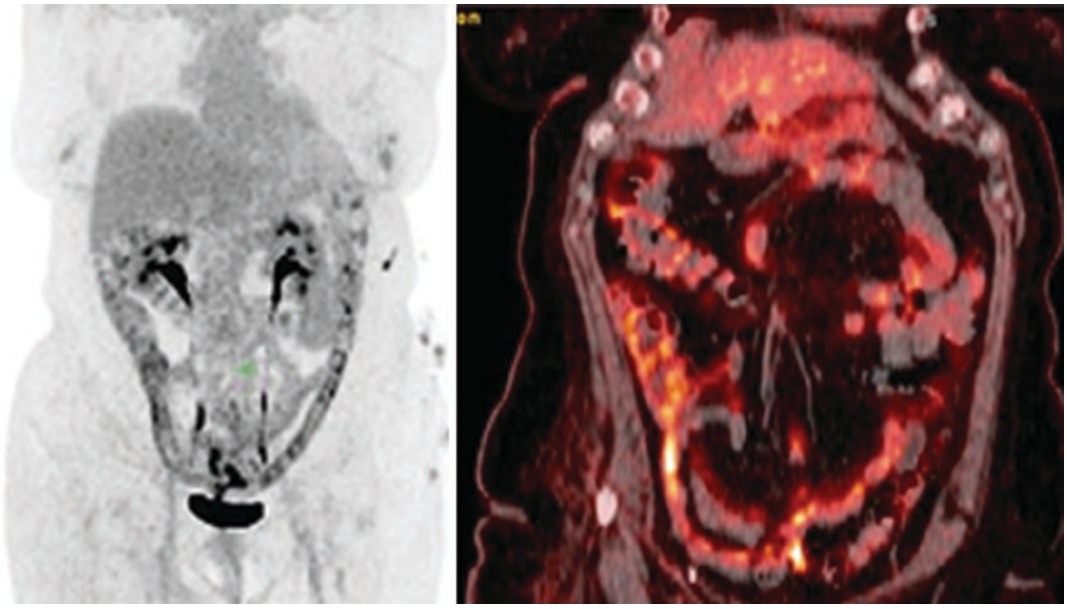

Fig. 5.22 Diffuse bowel uptake is seen with metformin use. The CT appears normal. It should be verified that the patient is actually on metformin

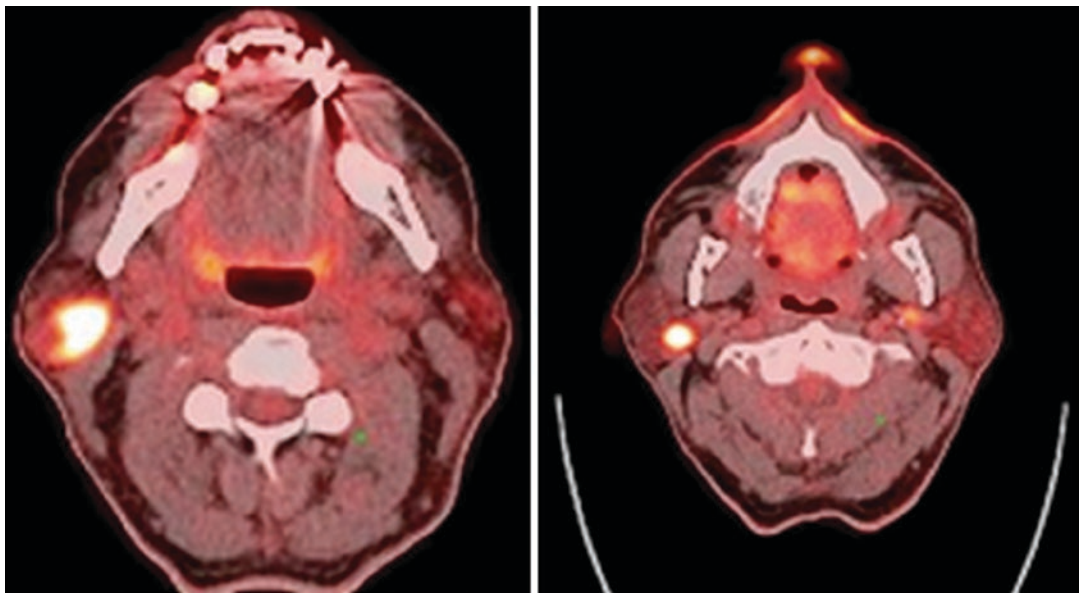

Fig. 5.23 Intense uptake from Warthin's tumors in the parotid gland

Incidental Findings on PET

A variety of areas of focal uptake can be noted on PET. In addition to metastases, some of these may be physiologic or even represent other primary tumors. In most cases these are usually benign but malignant frequently enough to require tissue diagnosis or other investigation.

Focal uptake in the parotid (Fig. 5.23) is seen in about 0.4% of cases and is malignant in about

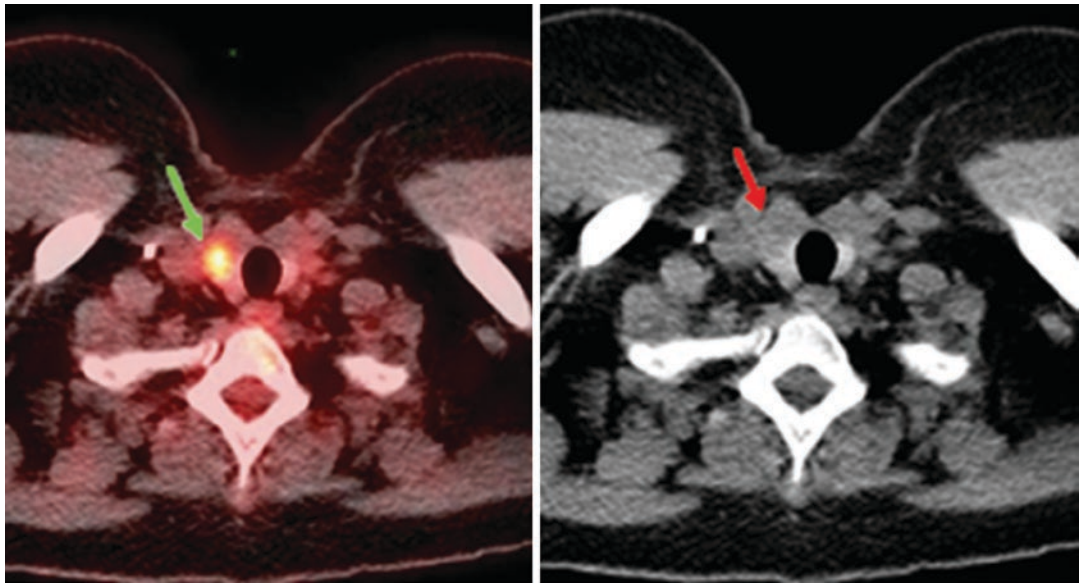

Fig. 5.24 Intensely avid thyroid nodule (arrow), corresponding to hypodense thyroid lesion. Metastases to thyroid exist, but primary nodules are much more common. Some are malignant

10% of those [14]. As such, it is more likely to represent a benign parotid tumor (Warthin's tumor is particularly notorious for being avid) than anything else. However, as some benign parotid tumors can become malignant, it is wise to at least refer these for further workup.

Focal uptake in the thyroid has been extensively studied and is the subject of three meta-analyses at the time of writing [15–17]. In summary, focal hot spots (Fig. 5.24) appear in about 2% of PETs [16], about 20–36% of incidentally discovered avid focal thyroid nodules are malignant [15–17], and only 1% of lesions are distant metastases [15]. As with many other tumors, while malignant lesions tend to have a higher SUVmax, there is enough overlap to prevent this from being useful [17]. Given the reasonably high frequency of thyroid malignancy, further workup of these lesions is useful.

Focal uptake in the breast occurs in 0.4% of cases (0.8% of women), but is malignant in 37–48% of these [18, 19], most commonly infiltrating ductal carcinoma. As such a mammogram and/or ultrasound should be obtained if focal uptake is visible.

Focal uptake in the colon is particularly concerning because even benign lesions (colonic adenomas) are often premalignant. Focal areas of colorectal uptake (Fig. 5.25) are seen in about 3.5% of cases, with 68% being premalignant or malignant, and SUVs not differing enough to tell apart benign, premalignant, or malignant lesions [20]. If it will affect clinical management, the patient should receive a colonoscopy to exclude a second malignancy; in the case of surveillance, the colon cancer may be more dangerous than the risk of recurrence from melanoma! However, in the case of patients with many other metastases, the presence of either a colonic metastasis or a second colon cancer may not make enough of a difference to justify an additional invasive procedure; our usual practice is thus to recommend colonoscopy "if clinically indicated." One should also look at the area on CT; if there is soft tissue stranding in the fat, free air, and many diverticuli, the patient may have diverticulitis instead (Fig. 5.26)!

It is worth paying attention to the uterus and ovaries, but the menstrual status of the patient should be kept in mind. Focal uptake in the ovaries may be physiologic if the woman is of childbearing age, as many focal uptake in the uterus (Fig. 5.27), although this should follow the uterine contour—a focal nodal area in the uterus is

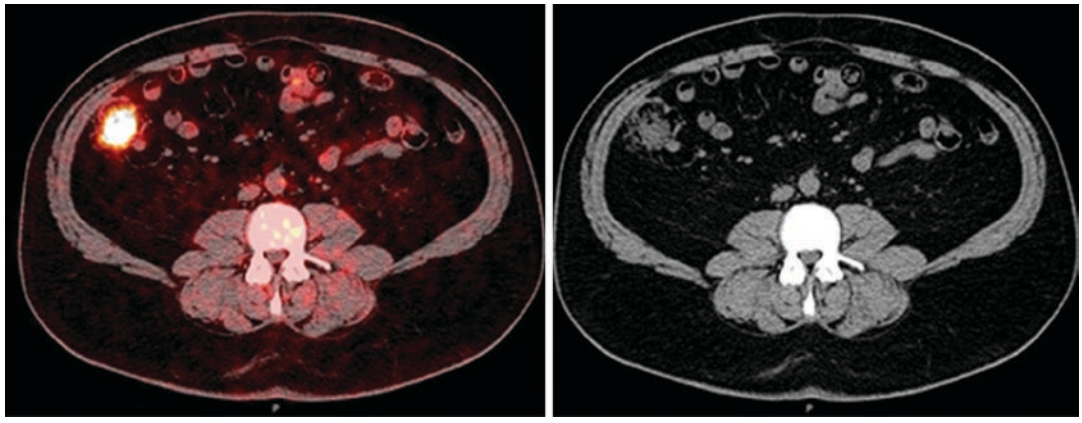

Fig. 5.25 Focal uptake in the colon may have a CT correlate or not, but either way if localized (rather than diffuse) should prompt a colonoscopy

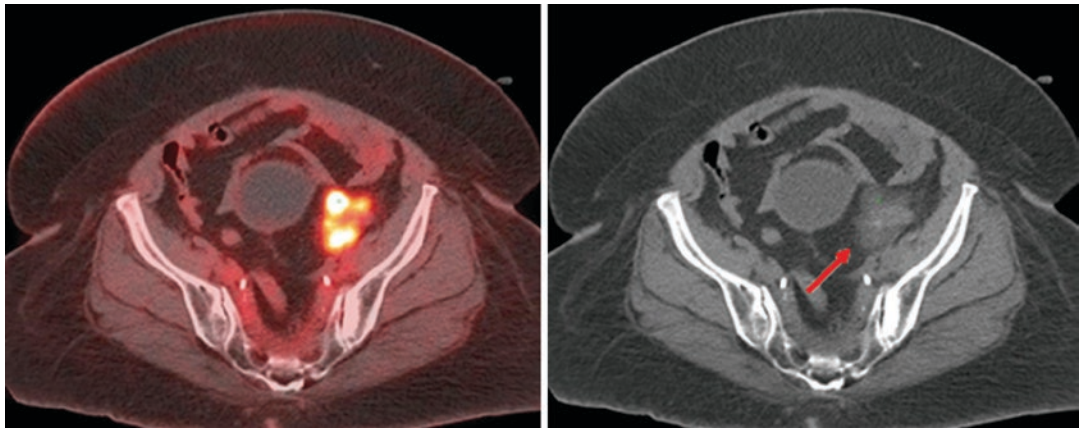

Fig. 5.26 Intense uptake corresponding to soft tissue stranding typical of diverticulitis. Unfortunately, this is often difficult to separate from metastasis

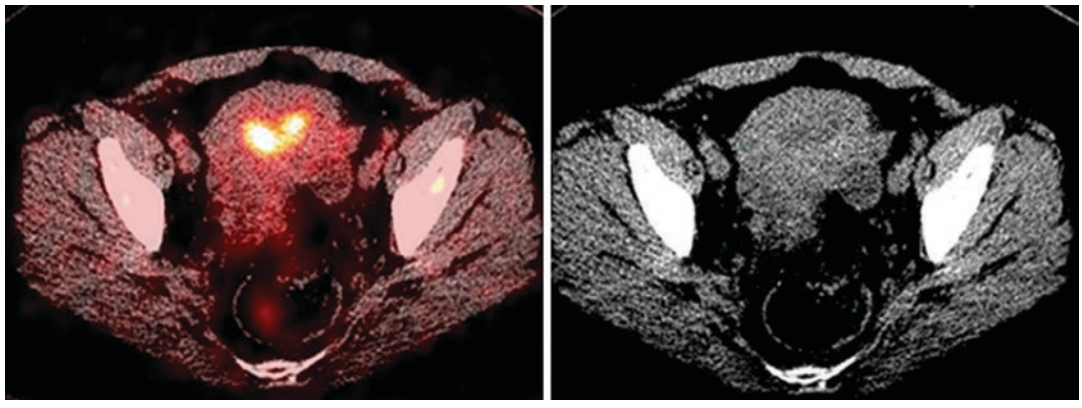

Fig. 5.27 Intense endometrial uptake reflects physiologically active endometrium in a woman of childbearing age. The uptake follows the contour of the endometrium on CT

suspicious. If the patient is not of childbearing age, or the lesion is otherwise suspicious on CT, an ultrasound is usually a good first step.

Prostate cancer is notorious for being non-FDG-avid, but this is not absolute. Very aggressive and unusual histopathologies of prostate cancer may be FDG-avid, and so incidental uptake does stand an increased chance of being malignant (Fig. 5.28). Incidental uptake is seen in the prostate in 2% of cases and is malignant in 17% of cases but 62% of those confirmed by biopsy [19]. As such further workup is wise and may begin with a PSA and digital rectal examination.

Naturally, an occult infection can also be responsible for focal FDG uptake. As such the CT should be examined to see if a clear explanation can be found; focally avid lung nodules in a typical peribronchial distribution may simply represent a lung infection (Fig. 5.29). If felt to be infectious, lung nodules may be followed up with CT alone; a PET is usually necessary as lesions visible on PET are usually visible on CT as well (the reverse is usually not true as many nodules may be too small to characterize).

Incidental Findings on CT

Incidental findings on CT are common; one study found them in 75% of cases [21]. Mercifully, most acute incidental findings on PET-CT, such as appendicitis, cholecystitis, and diverticulitis, are FDG-avid and have clear CT correlates. One that is cold on PET and must be dealt with immediately is the pneumothorax (Fig. 5.30); if not previously known, this should occasion a call to the clinician and on occasion a trip to the ED for the patient. In many cases it results from recent surgery and is known to the service, so a

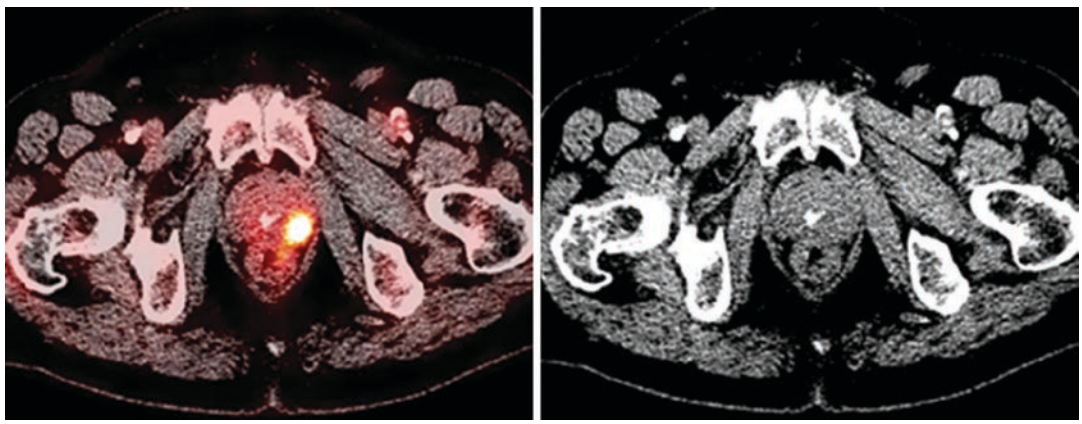

Fig. 5.28 Intense uptake in the prostate; these foci are malignant with a frequency high enough to justify workup. Often nothing is detectable on noncontrast CT

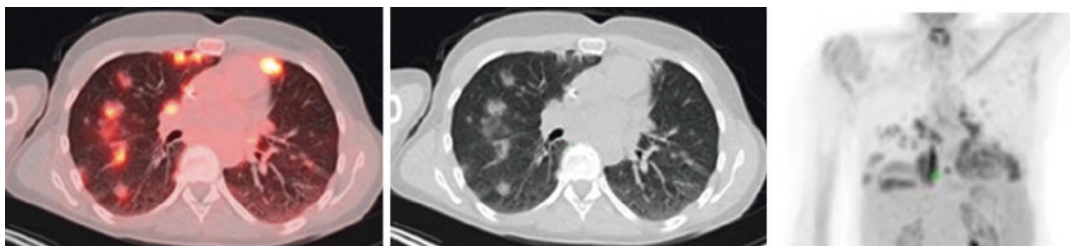

Fig. 5.29 Numerous metabolically active groundglass nodules. These do not have the solid appearance of lung metastases. While any one of these might be a primary lung carcinoma, the relatively diffuse, bilateral distribution is more consistent with infection

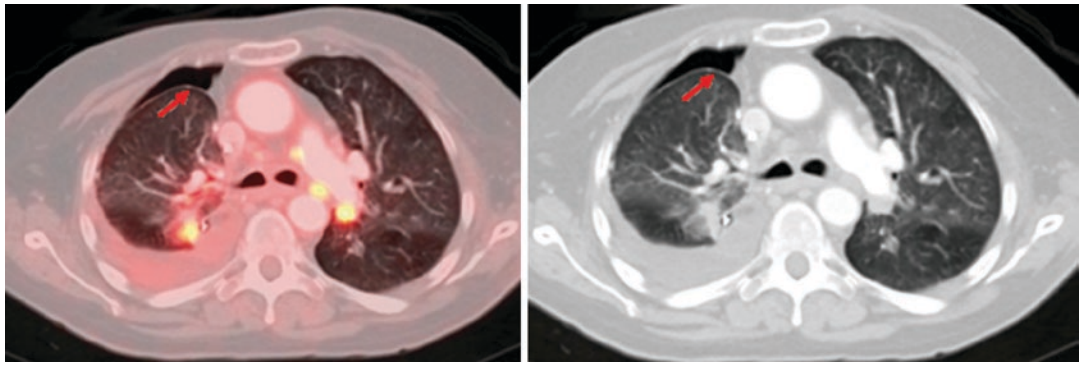

Fig. 5.30 Pneumothorax; note the area of absent lung markings located in the antidependent portion of the lung as air in the pleural space collects. This is slightly cold on PET as no FDG collects in the free air, but is better seen on CT (and all PET-CTs bear examination of the chest in the lung window to exclude this finding)

glance at the medical record is useful to avoid an embarrassing call.

Rarely, there may be an intracranial hemorrhage. While this can be difficult to see on PET, CT is fairly sensitive for this (particularly if acute), and hence examination of the head CT using brain windows is recommended to rule out this potentially lethal finding.

A variety of nonacute findings may be seen on CT, many non-avid on PET but nonetheless concerning or at least worthy of future follow-up. A lot of these are so frequent there are standardized protocols for handling them, which are updated every few years. The guidelines for handling lung nodules from the Fleischner Society were recently revised in 2017 [22] and are useful with incidentally discovered lung nodules.

The interpretation of abdominal lesions is its own, large field within medical imaging, but a few guidelines for incidental lesions may be given. Renal and liver cysts are usually visibly non-avid if large enough. If small enough, the usual guidelines for these lesions can be followed; generally, any lesion with CT attenuation under 20 Hounsfield units (HU) can be assumed to be a cyst. A renal (not hepatic) lesion with CT attenuation over 70 HU is assumed to be a hemorrhagic cyst and also benign. Adrenal nodules are similarly thought to be lipid-rich adenomas (and hence benign) with attenuation below 10 HU on a noncontrast examination; they are worrisome from the PET point of view with intensities greater than liver [23]. (Avid liver lesions are concerning given the frequency of metastasis to liver, and avid renal lesions are usually concerning as well given the high background uptake in the kidney.) Visceral lesions not meeting these criteria are not necessary malignant, but should be further worked up with a contrast-enhanced CT or MRI.

Apart from possible malignancies, one potentially dangerous finding that can be seen on abdominopelvic CT is an abdominal aortic aneurysm (Fig. 5.31). These are more common in patients with atherosclerosis; the diameter of the abdominal aorta should be no more than 3 cm. If higher, it is aneurysmal and should be followed at the very least; if over 5 cm surgery may be required.

A number of more minor incidental findings within the abdomen and pelvis are quite common. Kidney stones and gallstones may be seen and are usually nonemergent findings but bear mentioning. Diverticulosis without evidence of diverticulitis is quite common as well; one should mention it at least as a note to future clinicians. Avid areas within or near a colonic diverticulum may represent diverticulitis, and calling attention to this is useful for clinicians.

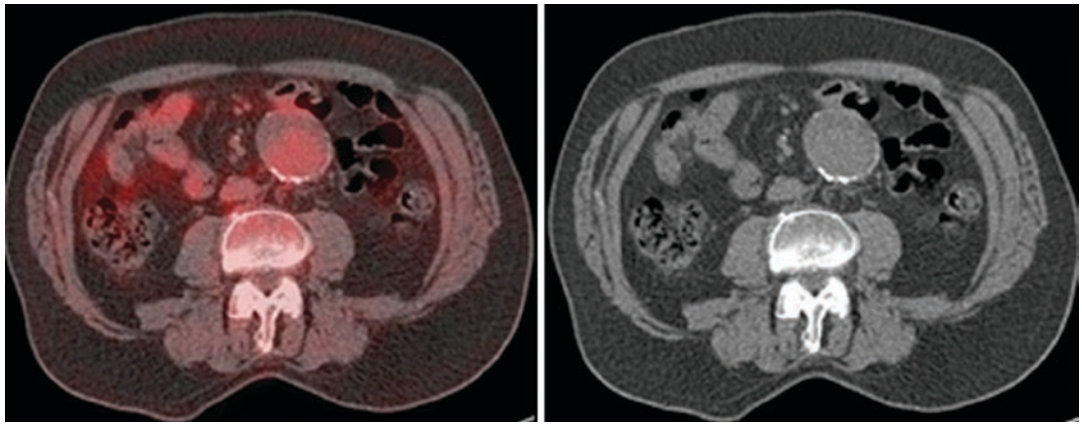

Fig. 5.31 Abdominal aortic aneurysm, viewed as a large abdominal aorta. This should be noted if seen

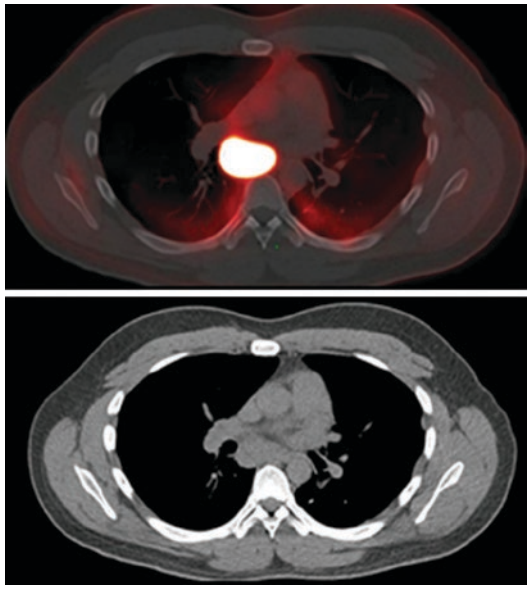

Fig. 5.32 This extremely hot node (SUVmax 55) appears to extend into the adjacent vertebral body on fused images, but is seen not to do so on unfused CT

Technical Artifacts (May Be False Positive or False Negative)

Volume Averaging Artifact

Very intense tumors will often appear larger on PET than on CT due to scatter and the relatively poor spatial resolution of the modality (Fig. 5.32), leading to the observation that assessing tumor size on PET is usually inaccurate. It is also well-known that calculations of SUVmax on tumors below about 3 cm are affected by the size of the tumor [13].

Attenuation Correction and Artifacts: Misregistration, Motion, Breathing

In most modern PET scanners, a CT scan is used for attenuation correction. While this is usually technically adequate, and allows the acquisition of a concurrent CT scan as well, in some cases (usually due to some variety of patient motion), attenuation correction artifacts can result. Even physiologic bowel motion can produce artifacts (Fig. 5.33), but musculoskeletal motion is more commonly the issue. Patients are advised to maintain shallow respiration (rather than taking a deep breath as with a conventional CT) and to hold still during the scan, but not everyone is able to comply, and even relatively mild motion during the scan can produce artifacts (Figs. 5.34 and 5.35). Even respiration can produce its own set of artifacts (Fig. 5.36), with lesions occasionally being projected from the liver into the lung (Fig. 5.37) or vice versa.

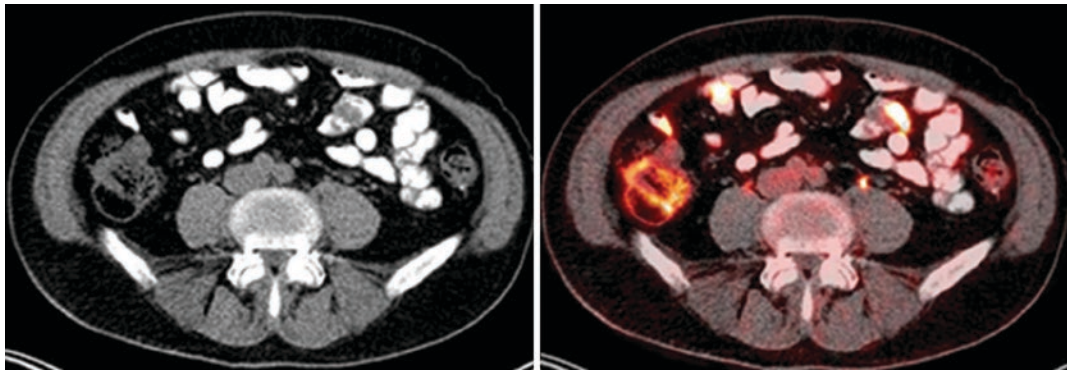

Fig. 5.33 Mass lesion in the bowel is imperfectly registered between PET and CT

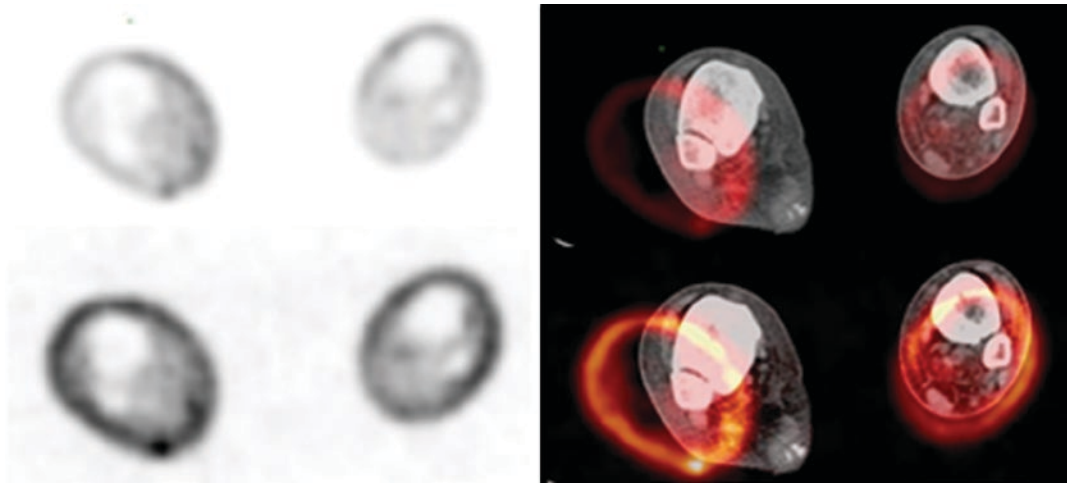

Fig. 5.34 AC (top row) and NAC (bottom row) PET and fused images. The (apparent) increased uptake in the medial right ankle is in fact an artifact of the lateral right ankle being projected over the air, with "corrected" attenuation being falsely low. NAC images show this is not the case and, in fact, if anything the lateral ankle is more intense

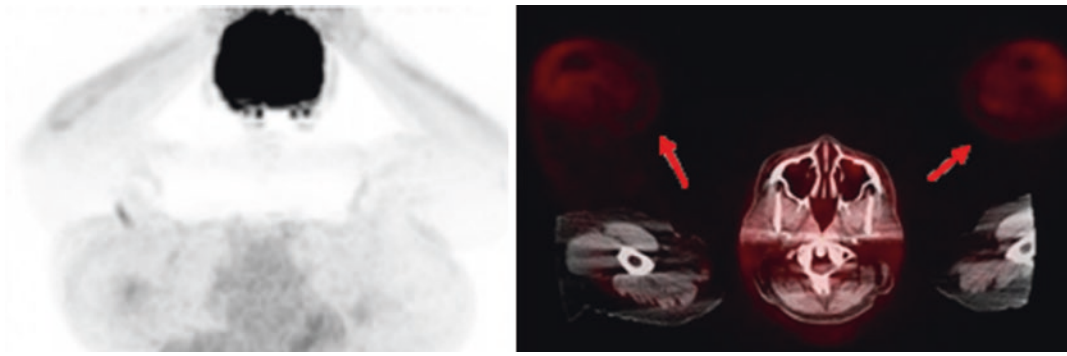

Fig. 5.35 The patient moved her arms downward during PET acquisition. Note the absent uptake in the neck region on MIP and the "gray" appearance of the proximal arms indicating no uptake, as well as the orange "ghosts" (arrows) anteriorly reflecting PET images registered to the empty air. This produces falsely low values for the PET as the PET scanner is attenuated but the CT does not reflect this. The PET scan was repeated in this area

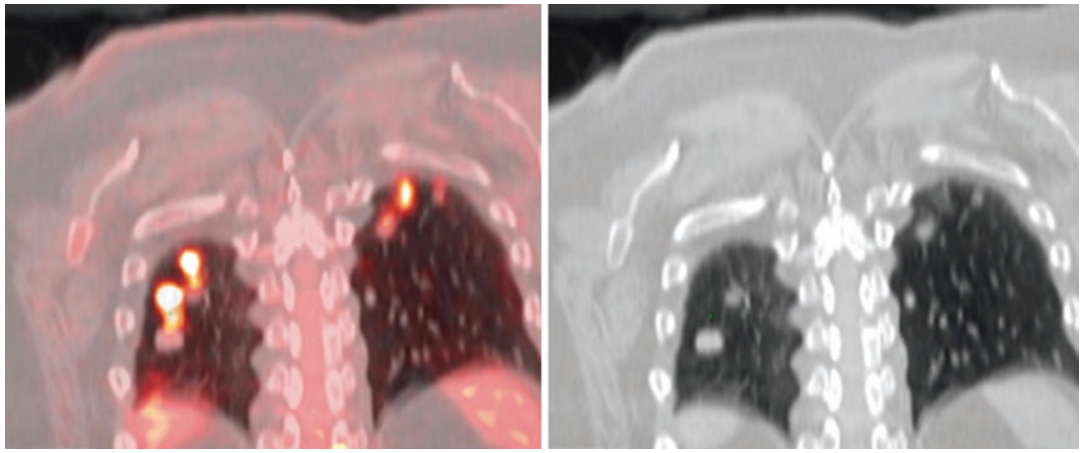

Fig. 5.36 Lung metastases from a clear cell sarcoma on PET are significantly displaced from their locations on CT

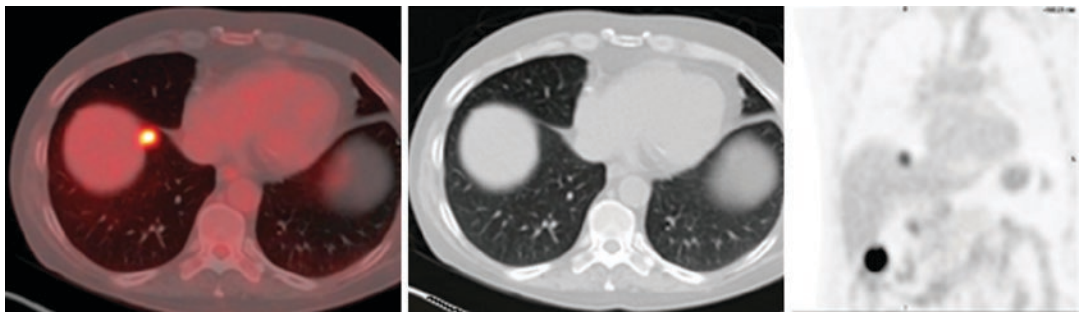

Fig. 5.37 Lesion apparently in the lung but not seen on CT is seen on coronal PET-only images to be localized in the liver

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