Imaging Findings in Melanoma

99

Roxani D. Efthymiadou

Cutaneous melanoma is the most serious type of skin cancer. Its incidence has increased rapidly during the past few decades probably due to the increased ultraviolet radiation exposure but also to the earlier and more accurate diagnosis. Melanoma is an aggressive disease which may spread almost to any organ of the body. It has been well established that early detection and accurate staging are of critical value for the appropriate treatment and patient's prognosis. Unfortunately, in many cases the lesions are detected late. The most common metastatic sides are the lungs, the liver, and central nervous system (CNS) [1].

The role of imaging modalities in staging of melanoma is extremely important. Imaging studies include plain radiographs, ultrasound (US), computed tomography (CT), magnetic tomography, lymphoscintigraphy, bone scan, and PET-CT.

The role of plain chest radiograph (CXR) is controversial. In daily practice CXR is mainly obtained for follow-up of cases of nonmetastatic melanoma. Although it is an inexpensive method with low radiation exposure, it is not recommended for patients with metastatic lung disease because of the low sensitivity of this procedure [2]. The low sensitivity is related with the usually very small size of the pulmonary metastases. Furthermore, many studies found no positive results among patients with asymptomatic localized disease who underwent CXR. In these patients, CXR proved to be not a cost-effective examination. On the other side, investigators support that CXR should be used as a widely available, low-cost and noninvasive imaging procedure. As a general rule, routine CXR is not recommended in asymptomatic patients with node-negative melanoma.

Current NCCN (National Comprehensive Cancer Network) guidelines recommend the use of regional nodal ultrasound in certain clinical settings, including physical examination with equivocal lymph node findings. Regional nodal ultrasound has shown to be superior to palpation alone for assessment of regional lymph node metastasis and surveillance of the regional nodes.

CT is the method of choice for staging of patients with melanoma, especially in TNM stage III or in recurrence of the disease [3]. The role of the procedure in the evaluation of asymptomatic patients with stage I or II remains controversial because of the high incidence of false-positive findings and the low detection rate.

The new-generation multidetector scanners provide detailed high-quality images with less artifacts in a really very short time. CT scans are performed pre- and post-intravenous contrast administration, during the arterial and the portal venous phase. Metastases of melanoma are usually hyperdense, so they are well detected in

R. D. Efthymiadou
CT, MRI and PET-CT Department, Hygeia Hospital, Nea Ionia, Attiki, Greece
e-mail: r.efthimiadi@hygeia.gr

A. D. Gouliamos et al. (eds.), *Imaging in Clinical Oncology*, https://doi.org/10.1007/978-3-319-68873-2_99

precontrast images. Intravenous contrast medium should be avoided in allergic patients and also in cases with renal failure in order to protect the kidneys from further renal damage. CT must be also avoided in pregnants and if possible in young population, because of the radiation exposure. US and MRI could be alternative choices in such cases. According to large studies, CT demonstrated sensitivity 58–75% and specificity 70–76% [4].

CT of the chest is the main imaging method for evaluating lung metastases which are very common in melanoma but also for detecting pleural or pericardial effusion or lymphadenopathy at the mediastinum and the axillae. As large autopsy series demonstrated, chest involvement was found in 70% of patients with melanoma. Respiratory failure due to lung metastatic disease is the main cause of death from melanoma [3, 4]. Multidetector CT of the lungs may reveal very small pulmonary nodules which cannot be detected with any other imaging procedure. The lung foci vary in size; they usually are in the range of 1–2 cm, but they may also be very small, even less than 5 mm or very big, and even more than 5 cm (Fig. 99.1). Metastatic disease at the lungs may have the type of lymphangitic spread which also can be detected by CT even in early stages. The method is performed post-intravenous contrast administration mainly for evaluating enlarged lymph nodes at the mediastinum which usually accompany lung lesions. Occasionally, mediastinal lymphadenopathy is the initial imaging finding of the disease. A pericardial effusion may be present as melanoma metastasizes at the heart more often than any other tumor. Secondary deposits may be found not only to the pericardium but even to the myocardium, and sometimes they are big enough to be recognized at CT images [4].

CT of the chest may also reveal secondary deposits at the bones and the soft tissue as the muscles and the subcutaneous fat (Fig. 99.2). Melanoma metastasizes to the breast more frequently than any other cancer. The lesions appear as single or multiple, well-defined noncalcified soft tissue masses.

Melanoma may metastasize to any organ of the abdomen as the liver, the spleen, the kidneys, the adrenals, the pancreas, the gall bladder, and the gastrointestinal tract [1, 4]. Oral contrast administration is necessary for an adequate opacification of the bowel. Intravenous contrast medium administration is also necessary in order to separate lymph nodes from the vessels and to obtain a detailed evaluation of the parenchymatous organs. Multiphase CT of the abdomen is the procedure of choice for detecting metastases at the liver and the spleen. Hepatic and splenic metastases are related to the stage of the disease. In large autopsy series, secondary deposits at the

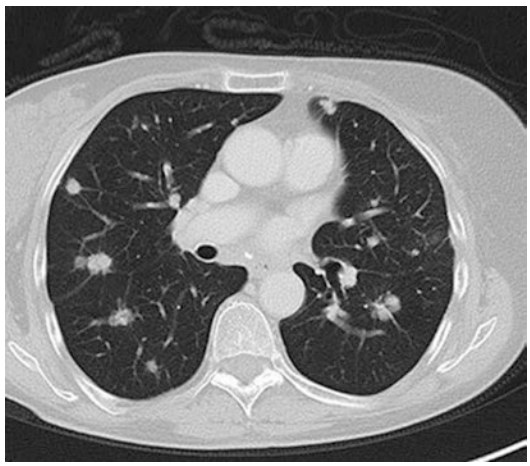

Fig. 99.1 CT of the chest: multiple ill-defined nodular lesions at both lungs in metastatic melanoma

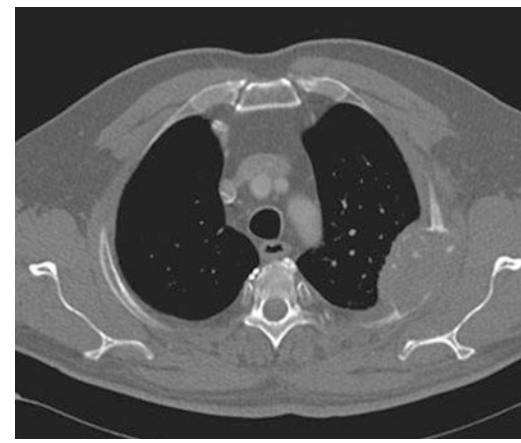

Fig. 99.2 CT of the chest: osteolytic metastasis from melanoma at the sixth left rib

liver were found in 58% of patients. As prereferred, oral and intravenous contrast administration are necessary for an adequate evaluation. Hepatic metastases may vary in size, shape, and density. They may be single or multiple, partly calcified, necrotic, or hemorrhagic, and they may enhance in a homogeneous, inhomogeneous, or ring-like pattern. Their size may vary from a few mm to more than 12 cm. The detailed anatomic study of the liver provided by CT and MRI is of critical importance for patients with metastatic disease who could benefit from surgery or ablation, in order to exclude any other unexpected foci of the disease [3].

Although splenic metastases are generally rare in patients with cancer, melanoma and ovarian carcinoma are the two most frequently spreading at the spleen neoplasms [4]. Splenic secondary deposits are found at almost 30% of patients with melanoma. Typically, they appear as single or multiple low-density lesions, usually solid, variable in size, better revealed in contrast-enhanced images. Rarely they take the form of cystic- or target-like lesions.

Gastrointestinal spread of melanoma is found in 4.4% of patients, may be present anywhere from the mouth to the anus but is most frequent in the small bowel. Imaging studies used to detect these metastases are CT of the abdomen and the pelvis, follow-through of the small bowel, and enteroclysis. Gastrointestinal spread may cause symptoms like pain, nausea, vomiting, etc. but may also be detected in the routine investigation in asymptomatic patients. The metastatic lesions on CT mimic primary or metastatic adenocarcinoma or even lymphoma. Ulcerating lesions can provoke complications as acute abdomen or seeding of the peritoneum. Metastases on the small bowel can be small or large, single or multiple. It is interesting that even patients with multiple secondary deposits may have no symptoms. Metastases to the large bowel are rare and occur as large and usually ulcerating tumors. Mesenteric spread appears as soft tissue mass at the mesentery or the omentum. Although rare, metastases of melanoma to the gall bladder are the most frequent metastases at this organ as they account for more than 50% of all secondary deposits at it [3, 4].

Secondary deposits may be observed at the kidneys and the adrenals mainly at cases with widespread metastatic disease. In autopsy series renal metastases were found in 35% of patients with melanoma. On CT scans, metastatic deposits appear as single or multiple, usually bilateral lesions, best revealed at post-contrast images. They may be solid with inhomogeneous density or cystic-like lesions with peripheral enhancement. In many studies, metastases in the perirenal and pararenal spaces were described [4].

Adrenal metastases were found in up to 50% of patients with melanoma in autopsy series. The secondary deposits may vary in size and appearance. They may be unilateral or bilateral, round or oblong with a maximum diameter in the range of 4–6 cm [4].

Nodal involvement is very common in melanoma. The evaluation of lymph node metastases revealed by CT is based on size criteria for every nodal group all over the body. Therefore, CT is insensitive for the detection of small metastases to the lymph nodes [3, 4]. On the other hand, the procedure may be complicated by false-positive findings as the enlarged lymph nodes detected by CT may not be metastatic: they may be reactive or inflammatory. In the evaluation of nodal involvement, other imaging modalities as lymphoscintigraphy and PET-CT may have the initial role.

Involvement of musculoskeletal system is common in metastatic melanoma. Secondary deposits may be found at the bones, the muscles, and the subcutaneous tissue all over the body. A lesion at the skin or the subcutaneous fat may be the initial sign of metastatic spread. Subcutaneous nodules surrounded by fat are a frequent finding in melanoma. They may represent a secondary deposit or even the primary tumor and can be easily detected on CT scans [1, 3]. The subcutaneous nodules can extend to the muscles or to the skin as an ulcerating lesion. Muscle metastases are relatively rare. Their typical appearance on CT is that of a hyperdense relative to muscle lesion. They may be single or multiple. Intravenous contrast medium administration permits a better definition of the tumor's borders.

Although rare, bone metastases may be the initial finding of spread of the disease. They have a poor prognosis with an average survival not more than a few months after their diagnosis. They are typically lytic and may be accompanied with soft tissue mass. Periosteal reaction is not common. Most metastatic bone lesions are found in the axial skeleton (almost 80% of them, according to a study, and specifically 35% in the ribs). CT scans may reveal bone metastatic lesions and the surrounding if existed soft tissue mass, all over the body, in the initial staging and the restaging of patients with melanoma [3]. The examination can be completed with three- dimensional (3D) reconstructed images, in order to provide the clinician more anatomic information. Bone scanning, MRI, and PET-CT are imaging procedures that may also be used in the evaluation of bone lesions.

Melanoma metastases at the CNS are very common. In fact, melanoma is the third after lung and breast cancer mostly metastasizing to the brain tumor. According to autopsy data, 49–73% of patients with widespread disease have cerebral metastases. Brain metastases carry a very grave prognosis, with a median survival of 4 months after the diagnosis and correspond to the second cause of death after lung involvement in patients with melanoma. On CT images brain metastases are detected as single or usually multiple lesions which may be hyperdense on noncontrast images and enhance homogenously or in a ring-like pattern after intravenous contrast administration. They can be infra- or supratentorial and in most cases are surrounded by edema. Cerebral lesions are more common than cerebellar. Rarely, CT images may demonstrate nodal subependymal lesions, meningeal spread, or even metastases at the choroid plexus. MRI permits a more sensitive and detailed evaluation of CNS in patients with melanoma [5].

US has not been widely used in staging of patients with melanoma. Its role may be complementary in selected cases. US can be performed in order to evaluate node beds that drain the primary site before sentinel node biopsy (SNL). This technique is based on the ability of the method to detect morphological changes in metastatic lymph nodes. Nodes with loss of the normal fatty appearance of their hilum can be selected for fine needle aspiration. Although US cannot replace SNL, it may be used in some cases to detect spread of the disease to the lymph nodes. The sensitivity of US for the detection of nodal metastasis is up to 82% with a positive predictive value of 52% [6]. High-frequency US is a useful imaging procedure for the evaluation of superficial nodes as the cervical or the inguinal nodes but not efficient enough for deeper nodes like the axillary, the iliac, and the mesenteric. US may be used as an alternative imaging method when CT the method of choice for staging melanoma in daily practice should be avoided like in young population, pregnants, and patients with renal failure or with allergy to iodinated contrast. In such cases US may be useful mainly for the evaluation of the abdomen and pelvis, the superficial nodes, and the soft tissue. Hepatic or splenic metastases typically appear as single or multiple, of various sizes, and hypoechoic lesions, which in sometimes may be heterogeneous due to hemorrhagic elements. US is useful to distinguish a cystic renal lesion from a solid one (more suspicious to be malignant) but also to detect possible secondary deposits to the gall bladder: focal mucosal thickening or polypoid lesions larger than 7 mm are suspicious to be malignant. Echocardiography is the imaging method of choice for detecting a pericardial effusion, quantifying its volume, and evaluating its hemodynamic effects. Although US is not the initial imaging procedure for staging melanoma, its role is under estimation. Further large studies are needed to confirm the cost-effectiveness of the method and to determine the specific patient population that can get profit.

The role of magnetic resonance imaging (MRI) in staging of melanoma is mainly complementary to CT, especially for the evaluation of the brain, the spinal canal, the musculoskeletal system, the anatomical structures of the head and neck, and the parenchymatous organs of the abdomen and the pelvis. The total accuracy of MRI for the detection of metastatic disease ranges from 77% to 79%.

MRI is more sensitive compared to the other imaging methods to identify secondary deposits

to the CNS [7]. Particularly, in patients with melanoma, MRI is more sensitive than CT in the evaluation of the brain and the spinal cord. Although CT is the initial imaging method in staging of melanoma, MRI of the CNS should be performed in patients with symptoms and normal CT scan or in cases of uncertain findings, where a further and more detailed evaluation is needed. Brain metastases of melanoma may have a wide range of appearances in MRI images. Metastases with the typical melanotic pattern demonstrate high signal intensity on T1-weighted images and low signal intensity on T2-weighted images, due to the contained melanin and blood products (Fig. 99.3). In the amelanotic pattern the metastases appear hypointense or isointense to the cortex on T1 images and hyperintense to isointense on T2 images. Except their typical melanotic and amelanotic patterns, brain secondary deposits may also have other types of appearances which mainly are related with the amount of the melanin and of the products of hemorrhage that they contain. Melanoma metastases may be extremely small, so that they can easily be mistaken for vessels or artifacts. As they are characterized by rapid growth, a close follow-up should be useful in order to detect them. Rarely, brain metastases may be miliary, located at the cortex or the subcortical white matter, or even they can be subependymal appearing as nodular periventricular areas with marked enhancement after intravenous contrast material administration. Although rare, meningeal involvement can be found in metastatic melanoma. The spread is more frequent in leptomeninges than in the dura, and it is better demonstrated in contrast-enhanced T1-weighted images. Metastases at the choroid plexus are uncommon, and they are usually observed in patients who have additional cerebral or meningeal metastases. They have variable signal intensity on T1 and T2 images and frequently demonstrate heterogeneous enhancement.

Except its obvious value in staging, MRI of the brain is also used for planning and monitoring Gamma Knife therapy in patients with metastatic melanoma.

MRI is the imaging method of choice for the evaluation of the spinal canal. Intramedullary or meningeal secondary deposits are uncommon and are related as the cerebral metastases with a grave prognosis. They are better recognized at T1 post-contrast images as enhanced lesions along the spinal cord or the cauda equina.

MRI is a useful procedure for a further investigation of focal lesions at the parenchymatous organs of the abdomen in order to differentiate

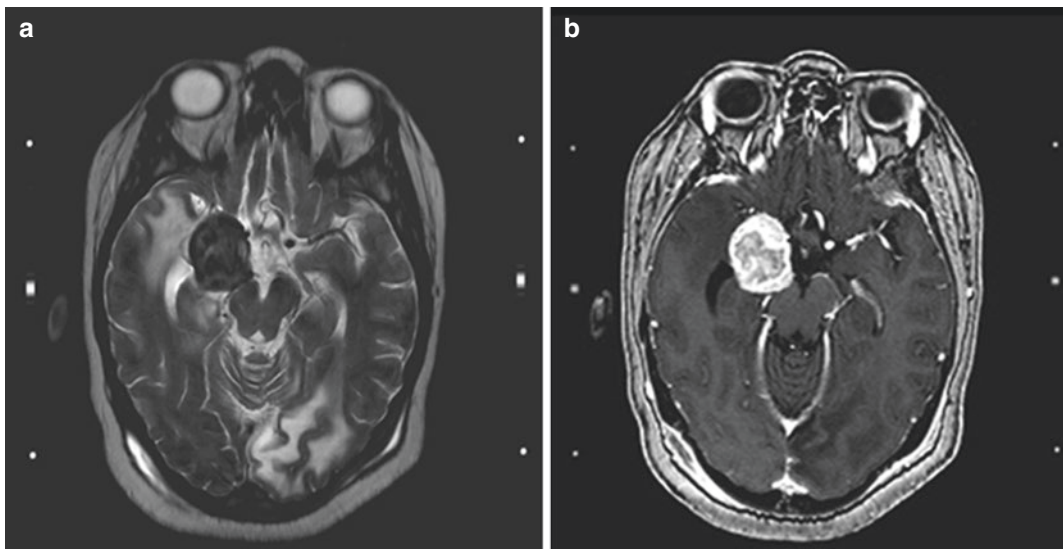

Fig. 99.3 MRI: melanotic pattern of brain metastasis in patient with melanoma on T2 (**a**) and T1p/c (**b**) images

benign from malignant entities. On MRI, hepatic metastases appear as areas with low signal intensity in T1 images and moderately high on T2 images, while hemangiomas typically have very high signal intensity (they are very bright) on T2 images and a characteristic pattern of enhancement on post-contrast T1 images (Fig. 99.4a, b).

MRI is an imaging modality with excellent results in the evaluation of bones and soft tissue. MRI may reveal signs of bone metastases much more earlier than CT as it has high sensitivity in evaluating marrow abnormalities but the specificity of the method is relatively low.

MRI is the best imaging modality for evaluating secondary deposits (which are uncommon) at the anatomical structures of the head as the orbits, the muscles, and the subcutaneous fat but also of the neck as the pharynx and the parotid glands [5].

Complementary to the anatomical information provided by radiological imaging procedures, nuclear medicine techniques play essential role in management of patients with melanoma providing functional information.

Bone scan is a simple, widely used procedure for screening the whole skeleton for secondary deposits. The method can identify osteoblastic activity at the site of metastasis months earlier than the plain films but cannot detect purely lytic lesions with no activity of osteoblasts. Bone scan is not recommended for routine staging of patients in melanoma because of the low specificity of the method and the fact that the bone metastases are not frequent in the early stage of the disease. However, bone scanning is recommended in symptomatic patients as the patients with bone pain, when plain radiographs or even CT scans are negative.

Lymphoscintigraphy is a nuclear medicine technique that demonstrates the pattern of lymphatic drainage to the sentinel lymph node (SLN), the first node receiving the lymph drainage from the primary neoplastic lesion before involving other nodes (Fig. 99.5). After intradermal injection or the radioactive tracer close to the primary tumor, the SLN is detected in most patients

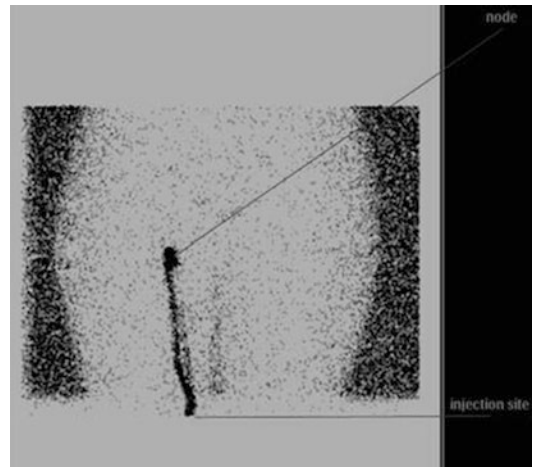

Fig. 99.5 Lymphoscintigraphy: sentinel lymph node at the right inguinal area from a primary site at the right femur

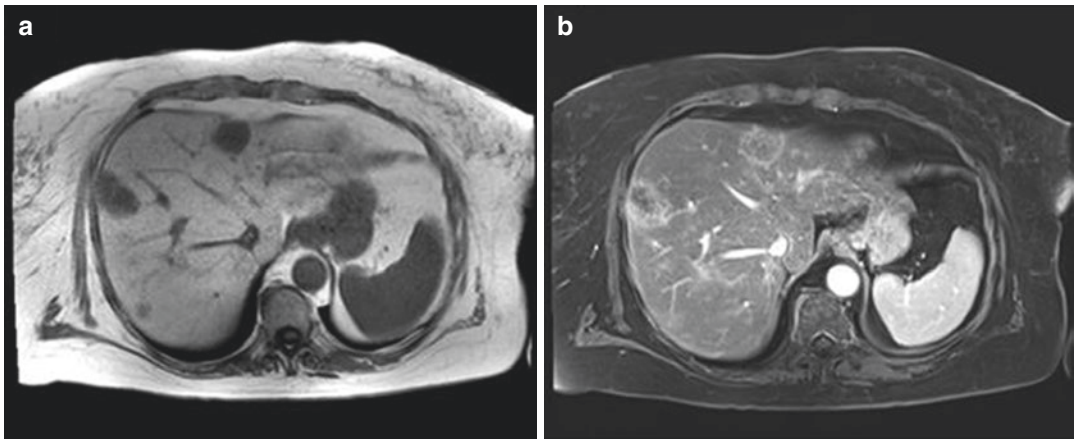

Fig. 99.4 Hepatic metastases on T1 (**a**) and T1 spir p/c (**b**) images in patient with metastatic melanoma

within 10–30 min with the use or gamma camera with single-photon emission computed tomography (SPECT) or with SPECT-CT. At the time of surgery, a hand-held gamma camera is used. If the sentinel node (SN) is negative for metastatic involvement, it is very likely that the rest regional nodes are also negative. The biopsy of SNL can play critical value for the management and the prognosis of the patient with melanoma. Although the features of the primary tumor are very significant for the staging and the prognosis, the status of SLN seems to be the most important prognostic factor in intermediate-thickness melanoma. The method, if performed by experienced stuff, has less than 5% false-negative findings [2, 3]. The radiation dose of lymphoscintigraphy is very low, as very small amount of radioactivity is injected and the CT, if added to SPECT, is of low-dose technique. Lymphoscintigraphy and SLN biopsy are indicated for the initial staging of clinically node-negative cases of melanoma and also for the patients being at risk for regional node spread upon the histological features of the primary lesion. For stage IA disease with adverse histological characteristics, stage IB, and stage II disease, SLN biopsy is recommended.

During the past few years, PET-CT has become a strong imaging tool for the evaluation of many malignancies. PET-CT is a fused method which combines in one single modality the detailed anatomical information provided by CT with the functional information provided by positron emission tomography (PET). The radiotracer used for PET is 18F-FGD, which is glucose labeled with 18F. 18F-FDG is trapped at cancer cells because they have increased metabolic activity and exclusively use glucose as a source of energy. Malignant melanoma is typically FDG-avid disease as most deposits even the small ones appear strongly hypermetabolic with very elevated standard uptake value (SUV) measurements (Figs. 99.6a, b). As many studies have shown, PET-CT is more accurate in the management of patients with melanoma than CT, MRI, or PET alone. The sensitivity of the method is higher compared to CT and MRI. PET-CT is strongly recommended for the evaluation of stage III or IV melanoma, with a sensitivity of 98%, specificity 94%, and accuracy 96% [8]. Compared to MRI, PET-CT is more accurate in N staging and in the detection of subcutaneous and skin metastases, while MRI is more sensitive in the evaluation of the liver, the bones, and the brain and the spinal canal [7]. According to a retrospective study of patients with all stages of melanoma (I–IV) and different time points in course of the disease [9], PET-CT turned out to be more accurate than CT in N and in M initial staging with an overall accuracy of 97%, while the accuracy of CT was 79%. PET-CT revealed much more visceral and nonvisceral metastases than CT alone and led to change patients' management in more than 35% of them [8]. PET-CT is also valuable for restaging and detecting recur-

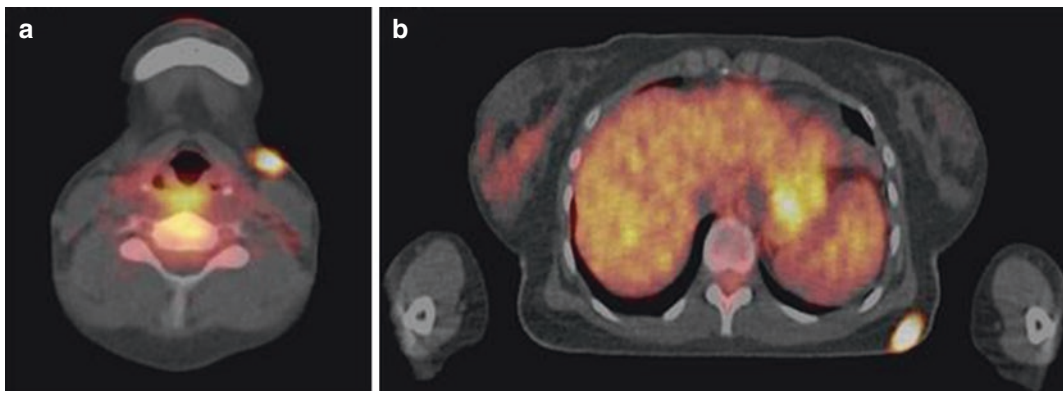

Fig. 99.6 (**a**) Fused PET-CT image: subtly enlarged hypermetabolic submandibular lymph node in metastatic melanoma, (**b**) Fused PET-CT image: hypermetabolic melanoma deposit at the subcutaneous fat

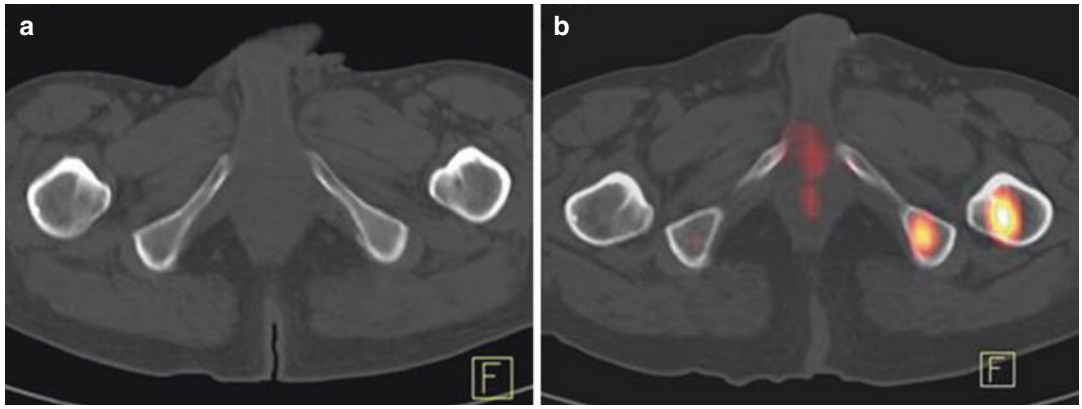

Fig. 99.7 Metastases from cutaneous melanoma at the left ischium and at the left femur on PET-CT images (**b**), not obvious on CT (**a**)

rent melanoma. As a whole body procedure PET-CT demonstrates the total extent of the disease but may also reveal unexpected findings (Figs. 99.7a, b). It is also an excellent imaging tool to clarify equivocal findings on conventional imaging. False-positive results may be due to brown fat, post-therapeutic changes (recent surgery or radiotherapy), normal activity in the bowel, the myocardium and the collecting urinary system, inflammation (infection or granulomatous disease), and benign tumors as adenomas and attenuation artifacts. False-negative findings conclude very small lung nodules (8 mm) which may be FDG negative even if they are metastatic. CT of the lungs remains the imaging method of choice for detection and follow-up for such small lung lesions. PET-CT cannot replace SN procedure in the early stages of the disease (stages I–II) for the detection of micrometastasis. However, FDG-PET-CT could replace conventional imaging in stage III and IV metastatic melanoma except of the evaluation of the brain (MRI provides better estimation) and of the lungs (CT remains the method of choice). Besides its high cost, studies have shown that PET-CT if properly used is a cost-effective method [9, 10].

The current guidelines recommend against further workup (i.e., baseline laboratory tests and imaging studies) in patients with stage 0 (melanoma in situ) and in asymptomatic patients with any thickness of invasive cutaneous melanoma (stages I and II). Further imaging (CT, PET-CT, MRI) should be obtained only as clinically indicated to evaluate specific signs or symptoms.

Current NCCN guidelines do not recommend surveillance (follow-up) laboratory or imaging studies for asymptomatic patients with stage IA, IB, and IIA melanoma (i.e., tumors ≤4 mm depth). Imaging studies (chest radiograph, CT and/or PET-CT) should be obtained as clinically indicated for confirmation of suspected metastasis or to delineate the extent of disease and may be considered to screen for recurrent/metastatic disease in patients with stage IIB–IV disease, although this latter recommendation remains controversial. Routine laboratory or radiologic imaging in asymptomatic melanoma patients of any stage is not recommended after 3–5 years of follow-up [11].

As above described, today, the clinicians have in their disposal a variety of imaging procedures for the initial staging, restaging, and follow-up of patients with melanoma. The information provided by imaging is of critical significance for the patient's management and prognosis.

References

1. King DM (2004) Imaging of metastatic melanoma. J HK Coll Radiol 7:66–69
2. Meyers MO, Yeh JJ, Frank J et al (2009) Method of detection of initial recurrence of stage II/III cutaneous melanoma: analysis of the utility of follow-up staging. Ann Surg Oncol 16(4):941

3. Mohr P, Eggermont AM, Hauschild A et al (2009) Staging of cutaneous melanoma. Ann Oncol 20(suppl 6):vi14–vi21
4. Fishman EK, Kuhlman JE, Schuchter LM et al (1990) CT of malignant melanoma in the chest, abdomen, and musculoskeletal system. Radiographics 10(4):603
5. Escott EJ (2001) A variety of appearances of malignant melanoma in the head: a review. Radiographics 21:625–639
6. Voit C, Van Akkooi AC, Schäfer-Hesterberg G et al (2010) Ultrasound morphology criteria predict metastatic disease of the sentinel nodes in patients with melanoma. J Clin Oncol 28(5):847
7. Pfannenberg C, Aschoff P, Schanz S et al (2007) Prospective comparison of 18F-fluorodeoxyglucose positron emission tomography/computed tomography and whole-body magnetic resonance imaging in staging of advanced malignant melanoma. Eur J Cancer 43(3):557
8. Strobel K, Dummer R, Husarik DB et al (2007) High-risk melanoma: accuracy of FDG PET/CT with added CT morphologic information for detection of metastases. Radiology 244(2):566
9. Reinhardt MJ, Joe AY, Jaeger U, Huber A et al (2006) Diagnostic performance of whole body dual modality 18F-FDG PET/CT imaging for N- and M-staging of malignant melanoma: experience with 250 consecutive patients. J Clin Oncol 24(7):1178
10. Jiménez-Requena F, Delgado-Bolton RC, Fernández-Pérez C et al (2010) Meta-analysis of the performance of (18)F-FDG PET in cutaneous melanoma. Eur J Nucl Med Mol Imaging 37(2):284
11. National comprehensive cancer care network. Clinical practice guidelines in oncology – v.2.2014: Melanoma