Journal of BUON **16:** 24-37, 2011

REVIEW ARTICLE

Skeletal metastases: An update of the literature with pictorial review

P. Zampakis, O. Romanos, P. Kraniotis, E.K. Solomou
Department of Radiology University Hospital of Patras, Patras, Greece

Summary

The skeleton is one of the common places were many tumors metastasize. Skeletal metastases may profoundly affect the patients' quality of life by making them unable to move freely and help themselves, while in some cases impingement upon the CNS structures can cause neurologic symptoms. Early diagnosis of bone metastases is therefore very important in order to prevent severe debilitating conditions. We review the role of different diagnostic methods available for the detection of bone metastases, as well as their response to treatment: bone scintigraphy, plain films, computed tomography (CT) and magnetic resonance imaging (MRI). The role of positron emission tomography (PET) and PET/CT is also discussed.

Key words: imaging, skeletal metastases

Introduction

Skeletal metastases are notoriously known to be commonplace in cancer patients. Actually nearly 70% of cancer patients will present with bone metastases at some stage. Breast, lung, and prostate cancers account for about 80% of all bone metastases. The skeleton is the third most common site of metastases of solid tumors, lagging just behind liver and lung metastases. The axial skeleton i.e. the pelvis, spine and ribs, is usually affected while the appendicular skeleton may be rarely affected [1,2].

Early diagnosis of bone metastases is very important in order to determine prognosis and optimize treatment, especially in patients with prostate or breast cancer, which tend to have higher survival rates [3-7].

Moreover, it should be stressed that the definitive diagnosis of skeletal metastases can be a difficult and challenging task, especially in asymptomatic patients, because of their variable imaging characteristics.

Bone scintigraphy, plain X-ray films, CT and MRI are the mainstay for detecting osseous metastases. Additionally PET and PET/CT were recently introduced as very promising modalities. Besides their unequivocal role for the diagnosis, during the last years imaging methods play an essential role for the evaluation of treatment response, while image-guided biopsy and intervention can effectively change for the better the quality of life in these patients.

The purpose of this review was to present the current status of imaging in the diagnosis and also in the monitoring response to treatment of metastatic bone disease.

Pathophysiology of skeletal metastases

Bone metastases can occur in association with almost all kinds of malignancies. The majority comes from primary tumors originating in the breast, prostate, lung, thyroid gland and kidney. These cancers account for almost 80% of the cases of metastatic bone disease causing significant morbidity. Furthermore, for some tumors, the skeletal system is by far the commonest secondary involvement (i.e. 80% in prostate cancer) as there is a predilection for the osseous structures [6]. In children, skeletal metastases are usually the result of primary tumors, like neuroblastoma, retinoblastoma, embryonal rhabdomyosarcoma, hepatoma and Ewing's sarcoma [8].

Correspondence to: Ekaterini Solomou, MD, PhD. Department of Radiology, University Hospital of Patras, Rion 26500, Greece.
Tel/fax: +30 2610 603422, E-mail: solomou@med.upatras.gr

Received 8-4-2010; Accepted 27-5-2010

It is well known that bone formation is a finely programmed and balanced process involving the continuous remodelling of bone, with main contributing elements being osteoclasts and osteoblasts. This dynamic process, which is controlled by special factors, may be disrupted by the migration of tumor cells into bone. Cancer cells may be able to produce zinc-depended proteinases, and therefore degrade extracellular matrix proteins and the basement membrane. They can subsequently migrate from the primary tumor, invade surrounding tissues and enter the blood and lymphatic systems. Hematogeneous spread seems to be the commonest route of dispersion via arterial or venous (i.e. Batson's plexus) routes.

Moreover, recent studies suggest that platelets may protect circulating tumor cells from the immune system, while special adhesion molecules may play an important role for the invasion of skeletal system from cancer cells [9-14].

Once these cells settle themselves within the bone microenvironment, a series of paracrine interactions takes place. As a result, an osteolytic or osteoblastic "insult" occurs. Some key molecular elements for these interactions are parathyroid hormone-related protein (PTHrP), tumor-produced endothelin 1 (ET-1) and endothelin A receptor (ETAR), bone morphogenetic protein 7 (BMP-7) and platelet-derived growth factor (PDGF) [15-22].

Targeted therapies that could either block initial cancer cell chemotaxis, invasion and adhesion and breaking so this "vicious circle", would contribute to the treatment of the disease [23].

Sites and types of metastatic skeletal lesions

Hematogeneous spread of skeletal metastases usually results in multiple lesions of variable size. However, solitary lesions can be seen in patients with carcinoma of the kidney or thyroid. In such cases the radiographic differentiation from a primary bone tumor can be extremely difficult.

The variability in size may help differentiate metastatic disease from hematologic malignancies, such as plasma cell myeloma, as the latter exhibits a more uniform pattern.

Imaging features of skeletal metastases actually reflect the underlying pathophysiology at the molecular level. Therefore, metastases can be broadly divided as either osteolytic due to bone resorption, osteosclerotic (or osteoblastic) due to bone formation, or mixed.

The most usual pattern of bone metastases is the osteolytic type, representing about 50% of skeletal metastases. These lesions are usually destructive and are much more likely to be associated with pathological fractures [24].

Unfortunately, regarding the differential diagnosis of bone metastases, there are no strict rules to correlate the type of metastasis and the primary tumor. Purely osteolytic lesions typically arise from carcinoma of the kidney, thyroid, uterus and gastrointestinal tumors, although this pattern can also be seen in breast cancer, multiple myeloma and neuroblastoma in children.

Sclerotic lesions are less common (35% of skeletal metastases), presenting mainly in patients with prostate cancer, but may also be present in patients with breast and lung carcinomas, brain primaries, carcinoid, as well as lymphoma.

Mixed osteolytic-osteoblastic metastases represent 15% of all cases and generally occur in carcinomas of the lung, breast, cervix, ovaries, testicles, but can be present in colon, prostate and thyroid cancer as well.

The majority of metastases (80%) are located in the axial skeleton or the skull. Involvement of hematopoietic active bone marrow can also be seen in the proximal part of the femur and humerus (Figure 1).

Spinal involvement is more frequent in the lumbar region, followed by the thoracic and cervical segments. Metastases are commonly seen in both the vertebral bodies and in the posterior parts of the vertebrae, with the latter being a hallmark of metastatic disease. Destructive lesions of the skull may be associated with the presence of a soft tissue mass and are often associated with renal or breast cancer.

Metaphyseal localization is predominant in long bones while diaphyseal or epiphyseal lesions may also be detected. Medullary bone is initially affected while involvement of the cortex occurs at a later stage. Less common sites of metastatic bone involvement (25%) are the ribs and sternum [25].

Rare sites of osseous involvement have been reported to include the elbows and knees, and even the hand and foot regions, referred to as "acrometastasis". These occur in just 0.007-0.3% of patients with malignancy, with the calcaneus and talus being the most common bones involved [26].

Imaging methods

Over the last years, diagnosis, follow-up and response to treatment for skeletal metastasis have become more accurate and reliable due to major improvements in imaging methods. Furthermore, the development of image-guided biopsies and interventions (i.e. radiofrequency ablation, stenting, stomias) have radically changed the quality of life of these patients.

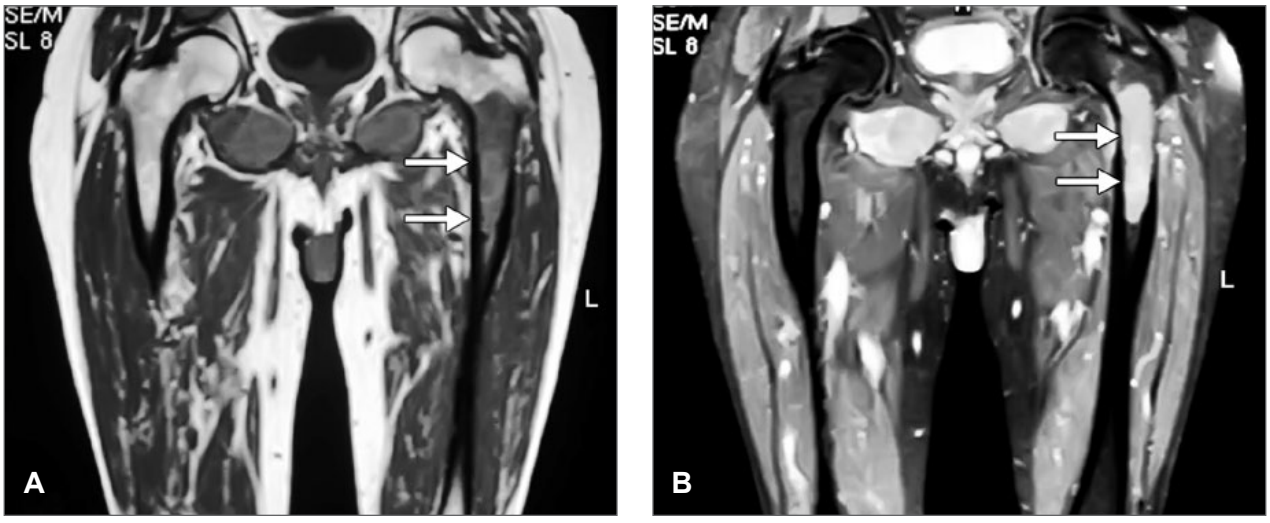

Figure 1. A: coronal T1-SE image of the femoral bones reveals a low signal area within the bone medulla in the metadiaphysis of the left femoral bone with minor involvement of the cortex (arrows). **B:** coronal T1 fat-sat+gadolinium shows abnormal enhancement of the affected area (arrows).

The imaging methods used for osseous metastases include plain film radiography, bone scintigraphy (BS), single slice CT and multi detector computed tomography (MDCT), MRI, PET and PET/CT, as well as single photon emission computed tomography (SPECT).

Plain radiography

Although plain radiography is cost-effective and easily applicable, it appears to be relatively insensitive, especially for lesions less than 2 cm in diameter. Moreover, it is well known that osteolytic changes are apparent on plain x-rays after several months from disease onset. This is due to the fact that at least 30-50% of the cancerous bone has to be resorbed before the lesion can be obvious on the X-ray films. It should also be stressed that, if there is no cortical bone involvement or no reactive new bone formation, lesions may not be apparent, even if they are extensively destructive [27].

Currently, plain radiography is being used to narrow down the differential diagnosis of a lesion that is detected using skeletal scintigraphy and is a helpful adjunct to bone scintigraphy.

There are three patterns of osteolytic lesions on plain X-Rays. These lesions could be either well defined (geographic bone destruction) or poorly defined, with an aggressive pattern, which can be either moth-eaten or permeative.

Geographic bone destruction represents the least severe form. It usually reflects the presence of a slowly growing lesion. An irregular or smooth margin may be present, sometimes with a sclerotic rim of variable thickness. On the other hand the moth-eaten bone destruction is a pattern indicating a more aggressive process. The margins of the lesion are poorly defined and the transitional zone from normal to abnormal bone is larger than in the geographic pattern. The permeative pattern of bone destruction represents the most aggressive among the three types of bone destruction seen in cases of bone metastases. Its characteristic feature is poor demarcation from the surrounding normal bone.

Osteoblastic lesions may be nodular or diffuse. Typically, nodular osteosclerotic lesions lack the spiculated appearance of a bone island.

Concerning spinal involvement, which is the commonest form, there may be variable radiologic findings. Pedicle destruction is the most common plain film finding. It usually occurs as a result of further extension of the metastatic deposit within the posterior part of the vertebral body. On plain anteroposterior radiographs it is seen as absence of one or both "eyes" of the vertebral body [28].

Indistinct posterior vertebral body margin may also be a subtle but useful plain film clue, to indicate bone destruction.

Another feature of metastatic disease that may differentiate it from infection is the preservation of disk height. In cases of collapsed vertebral bodies, differentiation from osteoporotic disease can be assumed because of the location of the lesions, as metastatic disease includes involvement of the upper thoracic spine. Presence of a soft tissue mass, pedicle destruction and angular or irregular deformity of the vertebral endplates are indicative of metastatic disease.

Osteolytic metastases may have the same radiographic appearance with subchondral cysts and Schmorl's

nodes in the spine and are therefore difficult to be differentiated [29]. Differential diagnosis of sclerotic lesions could be more difficult. An entirely radio opaque vertebral body (the ivory vertebra) should be differentiated from the so-called corduroy vertebral body (which shows accentuated vertical striations) seen in hemangiomas, or the rugger-jersey vertebral body (radiodense stripes at the top and bottom) characteristic of renal osteodystrophy etc.

Bone scintigraphy

Since its introduction in the 1970s, technetium (T)-99m bone scintigraphy has been the method of choice for establishing the presence of skeletal metastases. Because it is very sensitive (95%), cost-effective and can image the whole skeleton, it was used as a screening examination method, especially in asymptomatic patients with known primary tumors [30].

In general, T-99m diphosphonate radionuclide imaging depicts metastatic deposits as hot spots, as a result of their increased osteoblastic activity (Figure 2). As opposed to plain X-ray films, only a 5-10% change in the ratio of the lesion to that of normal bone is required for an abnormal focus to be detected.

Lack of specificity is the major limitation of the method. Differential diagnosis includes inflammatory (osteomyelitis) or degenerative lesions (arthritis), various metabolic disorders (osteoporosis, osteomalacia), as well as benign bone tumors [25,31].

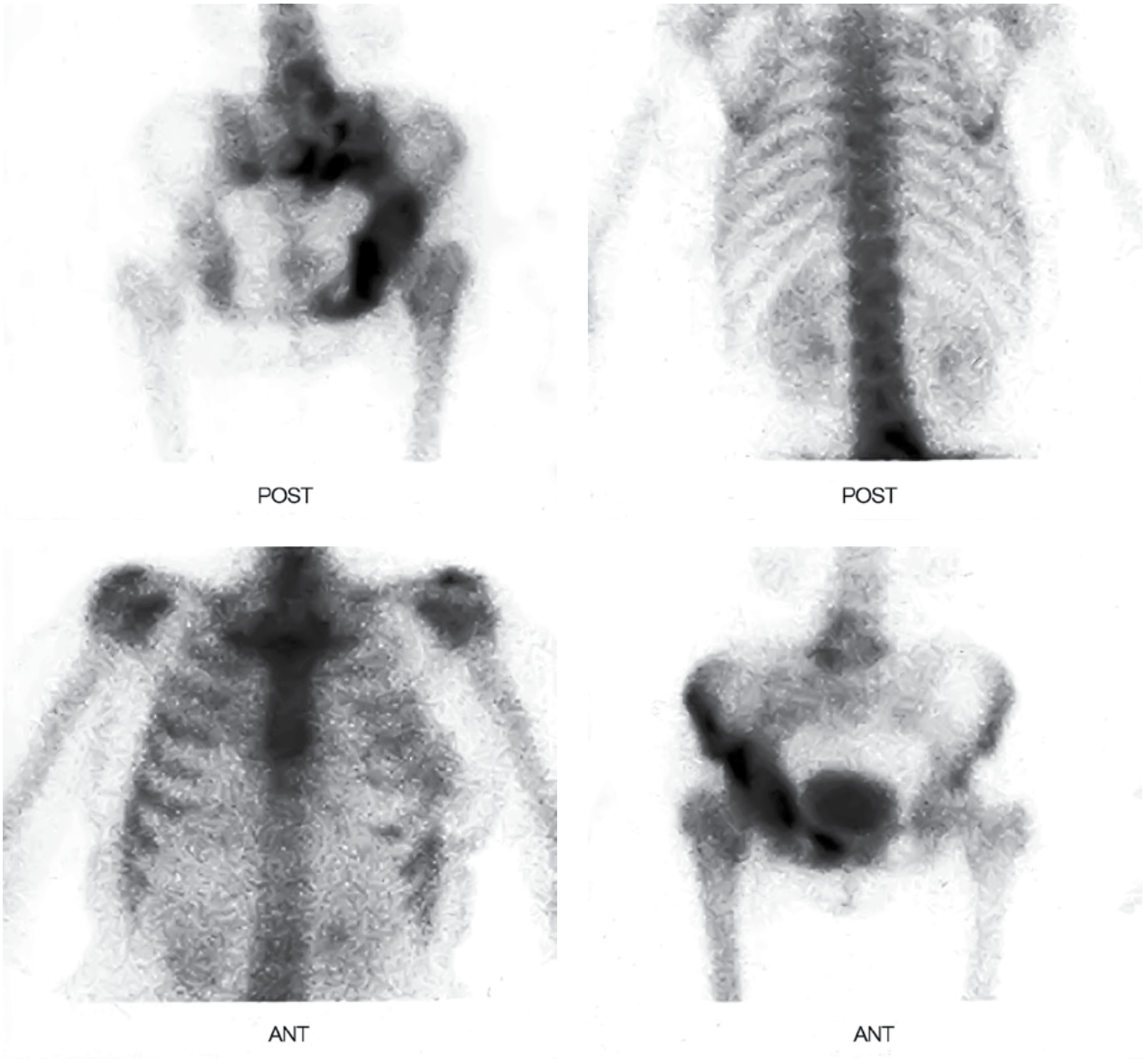

Figure 2. Bone scintigraphy of the skeleton reveals abnormal uptake in the right iliac and pubic bones, the right sacroiliac joint, as well as the L5 vertebra, in a patient with breast carcinoma.

It is well known that bone scintigraphy can also be false-negative, especially in cases of very aggressive metastases, when there is extensive bone destruction without any reactive new bone formation [24], or in patients with multiple myeloma as well as in other osteolytic lesions, because they do not take up the radioisotope as osteoblastic lesions do [32,33].

Another drawback of bone scintigraphy is that is less capable of depicting lesions located in the bone marrow and cannot depict soft tissue involvement. Anatomic detail provided by bone scintigraphy is also limited, so it is often essential that abnormal scans are interpreted in conjunction with other imaging techniques.

Multi-detector computed tomography (MDCT)

CT has become a valuable tool for the evaluation of possible metastatic skeletal involvement.

The high resolution images provided by CT can visualize bones without overlap; so even marginal differences in bone density in small lesions can be detected [34].

CT can easily demonstrate the extent and pattern of bone destruction and can depict the presence of cortical involvement or a soft tissue mass extending from the metastatic lesion, especially in areas with complex anatomy like the spine and pelvis (Figure 3).

Furthermore, CT not only provides an excellent survey of the axial skeleton, but it can also contribute to the evaluation of the stability of skeletal metastases, as well as help in surgical planning with the use of MDCT with multiplanar and three-dimensional reconstructions [35,36] (Figure 4). All these findings can be obtained at the same time while staging cancer patients with CT.

CT is now available almost in every hospital and therefore is an easily applicable method.

The CT patterns of metastases share similarities to those seen in plain film radiography.

The diagnosis of an osteolytic lesion on CT is based by the detection of destructive changes of the trabecular bone or the cortex, which are usually replaced by a soft tissue mass.

The osteoblastic lesions can be more difficult to diagnose. An indicative finding of malignancy includes an ill-defined area of increased bone density, with loss of definition of the trabecular pattern. Osteoblastic metastases may become densely sclerotic and may occasionally have sharply defined margins. In this case, differentiation between malignant lesions and benign processes may be impossible. Multiplicity of the hyperdense lesions is helpful in diagnosing metastases [36].

Other imaging findings of bone reaction to the presence of metastatic deposits seen on CT include periosteal reaction, expansile bone remodeling, pathologic fractures and the presence of a soft tissue density mass.

Periosteal reaction is limited or even absent in metastatic lesions, in contrast to the extensive periosteal reaction commonly seen in primary malignant bone

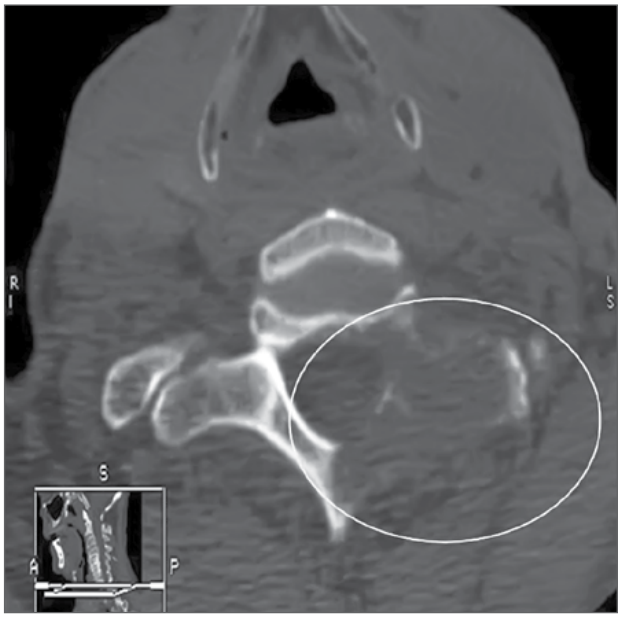

Figure 3. Axial CT of the cervical - upper thoracic spine at the level of T1 vertebra (bone windows) shows a lytic lesion of the posterior parts of T1 vertebra, on the left.

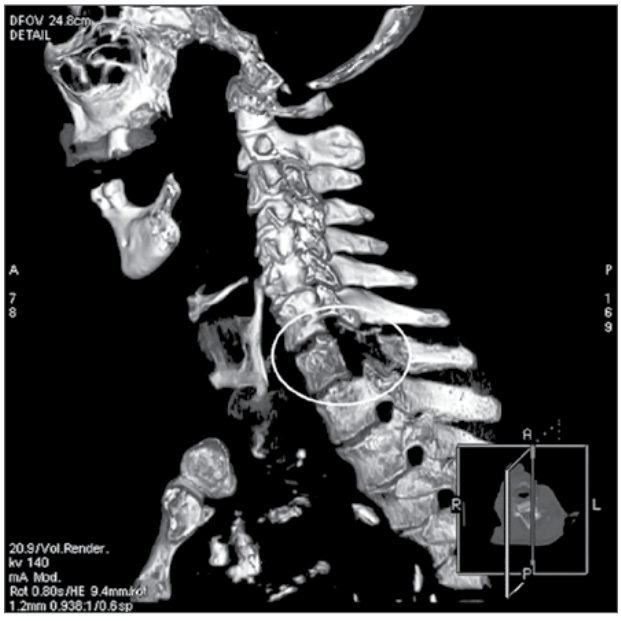

Figure 4. Volume rendering (VRT) algorithm reconstructions with the ability to have 3D images which can be rotated in different planes, in order to better detect bony abnormalities.

tumors. However, severe periosteal reaction leading to bone spiculation and a sunburst appearance is evident in some cases of metastases, especially in those arising from prostate carcinoma or gastrointestinal tumors [36,37].

Expansile bone remodeling can be seen in patients with carcinomas of the kidney, thyroid as well as in hepatocellular carcinoma. In some of these cases, a distinctive septated appearance accompanies the osseous expansion. It should be stressed that large expansile osteoblastic lesions may mimic Paget's disease or even osteosarcoma.

The measurement of Hounsfield Units is considered to be helpful in the differentiation between benign and malignant marrow lesions. An attenuation difference of more than 20HU between the two extremities has been reported to be abnormal [37].

Because these findings are subtle, they may be overlooked, as they are far less apparent than the marrow changes seen on MRI, and extra caution is required when looking for metastatic disease.

As thoracic, abdominal, and pelvic CT examinations are often carried out for oncological staging, it is important to check the examination on bone windows settings as well. In this way skeletal metastases may be detected during routine CT examinations in asymptomatic patients (Figure 5).

On the other hand CT may be also be useful in the localization of a primary tumor in the chest, abdomen and pelvis, in patients who present with bone pain and bone lesions compatible with metastatic disease, but without any history of known primary malignancy.

Continuous hardware improvements for CT imaging from single-slice scanners to 64 or 128-slice multidetector scanners have resulted in larger field of view (FOV) and faster acquisition times with higher image resolution.

In addition, fused SPECT/CT images can increase the diagnostic confidence compared with separate sets of scintigraphic and CT images, when it comes to differentiating malignant from benign bone lesions, as shown by Utsunomiya et al. [38].

Modern CT scanners result in reduction of ionizing radiation exposure as high as 70%, depending on the anatomical region, without limitations on image quality [35].

Additionally, CT enables the performance of biopsies in a minimally invasive manner. CT guidance is very important, in order to determine the safest and shortest route to the lesion for the precise placement of the needle, particularly when dealing with small and deep located lesions. New therapeutic possibilities, including ablative techniques for palliation have been developed. Radiofrequency (RF) ablation under CT guidance has been widely used in the last years for palliation in patients with bone metastases. Several studies have concluded so far that RF ablation provides an effective and safe alternative method of pain palliation in patients with osteolytic metastases [39].

The response to treatment is another important contribution of the modern CT scanners, helping the management of cancer patients. Recent studies have shown that CT is sensitive for the detection of changes within the bones, indicative of treatment response. The healing response to chemotherapy or radiation therapy

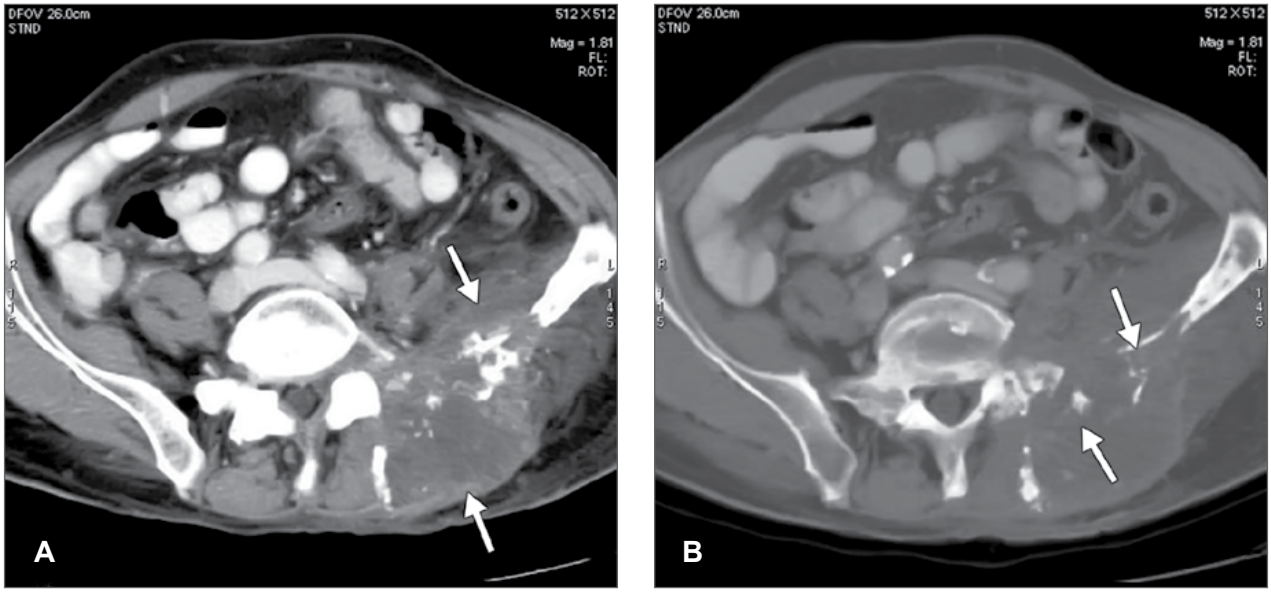

Figure 5. A: abdominal axial CT scan of the patient shown on Figure 3 (standard soft tissue windows) shows an inhomogeneous soft tissue mass destructing the left iliac bone, with extension to the adjacent muscles (arrows). **B:** the bone destruction is better detected on the bone windows, where cortical disruption and aggressive-type periosteal reaction can be seen (arrows).

of a purely osteolytic lesion follows a specific course, ranging from a subtle sclerotic rim in its periphery, to the progressive bone sclerosis. CT is a very sensitive method that may reveal even minor bony changes, indicating disease progression or response to treatment [27].

Furthermore, radiation therapy itself is also associated with a number of osseous alterations, such as osteopenia, trabecular coarsening, insufficiency fractures, ischemic bone necrosis and secondary neoplasia. These changes may sometimes complicate the accurate assessment of the metastatic process. Quantitative methods to evaluate bone response to treatment have been elusive. CT density can be used to evaluate response to treatment. Differences in attenuation values between pre and post treatment scans in patients with bone metastases can be measured giving thus an objective indicator of osseous response to treatment [40,41].

SPECT, PET-PET/CT

The implementation of PET has started to overcome the limitation of low specificity of bone scintigraphy. During the last years, PET has been established as a modern nuclear medicine method.

Because of the high rate of glycolysis, seen in high-grade malignancies, PET can depict early malignant bone marrow. The tracer used is 2-[18F] fluoro-2-deoxy-D-glucose (FDG) because it is a marker of enhanced glucose uptake, which is characteristic of malignant cells.

Another nuclear imaging method is planar SPECT. Although there are differences between FDG and 99mTc-diphosphonate, it is possible that the uptake mechanism in bones is the same.

Recent advances in CT scanners, as well as the clinical application of SPECT and PET fusion images have the potential to positively influence cancer patients' care. The development of SPECT-PET/CT scanners has introduced many new clinical applications in oncologic imaging. CT can be very useful for the anatomic localization of a lesion detected with SPECT and thus to clarify the nature of an abnormality with increased radiotracer uptake. Fused SPECT/CT images increased the diagnostic confidence, when compared with separated sets of scintigraphic and CT images for the differentiation of malignant from benign bone lesions [38].

MRI

MRI is reported to be the most sensitive imaging technique available for the detection of bone metastases, with a reported sensitivity of up to 100% in some studies [42-49].

The major advantage of MRI is that it does not involve ionizing radiation, is a non-invasive technique and presents great tissue contrast compared to other modalities already used. This technique can depict metastases at an early stage, while it can also help in tumor staging, screening, follow-up and response to treatment.

Especially for the spine, MRI, apart from the excellent sensitivity, is extremely helpful for the identification of threatening complications of metastatic disease (constriction of the spinal canal with/without compression of spinal cord), by visualizing with high clarification the vertebral body, as well as the paraspinal and intraspinal soft tissues.

Furthermore, it is useful in discriminating between benign and malignant vertebral collapse, as well as in the differential diagnosis of metastatic from degenerative changes of the vertebrae. For this reason it is frequently used to clarify equivocal findings in scintigraphy or radiography [43, 46, 50-53].

There are, nonetheless, a number of limitations and drawbacks in its application like the relatively long examination time, motion artefacts, reduced spatial resolution, limited availability and high cost. In particular, long acquisition times may not be tolerated by patients in poor condition [54-57]. In addition, there are some patients who cannot tolerate MRI due to claustrophobia or in whom MRI is contraindicated i.e. patients with cardiac pacemakers, metallic implants, etc [24].

A standard MRI protocol would include a T1 weighted spin-echo sequence in addition to either a T2 weighted turbo spin echo image or a short tau inversion recovery (STIR) /Fast STIR pulse sequence. T1 weighted images with fat suppression and gadolinium enhancement should also be used. Sagittal images are mostly useful for the examination of the spine, whereas complementary axial planes are useful if compression of the spinal cord is suspected. Coronal slices are used for imaging the pelvis and upper femora. Coil selection and slice thickness is decided according to the anatomic region of interest [24].

MRI of bone metastases also depends on the relationship between the degree of bone resorption or deposition. Metastases initially infiltrate the medullary cavity, destroying the cortex at the end [58].

On T1 weighted images, focal or diffuse areas of low signal intensity are considered to be metastases, due to replacement of the normal fatty marrow by the tumor. T1 weighted images before and after contrast administration must be evaluated in conjunction. Metastatic lesions in fatty bone marrow that are hy-

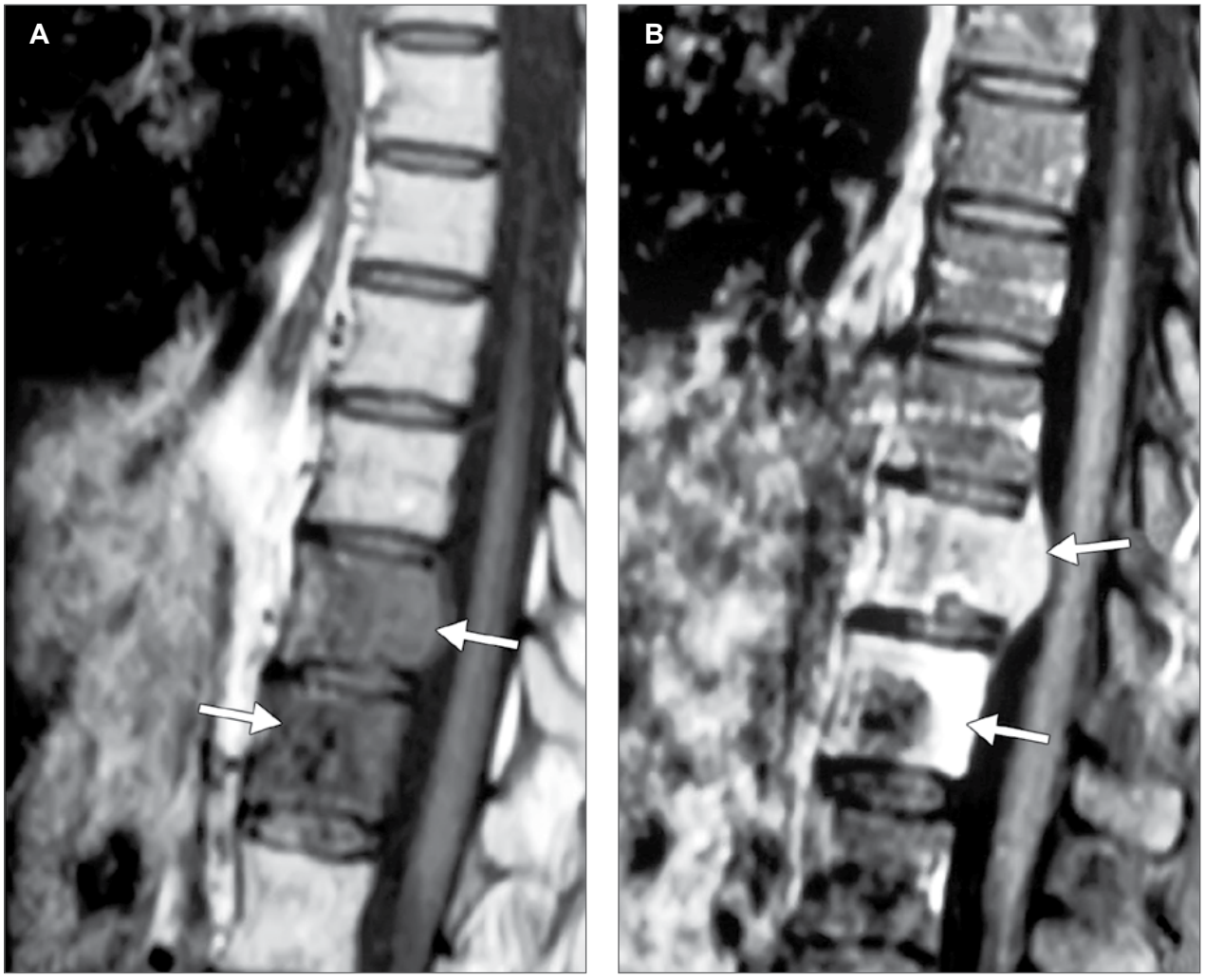

Figure 6. A: sagittal T1-SE image shows low signal intensity in the bodies of T11 and T12 vertebrae with posterior angulation of the T11 vertebra body and small compression of the anterior subarachnoid space (arrows). **B:** sagittal T1 fat-sat+gadolinium image shows enhancement of the affected vertebrae (arrows).

pointense on T1 images, exhibit contrast administration (Figure 6).

On the T2 weighted images metastases may have high, intermediate or low signal, depending on tumor morphology [31] (Figure 7).

On STIR images hyperintense areas, due to an increased content of water within tumor cells, may represent metastatic lesions, which are easily detected because of the contrast which is created by the dark background of the suppressed normal fatty marrow signal [28] (Figure 8). Osteoblastic metastases show a low signal intensity on both T1 and T2 weighted images, whereas their signal intensity on the STIR images is versatile, ranging from no changes in sclerotic metastases, to elevation of the signal in tumors with high cellular component.

It's not uncommon to identify edema surrounding bone metastases. Schweitzer et al. examined the sensitivity of the "halo sign" as a predictor of metastatic disease. This was defined as a rim of high signal surrounding an intraosseous lesion on T2-weighted images. This sign provided a sensitivity of 75% and specificity of 99% as a predictor of a metastatic focus. They found however that different metastatic lesions often demonstrated a variety of appearances, though halos were most commonly identified in prostatic cancer metastases [59].

Dynamic studies of signal enhancement after gadolinium chelate contrast injection may be helpful in differentiating between osseous metastases and benign bone marrow changes, such as hyperplastic bone marrow formation.

New technical advances have been developed in order to overcome field of view restrictions and increase patient comfort, but compromised spatial resolution, especially in peripheral body regions like the head/neck and lower extremities [60].

The introduction of multi-channel MR scanners,

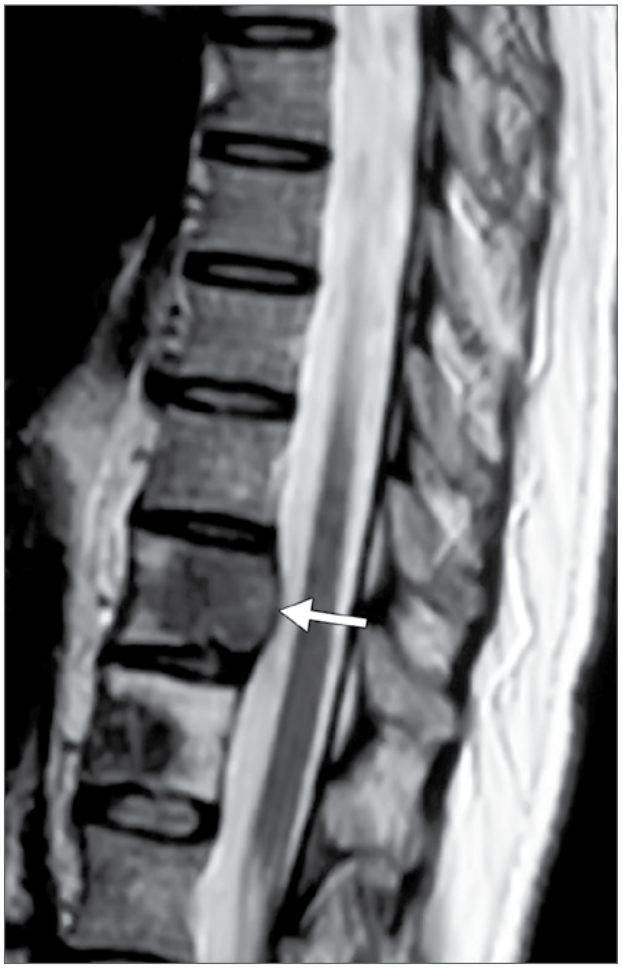

Figure 7. Sagittal T2-TSE image shows low signal intensity of the affected vertebrae without compression of the spinal cord (arrow).

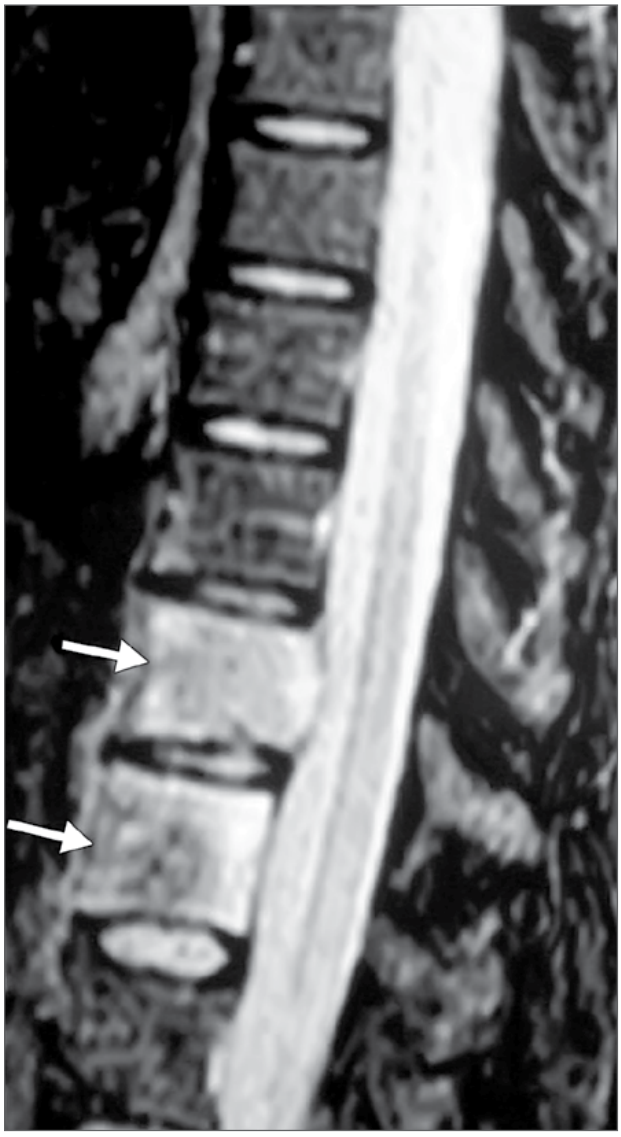

Figure 8. Sagittal stir image depicts abnormally high signal intensity within the T11 and T12 vertebral bodies, consistent with the presence of marrow edema (arrows).

with parallel imaging acquisition techniques (PAT) allows for the evaluation of the entire skeleton in shorter time with no spatial resolution compromise even when time-consuming but indispensable sequences are used (e.g., STIR sequences).

The new concept for whole body MRI i.e. continuously moving table technique with the use of PAT is very promising. Recently, a special reconstruction algorithm (SENSE) has been successfully applied on stationary receiver coils with arbitrary coil dimensions for continuous 3D-gradient echo imaging of the complete body without significant constraints in image quality. Several authors have reported promising initial results for 3D whole-body continuous data acquisition using this technique [61-64].

Discussion

The major advances in modern imaging techniques have radically changed the scenery regarding early and accurate detection of metastatic skeletal disease.

The main reason for that is the development of MDCT scanners that offered the opportunity for detailed fused images with PET scanning, along with the great advances in whole body MRI. Those two imaging techniques are currently the mainstay in accurate and detailed detection of bone metastases. They also contribute a lot to the follow-up and response to treatment of osseous metastases.

Skeletal scintigraphy has been being used for more than 30 years for the diagnosis of bone abnormalities. The combination of a high sensitivity rate and a low effective dose (about 4mSv) [24] standardized this technique as a reasonable screening examination method for oncological patients [65-70].

Nevertheless, during the last few years, the importance of skeletal scintigraphy has been reviewed, since studies have shown that detection of skeletal metastases in the bone marrow can be detected with MRI before scintigraphic evidence is present [71-74].

Radiography is commonly used to evaluate symptomatic sites and to confirm findings seen on bone scintigraphy. It has also been used to assess the risk of pathologic fracture, which seems to be high if 50% of the cortex is destroyed by a lesion.

When combined with skeletal scintigraphy, plain radiography is reported to be adequate in about 95% of diagnoses. Thus, negative or equivocal X-ray findings, or lesions in anatomically complex regions must be further investigated.

Radiographs have also been used for assessing response to treatment. The appearance of a sclerotic reactive rim in an osteolytic metastasis is the initial sign of response to treatment, whereas increasing sclerosis in the center of the lesion means progression of the healing process.

The development of imaging methods in radiology and nuclear medicine has offered new horizons in diagnosis, follow-up, and response to treatment, reflecting changes in cancer patient's management. Moreover, new interventional techniques have added to the same perspective.

The implementation of CT and especially MDCT, has greatly improved imaging of skeletal metastases. The method provides the ability of multiplanar reconstruction which offers a quick and reliable method for the detection of bone abnormalities with high resolution images. The rest of the diagnostic work-up for these patients can be done at the same time. This complete diagnostic evaluation in a single examination without having to reposition the patients - a procedure that is necessary in conventional studies- is very important when scanning patients in pain and in poor general condition.

MDCT is reported to be superior to radiography in depicting bone metastases. It is helpful when scintigraphic findings have no apparent radiographic correlation i.e. in cases difficult to image due to their topography.

Krahe et al. compared radiography and CT examinations in 112 patients with metastases of the spine. Plain radiography depicted 88% of the lesions identified with MDCT when the vertebral body was involved and only 66% when other parts of the vertebrae were affected. Intraspinal and paravertebral tumor extension was correctly assessed in only 23% and 33% of cases, respectively [75].

A recent study [35] has shown good correlation in the detection of bone metastases between bone scintigraphy and MDCT of the thorax-abdomen and pelvis in metastatic breast cancer patients. MDCT was very accurate in determining the presence of bone metastases. The authors of this paper suggest that, according to their findings, routine bone scintigraphy of patients presenting with metastatic breast cancer is not required if a CT of the thorax, abdomen and pelvis is performed. These results were similar with those of another study [76] which recommend whole body MDCT (vertex to knee) in replacement of bone scintigraphy in patients investigated for bone metastases.

However, it is not yet clear whether MDCT is equal to MRI for the assessment of bony metastases. First results have demonstrated a superior detection rate in favor of MRI. In addition, CT is not appropriate for bone metastases screening, as the radiation dose is high.

A disadvantage of the CT scanning is that advanced destructive lesions of the bone, particularly in the absence of reactive new bone or cortical involvement, may not be visible on CT scans. Additionally, its ability to detect early deposits in bone marrow is limited [25].

A great development in nuclear medicine imaging was the implementation of FDG-PET in the evaluation and management of patients with malignancy. With the use of this specific tracer, the enhanced glucose uptake by malignant cells can be depicted. However, this tracer is not specific for tumors and accumulates in infected cells as well.

FDG-PET scans are superior to bone scan in the detection of purely osteolytic bone metastasis, in terms of sensitivity [77].

Shie et al. performed a meta-analysis in order to compare FDG-PET and bone scintigraphy for the detection of osseous metastases in patients with breast cancer. FDG-PET appeared to have a higher specificity and thus may be better as a confirmatory examination than bone scintigraphy. However, it remains inconclusive whether FDG-PET or bone scintigraphy is superior in detecting osseous metastases from breast cancer [78].

Besides, FDG-PET has a high rate of false-positive results which makes additional examination with other modalities necessary. That is because 18F is too sensitive and one has to learn again how to read a "bone scan", as there are often many lesions present.

In some studies, FDG-PET was found to have a higher sensitivity (90%) in comparison to other modalities, such as whole body MRI and T-99m scintigraphy [79].

On the other hand, the sensitivity of the method for the evaluation of osteoblastic lesions is low, because of the acellular nature of these metastases [80].

To overcome the diagnostic "Achilles heels" of

both FDG-PET and CT scans over the last years, the combination of these methods has been implemented, as the two in one PET/CT has become a reality with the use of MDCT scanners.

In the study of Nakamoto et al. CT images obtained as part of PET/CT scanning were useful for yielding the precise location of bone lesions and this helped avoid the misdiagnosis of bone metastasis; However, CT revealed morphologic changes in only half of the lesions assigned as definitely or possible definitely positive as bone metastases on PET [81].

A study by Even-Sapir et al. showed that the specificity of PET/CT was significantly higher than that of PET alone (97 vs. 72%, respectively). Based on patient analysis, the sensitivity of PET and PET/CT was calculated to be 88% and 100%, respectively, whereas the specificity was 56% and 88%, respectively [82].

Furthermore, in another study PET/CT proved to have a very high positive predictive value (PPV) for bone metastases (98%) when the findings on PET and CT were concordant; however, in lesions with discordant PET and CT findings on the integrated examination, PPV was markedly diminished [83].

Modern MR images are reported to be superior to bone marrow and skeletal scintigraphy in terms of accuracy for the detection of bone metastasis and this has been verified by many studies [46,48,49,52,71,73,74, 84-87].

For example, Layer et al. compared the findings of MRI and bone marrow scintigraphy in the screening of skeletal metastases in breast cancer patients. They found that MRI was superior to bone marrow scintigraphy with respect to sensitivity (92 vs. 58%, respectively) and specificity (97 vs. 85%, respectively) [87]. Furthermore, MRI has a reported sensitivity in the literature of up to 100% for the detection of metastases [46].

Whole body MRI, with the development of new coils, new table concepts and ultra fast data acquisition, is a very promising modality challenging both whole body scintigraphy and whole body PET/CT. The first whole body MRI study reported a sensitivity of 96.5% and a specificity of 100% using Turbo-STIR imaging. In the same study, the conventional method of planar skeletal scintigraphy had a sensitivity of 72% and a specificity of 98% [88]. Similar high rates of detection were revealed by Steinborn et al. in cases of various malignant primary diseases. The whole body MRI detected 91.4% of the metastases that were verified during the course of the disease, whereas skeletal scintigraphy revealed only 89 of the 105 lesions (85%) [74].

Only a few study studies have directly compared the performance of whole body MRI with PET/CT for the detection of skeletal metastases.

Antoch et al. as well as Schmidt et al. found that specificity was higher in PET/CT (80%) vs. whole body MRI (76%). The additional metabolic information of PET helps in the discrimination between benign and malignant lesions [89-91].

Further comparative studies are needed in order to establish the role of whole body PET/CT vs. whole body MRI; however, special diagnostic problems may occur in children because of their highly cellular hematopoietic marrow, which may impair the detection of bone marrow metastases [79].

Most false-negatives in scintigraphy were found in the spine, while diagnostic problems for whole body MRI occur in the thoracic cage and skull, especially when coronal imaging planes are used, a problem that is certainly increased by motion artefacts [55,61]. These problems might be overcome when using fast turbo spin echo sequences for thoracic imaging complemented with axial slices when necessary.

Conclusions

Improvements in imaging technology have led to greater sensitivity rates for the detection of bone metastases and better identification of the primary tumor. They can also provide greater safety in guiding needle biopsy and palliative treatment.

Plain radiography should not be used for the depiction of bone metastases, as its sensitivity is very low compared to other imaging modalities. Plain films may have a supplementary role and can be used to evaluate symptomatic sites, as well as to confirm findings of bone scintigraphy.

Bone scintigraphy has been used as the screening method of choice for the evaluation of bone metastatic disease. Nonetheless, during the last few years, MRI has been gaining ground as the gold standard for the evaluation of bone metastases in patients with known or suspected primary malignancy, especially with the implementation of whole body MR imaging.

PET depicts early malignant bone marrow infiltration. The combined PET/CT scanners allow full body imaging providing both anatomical and functional data during one examination period.

MDCT plays an important role in the management of cancer patients in clinical routine and gives an excellent survey of the axial skeleton by demonstrating osteolytic and osteoblastic metastases. It also provides significant information regarding the stability of the spine and serves as guidance in performing percutaneous biopsies and palliative treatments.

References

1. Falkmer U, Järhult J, Wersäll P, Cavallin-Stahl E. A systemic overview of radiation therapy effects in skeletal metastases. Acta Oncologica 2003; 42: 620-633.
2. Galasko CSB. The Anatomy and Pathways of Skeletal Metastases In: Weiss I, Gilbert AH (Eds): Bone metastasis. GK Hall, Boston, 1981, pp 49-36.
3. Cote RJ, Hawes D, Chaiwun B, Beattie EJ Jr. Detection of occult metastases in lung carcinomas: progress and implications for lung cancer staging. J Surg Oncol 1998; 69: 265-274.
4. Janni W, Gastroph S, Hepp F et al. Prognostic significance of an increased number of micrometastatic tumor cells in the bone marrow of patients with first recurrence of breast carcinoma. Cancer 2000; 88: 2252-2259.
5. Yamashita K, Denno K, Ueda T et al. Prognostic significance of bone metastases in patients with metastatic prostate cancer. Cancer 1993; 71: 1297-1302.
6. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001; 27: 165-176.
7. Clemons M. Should all breast cancer patients with symptomatic bone metastases be treated with bisphosphonates? The case in support. Clin Oncol 2004; 16: 108-111.
8. Leeson MC, Makley JT, Carter JR. Metastatic skeletal disease in the pediatric population. J Pediatr Orthop 1985; 5: 261-267.
9. Palumbo JS, Talmage KE, Massari JV et al. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood 2005; 105: 178-185.
10. Müller A, Homey B, Soto H et al. Involvement of chemokine receptors in breast cancer metastasis. Nature 2001; 410: 50-56.
11. Sun YX, Schneider A, Jung Y et al. Skeletal localization and neutralization of the SDF-1(CXCL12)/CXCR4 axis blocks prostate cancer metastasis and growth in osseous sites in vivo. J Bone Miner Res 2005; 20: 318-329.
12. Wang J, Loberg R, Taichman RS. The pivotal role of CXCL12 (SDF-1)/CXCR4 axis in bone metastasis. Cancer Metastasis Rev 2006; 25: 573-587.
13. Sung V, Stubbs JT 3rd, Fisher L, Aaron AD, Thompson EW. Bone sialoprotein supports breast cancer cell adhesion proliferation and migration through differential usage of the alpha(v)beta3 and alpha(v)beta5 integrins. J Cell Physiol 1998; 176: 482-494.
14. Felding-Habermann B, O'Toole TE, Smith JW et al. Integrin activation controls metastasis in human breast cancer. Proc Natl Acad Sci U S A 2001; 98: 1853-1858.
15. Guise TA, Yin JJ, Taylor SD et al. Evidence for a causal role of parathyroid hormone-related protein in the pathogenesis of human breast cancer-mediated osteolysis. J Clin Invest 1996; 98: 1544-1549.
16. Thomas RJ, Guise TA, Yin JJ et al. Breast cancer cells interact with osteoblasts to support osteoclast formation. Endocrinology 1999; 140: 4451-4458.
17. Yin JJ, Mohammad KS, Käkönen SM et al. A causal role for endothelin-1 in the pathogenesis of osteoblastic bone metastases. Proc Natl Acad Sci U S A 2003; 100: 10954-10959.
18. Buijs JT, Rentsch CA, van der Horst G et al. BMP7, a putative regulator of epithelial homeostasis in the human prostate, is a potent inhibitor of prostate cancer bone metastasis in vivo. Am J Pathol 2007; 171: 1047-1057.
19. Logothetis CJ, Navone NM, Lin SH. Understanding the Biology of Bone Metastases: Key to the Effective Treatment of Prostate Cancer. Clin Cancer Res 2008; 14: 1599-602 (Review).
20. Canalis E, McCarthy TL, Centrella M. Effects of platelet- derived growth factor on bone formation in vitro. J Cell Physiol 1989; 140: 530-537.
21. Langley RR, Fan D, Tsan RZ et al. Activation of the platelet-derived growth factor-receptor enhances survival of murine bone endothelial cells. Cancer Res 2004; 64: 3727-3730.
22. Uehara H, Kim SJ, Karashima T et al. Effects of blocking platelet-derived growth factor-receptor signalling in a mouse model of experimental prostate cancer bone metastases. J Natl Cancer Inst 2003; 95: 458-470.
23. Clines GA, Guise TA. Molecular mechanisms and treatment of bone metastasis. Expert Rev Mol Med 2008; 10: e7.
24. Traill Z, Richards MA, Moore NR. Magnetic Resonance Imaging of metastatic bone disease. Clin Orthop Related Res 1995; 312: 76-88.
25. Ghanem N, Uhl M, Brink I et al. Diagnostic value of MRI in comparison to scintigraphy, PET, MS-CT and PET/CT for the detection of metastases of bone. Eur J Radiol 2005; 55: 41-55.
26. Maheshwari AV, Chiappetta G, Kugler CD, Pitcher JD Jr, Temple HT. Metastatic skeletal disease of the foot: case reports and literature review. Foot Ankle Int 2008; 29: 699-710 (Review).
27. Resnik D, Kransdorf MJ. Skeletal metastasis. In: Resnik D, Kransdorf MJ (Eds): Bone and Joint Imaging (3rd Edn). Elsevier Saunders Philadelphia, Pensylvania, 2005, pp1245-1264.
28. Peh WC (2002). Bone metastases. http: //www.emedicine.com/radio/TOPIC88.HTM
29. Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT. Bone imaging in metastatic breast cancer. J Clin Oncol 2004; 22: 2942-2954.
30. Algra PR, Bloem JL, Tissing H, Falke TH, Arndt JW, Verboom LJ. Detection of vertebral metastases: Comparison between MR imaging and bone scintigraphy. Radiographics 1991; 11: 219-232.
31. Iiaslan H, Sundaram M. Advances in musculoskeletal tumor imaging. Orthop Clin North Am 2006; 37: 375-391.
32. Wilkinson AN, Viola R, Brundage MD. (2008) Managing skeletal related events resulting from bone metastases. BMJ 337: a2041. doi: 10.1136/bmj.a2041 (Review).
33. Jadvar H, Gamie S, Ramanna L, Conti PS. Musculoskeletal system. Semin Nucl Med 2004; 34: 254-261 (Review).
34. Antevil JL, Sise MJ, Sack DI, Kidder B, Hopper A, Brown CV. Spiral computed tomography for the initial evaluation of spine trauma: a new standard of care? J Trauma 2006; 61: 382- 387.
35. Bristow AR, Agrawal A, Evans AJ et al. Can computerised tomography replace bone scintigraphy in detecting bone metastases from breast cancer? A prospective study. The Breast 2008; 17: 100-105.
36. Rafii M, Firooznia H, Kramer E, Golimbu C, Sanger J. The role of computed tomography in evaluation of skeletal metastases. J Comput Tomogr 1988; 12: 19-24.
37. Helms CA, Cann CE, Brunelle FO, Gilula LA, Chafetz N, Genant HK. Detection of bone marrow metastases using quantitative computed tomography. Radiology 1981; 40: 745-750.
38. Utsunomiya D, Shiraishi S, Imuta M et al. Added Value of SPECT/CT Fusion in Assessing Suspected Bone Metastasis:

Comparison with Scintigraphy Alone and Nonfused Scintigraphy and CT. Radiology 2006; 238: 264-271.
39. Thanos L, Mylona S, Galani P et al. Radiofrequency ablation of osseous metastases for the palliation of pain. Skeletal Radiol 2008; 37: 189-194.
40. Vassiliou V, Kalogeropoulou C, Giannopoulou E, Leotsinidis M, Tsota I, Kardamakis D. A novel study investigates the therapeutic outcome of patients with lytic, mixed and sclerotic bone metastases treated with combined radiotherapy and ibandronate. Clin Exp Metastasis 2007; 24: 169-178.
41. Vassiliou V, Kalogeropoulou C, Christopoulos C, Solomou E, Leotsinides M, Kardamakis D. Combination of ibandronate and radiotherapy for the treatment of bone metastases: clinical evaluation and radiologic assessment. Int J Radiat Oncol Biol Phys 2007; 67: 264-272.
42. Vanel D. MRI of bone metastases: the choice of the sequence. Cancer Imaging 2003; 4: 30-35.
43. Daffner RH, Lupetin AR, Dash N, Deeb ZL, Sefczek RJ, Schapiro RL. MRI in the detection of malignant infiltration of bone marrow. AJR Am J Roentgenol 1986; 146: 353-358.
44. Hanna SL, Fletcher BD, Fairclough DL, Jenkins JH 3rd, Le AH. Magnetic resonance imaging of disseminated bone marrow disease in patients treated for malignancy. Skelet Radiol 1991; 20: 79-84.
45. Neumann K, Hosten N, Venz S. Screening for skeletal metastases of the spine and pelvis: gradient-echo opposed-phase MRI compared with bone scintigraphy. Eur Radiol 1995; 5: 276-284.
46. Avrahami E, Tadmor R, Dally O, Hadar H. Early MR demonstration of spinal metastases in patients with normal radiographs and CT and radionuclide bone scans. J Comput Assist Tomogr 1989; 13: 598-602.
47. Delbeke D, Powers TA, Sandler MP. Correlative radionuclide and magnetic resonance imaging in evaluation of the spine. Clin Nucl Med 1989; 14: 742-749.
48. Kattapuram SV, Khurana JS, Scott JA, El-Khoury GY. Negative scintigraphy with positive magnetic resonance imaging in bone metastases. Skelet Radiol 1990; 19: 113-116.
49. Frank JA, Ling A, Patronas NJ et al. Detection of malignant bone tumors: MR imaging vs scintigraphy. AJR Am J Roentgenol 1990; 155: 1043-1048.
50. Albert K. Evaluating bone metastases. Clin J Oncol Nurs 2007; 11: 193-197.
51. Nyman R, Rehn S, Glimelius B et al. MRI in diffuse malignant bone marrow diseases. Acta Radiol 1987; 28: 199-205.
52. Colman LK, Porter BA, Redmond J et al. Early diagnosis of spinal metastases by CT and MR studies. J Comput Assist Tomogr 1988; 12: 423-426.
53. Mehta RC, Wilson MA, Perlman SB. False negative bone scan in extensive metastatic disease: CT and MRI findings. J Comput Assist Tomogr 1989; 13: 717-719.
54. Ghanem N, Altehoefer C, Högerle S et al. Comparative diagnostic value and therapeutic relevance of magnetic resonance imaging and bone marrow scintigraphy in patients with metastatic solid tumors of the axial skeleton. Eur J Radiol 2002; 43: 256-261.
55. Lauenstein TC, Goehde SC, Herborn CU et al. Whole-body MR imaging: evaluation of patients for metastases. Radiology 2004; 233: 139-148.
56. Haubold-Reuter BG, Duewell S, Schilcher BR, Marincek B, von Schulthess GK. Musculoskeletal radiology: fast spin echo MRI and bone scintigraphy in the detection of skeletal metastases. Eur Radiol 1993; 3: 316-320.
57. Yamaguchi T. Intertrabecular vertebral metastases: metastases only detectable on MR imaging. Semin Musculoskelet Radiol 2001; 5: 171-175.
58. Peh WCG, Mutarrak M. Clinics in Diagnostic Imaging. Singapore Med J 2003; 44: 101-105.
59. Schweitzer ME, Levine C, Mitchell DG, Gannon FH, Gomella LG. Bull's eyes and halos: useful MR discriminators of osseous metastases. Radiology 1993; 188: 249-252.
60. Hawighorst H, Libicher M, Knopp MV, Moehler T, Kauffmann GW, Kaick G. Evaluation of angiogenesis and perfusion of bone marrow lesions: role of semiquantitative and quantitative dynamic MRI. J Magn Reson Imaging 1999; 10: 286-294.
61. Lauenstein T, Freudenberg L, Goehde S et al. Whole body MRI using a rolling table platform for the detection of bone metastases. Eur Radiol 2002; 12: 2091-2099.
62. Keupp J, Boernert P, Aldefeld B. Continuously moving table SENSE imaging with exact reconstruction using a 16-coil array. Proc Intl Soc Magn Reson Med 2005; 13: 483-489.
63. Zenge MO, Ladd ME, Vogt FM, Brauck K, Barkhausen J, Quick HH. Whole-body magnetic resonance imaging featuring moving table continuous data acquisition with high-precision position feedback. Magn Reson Med 2005; 54: 707-711.
64. Schmidt GP, Reiser MF, Baur-Melnyk A. Whole-body imaging of the musculoskeletal system: the value of MR imaging. Skeletal Radiol 2007; 36: 1109-1119.
65. Jacobson AF, Fogelman I. Bone scanning in clinical oncology: does it have a future? Eur J Nucl Med 1998; 25: 1219-1223.
66. Moser E. Die Bedeutung der Skelettszintigraphie in der Nachsorge von Malignompatienten. Radiologe 1990; 30: 465-471.
67. Hetzel M, Hetzel J, Arslandemir C, Nussle K, Schirrmeister H. Reliability of symptoms to determine use of bone scans to identify bone metastases in lung cancer: prospective study. BMJ 2004; 328: 1051-1052.
68. Bathmann J, Sigmund G, Gufler H, Stover B, Brautigam P, Moser E. Vergleich von Skelettszintigraphie, Magnetresonanztomographie und konventioneller Rontgendiagnostik in der Fruherkennung ossarer Metastasen. Nuklearmedizin 1989; 32: A10.
69. Moser E. Knochenmetastasen — nuklearmedizinsche Diagnostik Skelett-, Knochenmarkszintigraphie oder spezifische Verfahren. Krankenhaus Arzt 1997; 70: 435-439.
70. Brink I, Moser E. Nuclear medicine for diagnostics and therapy - firm and efficient detection of skeletal metastases. Klinkarzt 2000; 29: 276-280.
71. Altehoefer C, Ghanem N, Hogerle S, Moser E, Langer M. Comparative detectability of bone metastases and impact on therapy of magnetic resonance imaging and bone scintigraphy in patients with breast cancer. Eur J Radiol 2001; 40: 16-23.
72. Layer G, Steudel A, Schuller H et al. Magnetic resonance imaging to detect bone marrow metastases in the initial staging of small cell lung carcinoma and breast carcinoma. Cancer 1999; 85: 1004-1009.
73. Steinborn M, Tilling R, Heuck A, Brugel M, Stabler A, Reiser M. Diagnostik der Metastasierung im Knochenmark mittels MRT. Radiologe 2000; 40: 826-834.
74. Steinborn MM, Heuck AF, Tiling R, Bruegel M, Gauger L, Reiser MF. Whole-body bone marrow MRI in patients with metastatic disease to skeletal system. J Comput Assist Tomogr 1999; 23: 123-129.
75. Krahe T, Nicolas V, Ring S, Warmuth-Metz M, Köster O'Rofo.

Diagnostic evaluation of full x-ray pictures and computed tomography of bone tumors of the spine. ROFO 1989; 150: 13-19.
76. Groves AM, Beadsmoore CJ, Cheow HK et al. Can 16-detector multislice CT exclude skeletal lesions during tumour staging? Implications for the cancer patient. Eur Radiol 2006; 16: 1066-1073.
77. Chung JK, So Y, Lee JS et al. Value of FDG-PET in papillary thyroid carcinoma with negative 131I whole-body scan. J Nucl Med 1999; 40: 986-992.
78. Shie P, Cardarelli R, Brandon D, Erdman W, Abdulrahim N. Meta-analysis: comparison of F-18 Fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastases in patients with breast cancer. Clin Nucl Med 2008; 33: 97-101.
79. Daldrup-Link HE, Franzius C, Link TM et al. Whole-body MR imaging for detection of bone metastases in children and young adults: comparison with skeletal scintigraphy and FDG-PET. Am J Roentgenol 2001; 177: 229-236.
80. Cook GJ, Houston S, Rubens R, Maisey MN, Fogelman I. Detection of bone metastases in breast cancer by 18b FDG-PET: different metabolic activity in osteoblastic and osteolytic lesions. J Clin Oncol 1998; 16: 3375-3379.
81. Nakamoto Y, Cohade C, Tatsumi M, Hammoud D, Wahl RL. CT Appearance of Bone Metastases Detected with FDG PET as Part of the Same PET/CT Examination. Radiology 2005; 237: 627-634.
82. Even-Sapir E, Mishani E, Flusser G, Metser U. 18F-Fluoride positron emission tomography and positron emission tomography/computed tomography. Semin Nucl Med 2007; 37: 462-469.
83. Taira AV, Herfkens RJ, Gambhir SS, Quon A. Detection of Bone Metastases: Assessment of Integrated FDG PET/CT Imaging. Radiology 2007; 243: 204-211.
84. Soderlund V. Radiological diagnosis of skeletal metastases. Eur Radiol 1996; 6: 587-595.
85. Vanel D, Bittoun J, Tardivon A. MRI of bone metastases. Eur Radiol 1998; 8: 1345-1351.
86. Petren-Mallmin M, Andreasson I, Nyman R, Hemmingsson A. Detection of breast cancer metastases in the cervical spine. Acta Radiol 1993; 34: 543-548.
87. Layer G, Steudel A, Schuller H, van Kaick G, Grunwald F. Magnetic resonance imaging to detect bone marrow metastases in the initial staging of small cell lung carcinoma and breast carcinoma. Cancer 1999; 85: 1004-1009.
88. Eustace S, Tello R, DeCarvalho V, Carey J, Melhem E, Yucel EK. A comparison of whole-body turbo-STIR MR imaging and planar 99mTc-methylene diphosphonate scintigraphy in the examination of patients with suspected skeletal metastases. Am J Roentgenol 1997; 169: 1661-1665.
89. Antoch G, Saoudi N, Kuehl H et al. Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. J Clin Oncol 2004; 22: 4357-4368.
90. Schmidt GP, Baur-Melnyk A, Herzog P et al. High-resolution whole-body magnetic resonance image tumor staging with the use of parallel imaging vs dual-modality positron emission tomography-computed tomography: experience on 32-channel system. Invest Radiol 2005; 40: 743-753.
91. Schmidt GP, Schoenberg SO, Schmid R et al. Screening for bone metastases: whole-body MRI using a 32-channel system versus dual-modality PET-CT. Eur Radiol 2007; 17: 939-949.