17 Imaging of Bone Metastases

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CONTENTS

17.1 Introduction

Renal cell carcinoma is the most common malignant neoplasm of the kidney. About 25,000 cases are diagnosed annually in the United States (Brodsky and Garnick 1989), of which 20–60% have distant metastases at the time of diagnosis (Bohnenkamp et al. 1980; Skinner et al. 1971; Takashi et al. 1995). These metastases account for about 10% of all pathologic bone fractures and 5% of cases with spinal cord compression (Nielsen et al. 1991).

Following the lung, the skeleton is the second most common site of metastasis, accounting for about 20–40% of metastases (Bohnenkamp et al. 1980; Henriksson et al. 1992). In many cases, the metastasis is diagnosed before the primary tumor. In fact, renal cell carcinoma is said to be the prototype of a tumor that presents as skeletal metastasis with a clinically occult primary tumor (Tongaonkar et al. 1992). Such cases comprise up to 48% of patients with osseous involvement (Nielsen et al. 1991) and 4% of all patients with renal cell carcinoma (Forbes et al. 1977); therefore, renal cell carcinoma must be strongly considered among differential diagnoses for any metastatic bone tumor with an unknown primary tumor (Dorfman and Czerniak 1998).

Solitary osseous metastases are relatively frequent in renal cell carcinoma, occurring in 2.5% of all renal cell carcinoma patients (Ghert et al. 2001; Saitoh 1981; Tongaonkar et al. 1992; Wilner 1982). Conversely, the most common site of solitary metastases is bone (Althausen et al. 1997; Saitoh 1981; Tongaonkar et al. 1992). Dissemination by solitary or multiple metastases will occur eventually in up to 50% of patients initially treated for localized disease (Henriksson et al. 1992; Saitoh 1981), sometimes following a long quiescent period of 10, 20, or even 30 or more years after removal of the primary tumor (Forbes et al. 1977). The reason for this long quiescent period is unknown; hypotheses include an underlying tumor-host interaction or an immune response (Hrushesky and Murphy 1973; Varkarakis et al. 1974).

Partial or complete regression of metastatic renal cell carcinoma has been reported, either spontaneously or associated with reduction of the primary tumor burden (Fidler 1992; Ibayashi et al. 1993; Kerbl and Pauer 1993); however, the reported prognoses vary widely, from dismal in some reports, with an average life expectancy of 12–24 months or even less (Dekernion et al. 1978; Jung et al. 2003; Middleton 1967; Montie et al. 1977; Skinner et al. 1971; Thompson et al. 1975), to more favorable in others, with more than a 50% survival rate after 5 years (Althausen et al. 1997).

Although the majority of skeletal metastases from renal cell carcinoma are relatively resistant to radiation and chemotherapy (Jung et al. 2003), patients with a solitary metastasis are known to have prolonged survival, especially after aggressive therapy such as radical surgical excision (Dineen et al. 1988; Huguenin et al. 1998; Middleton 1967; Montie et

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al. 1977; Tolia and Whitmore 1975; Tongaonkar et al. 1992). Surgical resection of solitary skeletal metastases has been reported to significantly prolong life (Kozlowski 1994; Smith et al. 1992; Takashi et al. 1995); therefore, it is important to recognize and diagnose skeletal metastases, to provide appropriate treatment, and to prolong survival.

17.2 Pathophysiology

Metastatic renal cell carcinomas typically have clear cell features, which are seen on microscopic examination of biopsy samples of skeletal metastases (Fig. 17.1) and which suggest a primary tumor of renal origin. About 10% of renal cell carcinomas undergo dedifferentiation into high-grade spindle cell or pleomorphic sarcomatoid carcinoma. When sarcomatoid elements are the only components present in the metastatic lesions, the lesion may be misdiagnosed as a primary bone lesion, such as a fibrosarcoma or malignant fibrous histiocytoma. In such cases, clinical findings together with appropriate markers may help to identify the metastatic nature of the lesion (Dorfman and Czerniak 1998).

Renal cell carcinomas are highly vascular tumors, and similar to their primary tumors, osseous metastases are reported to be hypervascular in 65–75% of cases (Barton et al. 1996). Life-threatening blood loss at surgery may be reduced by preoperative angiography and embolization (Layelle et al. 1998; Sun and Lang 1998).

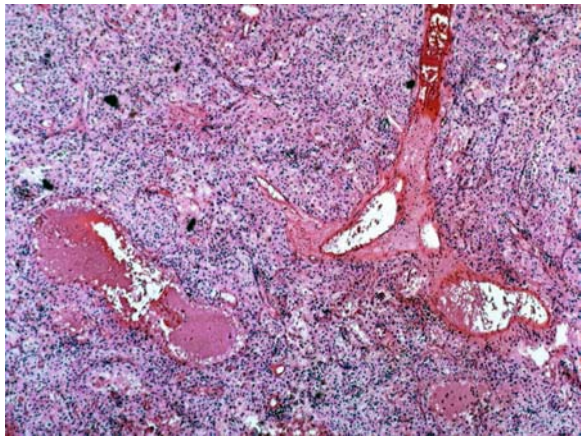


Fig. 17.1. Microscopic findings of metastatic renal cell carcinoma in the femur of a 66-year-old man. Numerous vascular structures with red blood cells surrounded by tubules and nests of cells containing small nuclei set in abundant and clear cytoplasm can be seen (Hematoxylin and eosin stain; original magnification, ×100).

Renal cell carcinoma spreads mainly in three ways: (a) by direct extension; (b) by involvement of lymphatic channels, including lymph nodes of the renal pedicle, that ultimately drain into the paraaortic, hilar, paratracheal, and mediastinal regions; and (c) by invasion of renal veins with subsequent extension to the inferior vena cava, right atrium, and pulmonary vessels, which results in pulmonary metastasis (Kim et al. 1983; Resnick and Niwayama 1995; Wilner 1982). Paravertebral vein plexus involvement results in metastasis to the axial skeleton (Kim et al. 1983).

17.3 Imaging Findings

17.3.1 Radiographic Findings

The most common sites of metastasis are the thoracolumbar spine, pelvic bone, ribs, and proximal humerus and femur, with solitary metastases most often found in the pelvis, spine, and long tubular bones (Resnick and Niwayama 1995; Saitoh 1981; Wilner 1982). Metastases in the small bones of the extremities are also reported (Forbes et al. 1977; Ghert et al. 2001). Most lesions develop in the metaphysis, but epiphyseal extension or diaphyseal lesions are also observed (Forbes et al. 1977).

The predominant radiographic finding is osteolysis (Resnick and Niwayama 1995). The lesions are either purely osteolytic or predominantly osteolytic in about 90% of cases (Figs. 17.2a, 17.3a; Wilner 1982). Mixed osteolytic and osteosclerotic patterns are found in only a minority of lesions (Fig. 17.4; Wilner 1982). Very occasionally, osteoblastic metastasis has been reported (Neugut et al. 1981). Lytic lesions may consist of a single large lytic lesion (Fig. 17.5) or patchy moth-eaten areas of bone destruction (Fig. 17.4; Wilner 1982).

Cortical involvement is another predominant and constant feature of the metastatic lesions. Erosion or gross destruction of the cortex may be present (Figs. 17.6, 17.7a; Forbes et al. 1977; Wilner 1982). Most lesions extend into the surrounding soft tissue after local destruction of the cortex; Less frequently, intramedullary extension with widening and endosteal scalloping of the lesions occurs (Fig. 17.8; Forbes et al. 1977). Periosteal reaction is rare, and if pres-

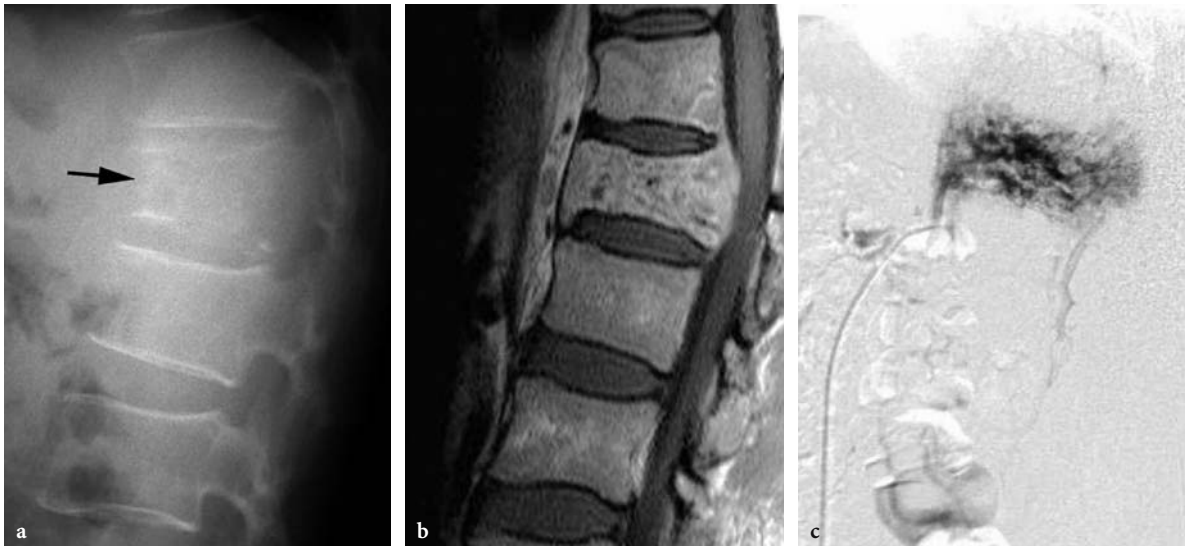


Fig. 17.2a-c. Osteolytic vertebral bone metastasis in a 54-year-old man. **a** Lateral radiograph of lumbar spine shows an osteolytic lesion at the L1 vertebral body (*arrow*), with anterior wedging, indicative of compression fracture. **b** Sagittal spin-echo T1-weighted MR image shows intermediate signal intensity masses in the T12 and L1 vertebral bodies with multiple dot-like and tubular hypointense structures within the L1 vertebral body. **c** Lateral selective angiogram shows engorged vessels with arteriovenous shunting in the L1 vertebral body. (With permission from Choi et al. 2003)

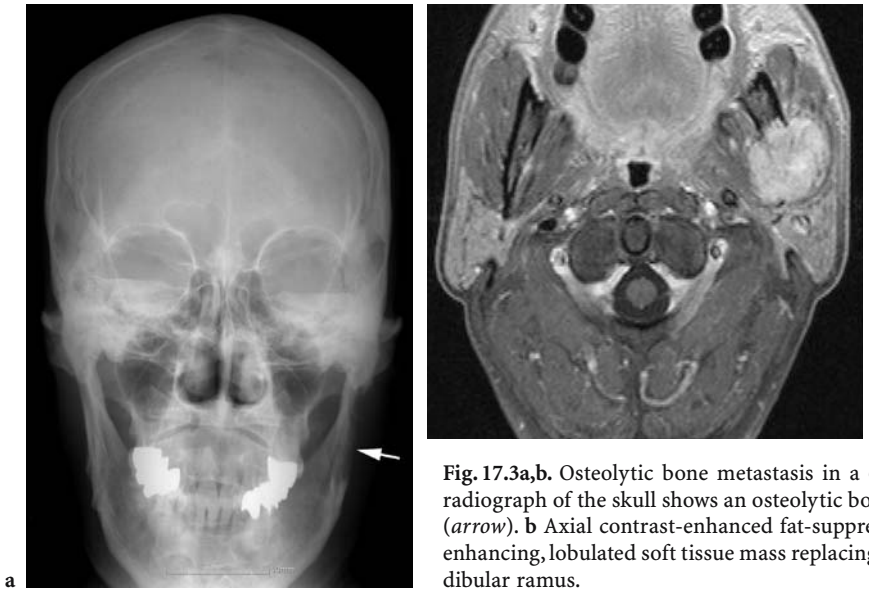


Fig. 17.3a,b. Osteolytic bone metastasis in a 64-year-old man. **a** Anteroposterior radiograph of the skull shows an osteolytic bone lesion of the left mandible ramus (*arrow*). **b** Axial contrast-enhanced fat-suppressed T1-weighted MR image shows enhancing, lobulated soft tissue mass replacing the destroyed bone in the left mandibular ramus.

ent, only faint or moderate (Wilner 1982). Margination has been described as indistinct in most cases (Fig. 17.9; Forbes et al. 1977), and more apparent than in other metastases (Figs. 17.5, 17.10a) in other reports (Wilner 1982). Margination may become more distinct after radiation therapy, but this does not have favorable implications (Forbes et al. 1977).

Another feature of the metastatic lesions is a septate appearance (Fig. 17.10a), with large, well-defined, coarse, heavy septa that traverse the area of destruction, and which is seen in about 17% of cases (Wilner 1982). Although in some studies the septate form has been deemed distinctive enough to suggest that the primary tumor is a renal cell carcinoma (Wilner 1982), the findings are neither sensitive nor specific and cannot be considered pathognomonic.

Another feature is the presence of a periosteal soft tissue mass (Figs. 17.3b, 17.11), which is related to the

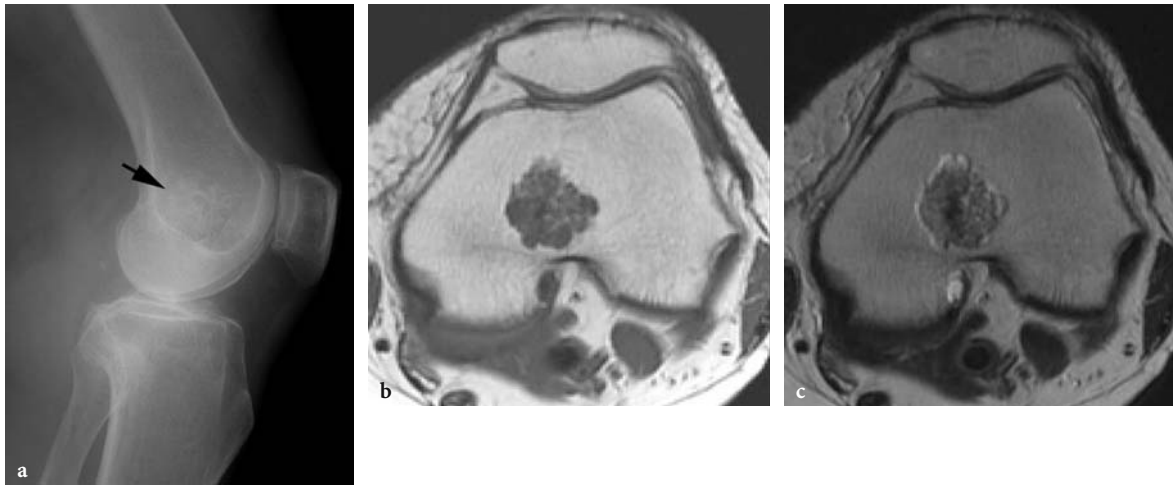


Fig. 17.4a-c. Mixed bone metastasis in an 81-year-old woman. **a** Lateral radiograph of the left knee shows an ill-defined permeative lesion with mixed osteolytic and osteoblastic foci (*arrow*) in the left distal femur. This lesion shows mixed signal intensity on axial **b** unenhanced T1- and **c** T2-weighted MR images.

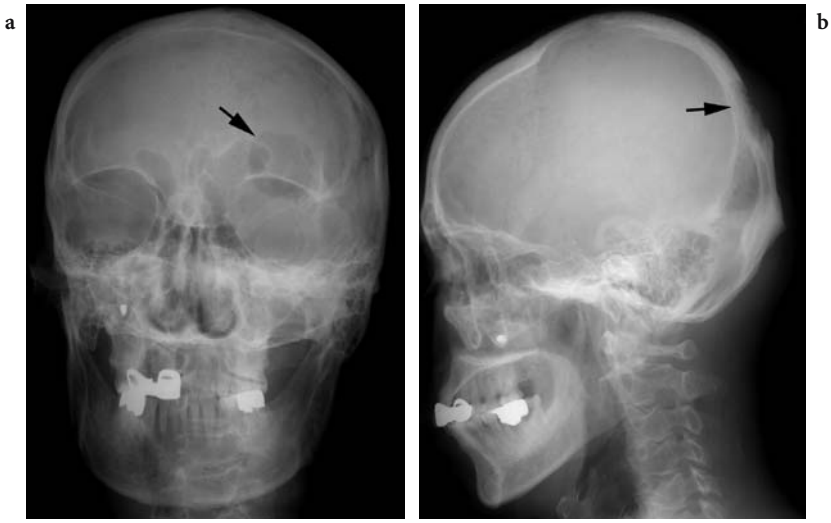


Fig. 17.5a,b. Osteolytic bone metastasis in a 67-year-old man. **a** Anteroposterior and **b** lateral radiographs of the skull show a single, large, relatively well-defined osteolytic lesion (*arrow*) with bulging soft tissue density at the left occipital bone.

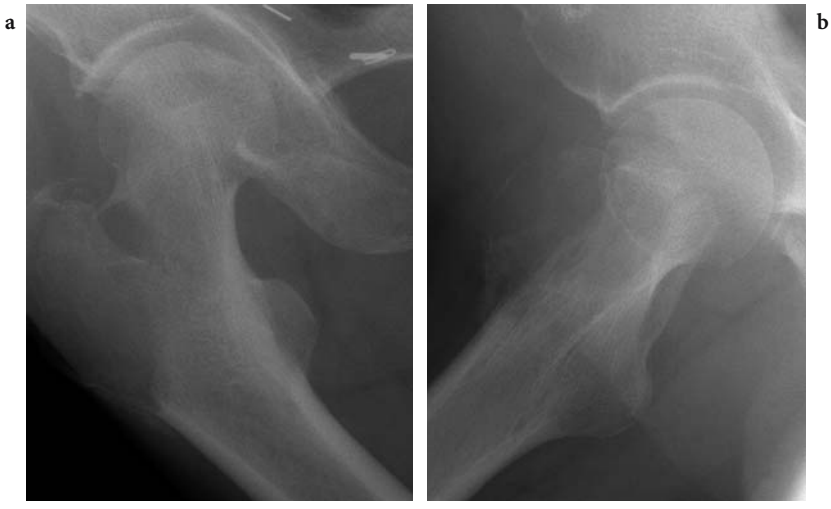


Fig. 17.6a,b. Osteolytic bone metastasis in a 66-year-old man. **a** Anteroposterior and **b** lateral radiographs of the right proximal femur show an ill-defined osteolytic lesion of slightly expansile nature accompanied by focal destruction of the cortex, mainly involving the greater trochanter area.

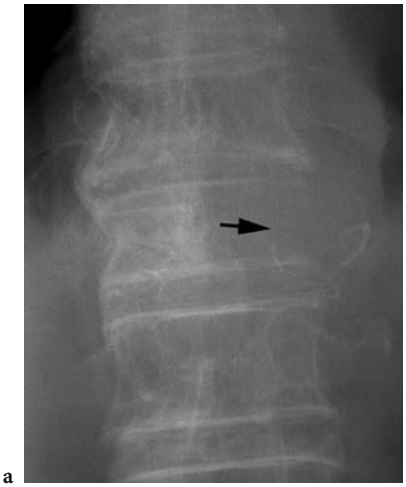
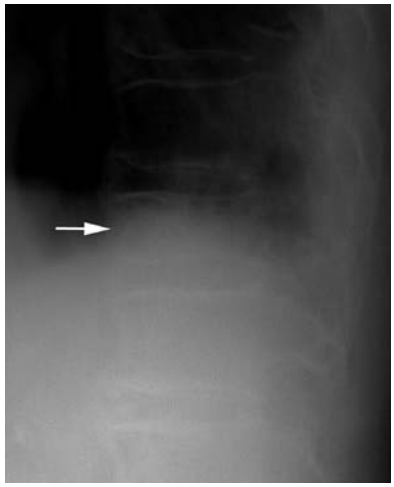
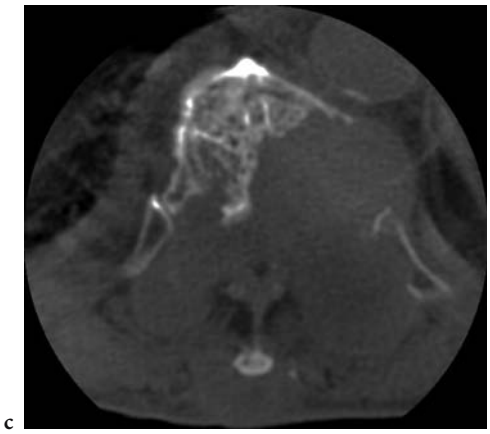
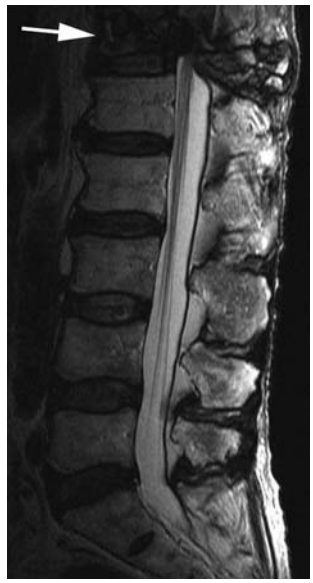
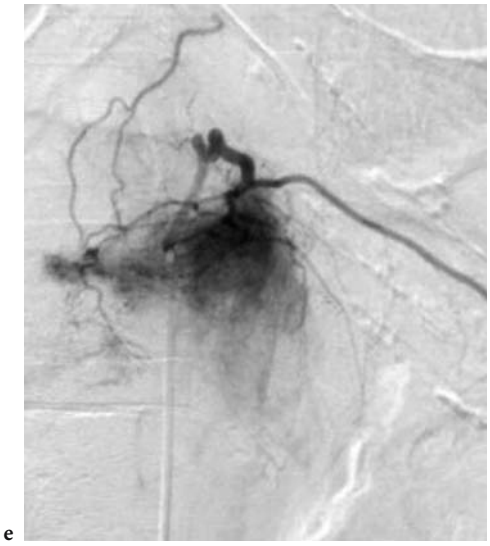






Fig. 17.7a-e. Metastatic vertebral compression fracture in an 87-year-old man. **a** Anteroposterior radiograph of the thoraco-lumbar spine junction shows cortex destruction at the left side of the T12 vertebral body with obliteration of the left pedicle (*arrow*). **b** Lateral radiograph of the thoraco-lumbar spine shows decreased vertebral body height of the T12 vertebral body (*arrow*). **c** Axial CT scan at the level of the T12 shows bone destruction with soft tissue mass formation. **d** Sagittal T2-weighted MR image demonstrates compression fracture with fracture line (*arrow*). **e** Selective angiogram shows hypervascular mass with supply from the T11 intercostal artery.

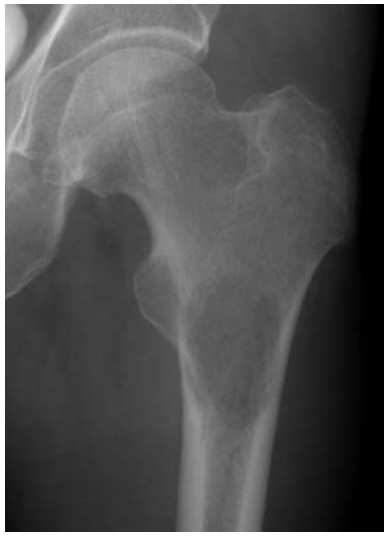


Fig. 17.8. Osteolytic bone metastasis in a 65-year-old man. Anteroposterior radiograph of the left proximal femur shows an ovoid, somewhat ill-defined osteolytic metadiaphyseal lesion with intramedullary extension and slight endosteal scalloping.

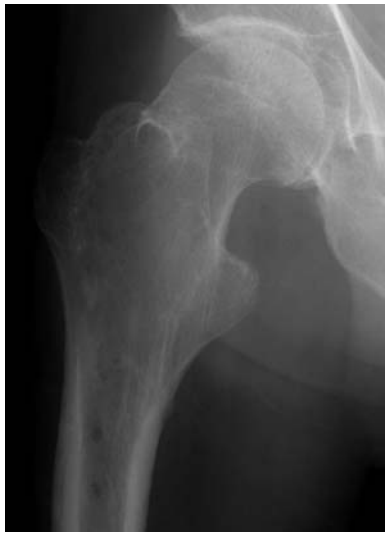


Fig. 17.9. Osteolytic bone metastasis in a 67-year-old man. Anteroposterior radiograph of the right proximal femur shows an ill-defined osteolytic metaphyseal lesion.

size of the osseous component of the tumor (Forbes et al. 1977; Wilner 1982). Pathologic fracture may occur, most frequently in the spine (Figs. 17.2a, 17.7b) and long tubular bones, and may be accompanied by marked bone destruction (Forbes et al. 1977; Wilner 1982).

Calcifications are only rarely seen (Fig. 17.11d) before radiation therapy but are seen more frequently in either the adjacent soft tissue or within the bone itself after radiation therapy (Forbes et al. 1977).

Joint destruction or involvement of a synovial-lined joint is unusual, although lesions in the pelvis or sacrum with extension across the sacroiliac joint are seen occasionally (Fig. 17.12a; Forbes et al. 1977).

When a septate, osteolytic solitary lesion is seen, differential diagnoses may include giant cell tumor, angiomatous lesions, solitary myeloma, and metastatic tumors of nonrenal primary origin (Wilner 1982). When an osteolytic lesion is located in the cortex, further differential diagnoses may include subperiosteal osteosarcoma, chondrosarcoma, or a primary soft tissue sarcoma with bone invasion (Coerkamp and Kroon 1988). When a solitary cortical lesion with distinct margin is observed, diagnostic considerations may include fibrous cortical

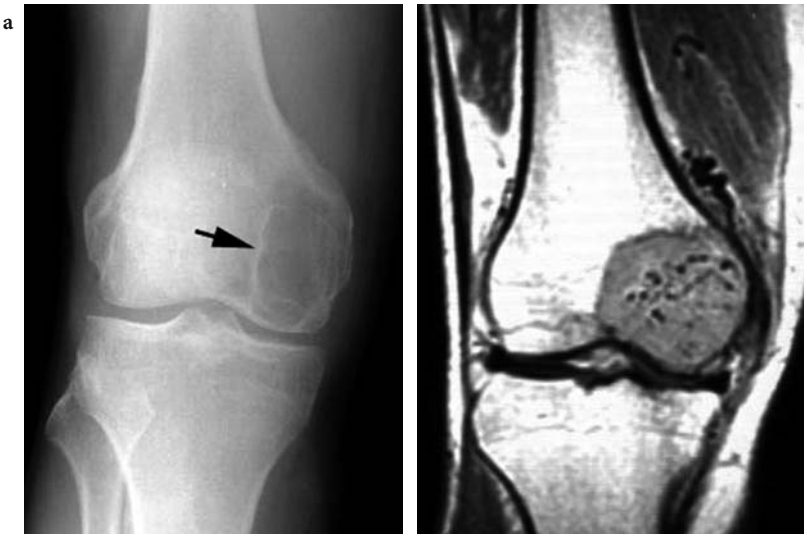


Fig. 17.10a,b. Osteolytic bone metastasis in a 61-year-old man. **a** Anteroposterior radiograph of the right knee shows a partially well-defined osteolytic lesion with suspicious internal septa (*arrow*) in the medial femoral condyle epiphysis. **b** Coronal spin-echo T1-weighted MR image shows hypointense mass with multiple, very hypointense dot-like or tubular structures inside and adjacent to the mass. (With permission from Choi et al. 2003)

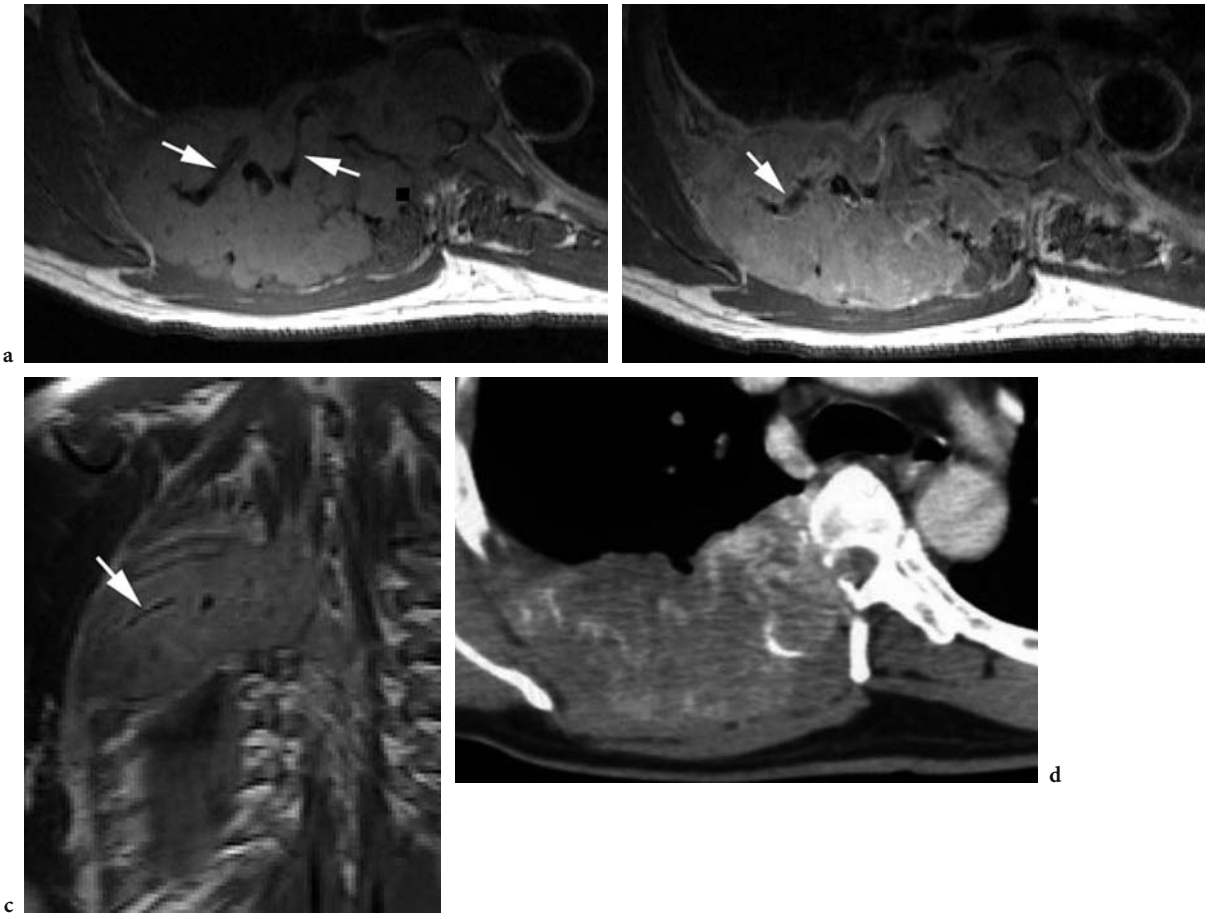


Fig. 17.11a-d. Rib metastasis in a 54-year-old man. **a** Axial unenhanced T1-weighted MR image shows a large hyperintense soft tissue mass lesion with signal intensity higher than muscle. The lesion demonstrates enhancement on **b** axial and **c** coronal contrast-enhanced T1-weighted MR images. On all MR images, multiple tubular and dot-like dark signal intensity structures (*arrows*) are noted within the mass, suggestive of "flow void". **d** Axial CT scan shows hyperdense foci within the lesions, which are partly due to enhancing vessels as well as to calcifications probably from bone destruction. (With permission from Choi et al. 2003)

defect, brown tumor in hyperparathyroidism, osteoid osteoma, fibrous dysplasia, Brodie abscess, plasmacytoma, adamantinoma, lipoma, or hemangioma (Willinsky et al. 1982).

17.3.2 CT and MR Imaging Findings

Little has been reported about the CT and MR imaging findings of metastatic lesions from renal cell carcinoma, probably due to the lack of specificity of the findings. Magnetic resonance imaging has become a common technique for evaluation of bone and soft tissue tumors and yet it lacks specificity. A case report on the tissue characterization of renal cell carcinoma and its osseous metastasis on MR imaging reported similar signal intensities from the renal cell carcinoma and the metastatic lesion (Pettersson et al. 1985); however, signal intensity of the lesions varies (Choi et al. 2003). Most lesions show enhancement well (Choi et al. 2003). There is a report on the significance of the "flow-void" sign seen in osseous metastases of renal cell carcinoma on MR imaging, which are numerous dot-like or tubular structures of low signal intensity and represent dilated vessels supplying or draining the tumor (Figs. 17.2b, 17.10b, 17.11). Although the sensitivity and specificity of this sign have not been determined, awareness of the sign may help in suggesting the diagnosis and planning treatment of an occult or forgotten primary renal tumor (Choi et al. 2003).

Both CT and MR imaging may help in visualization of the bone destruction and defining the extent of the tumor (Figs. 17.12a, 17.13). In addition, Com-

puted tomography may help to detect the presence and amount of calcification (Fig. 17.11d) or new bone formation.

17.3.3 Angiography

Angiography reveals the hypervascular nature of the metastatic lesions in renal cell carcinoma (Figs. 17.2c, 17.7e; Bowers et al. 1982). Transcatheter embolization of the metastatic tumor has been advocated for preoperative arterial embolization to reduce bleeding at surgery, to reduce the viable tumor burden in patients with unresectable metastases, and to relieve pain in intractable cases with bone pain (Barton et al. 1996; Bowers et al. 1982).

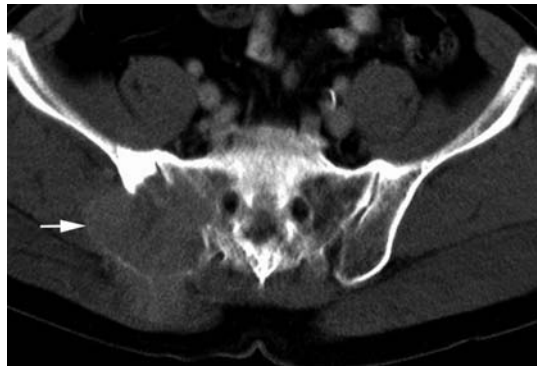
17.3.4 Radionuclide Imaging

Bone scanning has been deemed superior to radiography, although a normal bone scan result does not mean the absence of bone metastases (Cole et al. 1975; Kim et al. 1983).

Different tracers have been used in skeletal bone scintigraphy for screening of metastases, including Tc-99m methylene diphosphate (MDP), Tc-99m sodium medronate, Tc-99m pyrophosphate, and Tc-99m 2,3 dimercaptosuccinic acid (Borzutzky and Turbiner 1985). Scanning of photopenic metastases, i.e., metastases with an absence of uptake on bone scans, may be affected by the following factors: size of the lytic area; relative lack of reactive new bone formation; lack of significant hyperemia; and infarction of area due to obstruction of its supply vessels by tumor cells (Borzutzky and Turbiner 1985). The sensitivity of bone scanning is reported to vary, from 33 to 94%, and specificity is reported to be 86% (Koga et al. 2001; Wilner 1982).

In a relatively recent report, the authors advocated omitting bone scans in patients with stage T1-3aN0M0 tumors and no pain (Koga et al. 2001); however, bone scans still remain useful in early detection of metastasis and localizing the site of metastasis (Fig. 17.12b; Koga et al. 2001).

The role of positron emission tomography (PET) in oncology is expanding rapidly (Hain and Maisey 2003). In renal cancer, PET can define the primary tumor, provide better staging of local recurrence than CT, and can define metastatic disease (Hain



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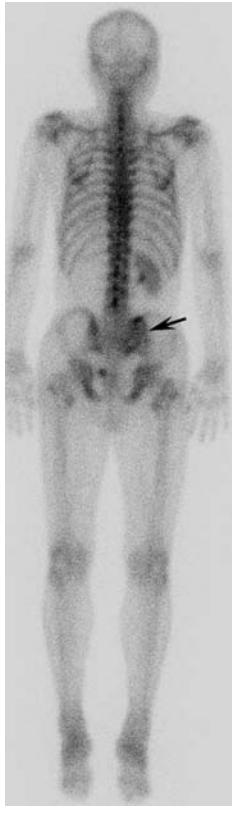

b

Fig. 17.12a,b. Osteolytic bone metastasis in a 62-year-old man. **a** Axial contrast-enhanced CT scan of the pelvis shows an osteolytic lesion with soft tissue mass formation and extension into the right sacral ala well (*arrow*). **b** Posterior view of whole-body Tc-99m MDP bone scan shows increased uptake around the right sacroiliac joint area (*arrow*).

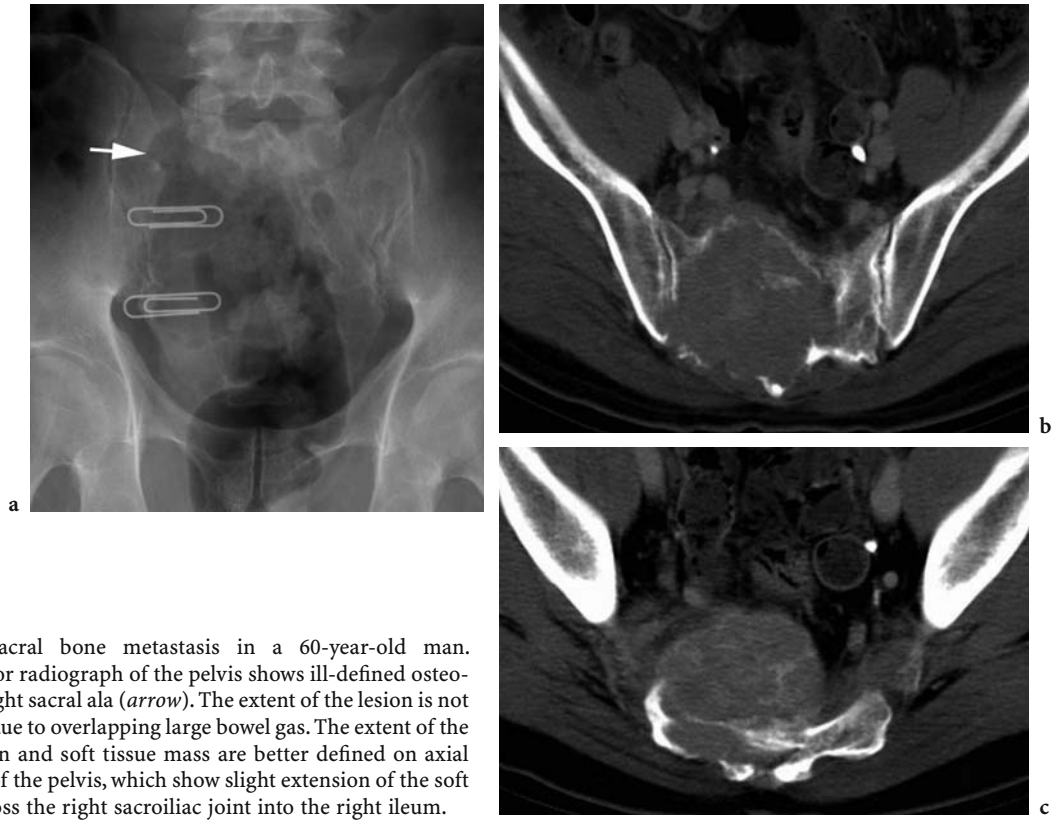

Fig. 17.13a-c. Sacral bone metastasis in a 60-year-old man. **a** Anteroposterior radiograph of the pelvis shows ill-defined osteolytic lesion in right sacral ala (*arrow*). The extent of the lesion is not well visualized due to overlapping large bowel gas. The extent of the bone destruction and soft tissue mass are better defined on axial CT scans (**b**, **c**) of the pelvis, which show slight extension of the soft tissue mass across the right sacroiliac joint into the right ileum.

and Maisey 2003). Although PET has been deemed not as good as bone scans for defining bone metastases, there have been case reports in which PET detected bone metastases not identified on bone scanning as well as intramedullary spinal cord metastases (Poggi et al. 2001; Seto et al. 2000). The role of PET in imaging of bone metastases in renal cell carcinoma remains to be clarified.

17.4 Skeletal Metastases in Pediatric Renal Tumors

Many pediatric tumors metastasize to the skeleton. The best-known metastasizing tumor of renal origin in children is Wilms tumor. The reported incidence of skeletal metastases from Wilms tumor varies, ranging from 0.5 to 13% (Lamego and Zerbini 1983; Marsden and Lawler 1978). Skeletal metastases, when present, are associated with widespread tumor (Bond and Martin 1975). The metastatic lesions of Wilms tumor have been described as predominantly lytic with either permeative, or more commonly, geographic patterns of bone destruction and poorly defined margins (Masselot et al. 1972; Rudhe 1969).

However, results of several studies analyzing bone-metastasizing renal tumors of children indicate that in many of the cases the bone metastases were actually from primary renal tumors other than Wilms tumor (Lamego and Zerbini 1983; Marsden and Lawler 1978). This distinct type of tumor became known as "bone metastasizing renal tumor of childhood" as described by Marsden et al. (1978) after its first identification by Kidd (1970). Then the tumor was renamed with the descriptive term "clear cell" proposed by Beckwith and Palmar to distinguish it from malignant rhabdoid tumor of the kidney (Parikh et al. 1998); hence, it became known as clear cell sarcoma of the kidney. It is an uncommon tumor and accounts for about 4% of all pediatric renal tumors, primarily affecting young children with a mean age of 3 years (Dorfman and Czerniak 1998; Parikh et al. 1998). It is an entity distinct from Wilms tumor, with an aggressive clinical behavior and poorer prognosis than Wilms tumor and a very high rate of skeletal metastases, ranging from 42 to 69% (Parikh et al. 1998; Green

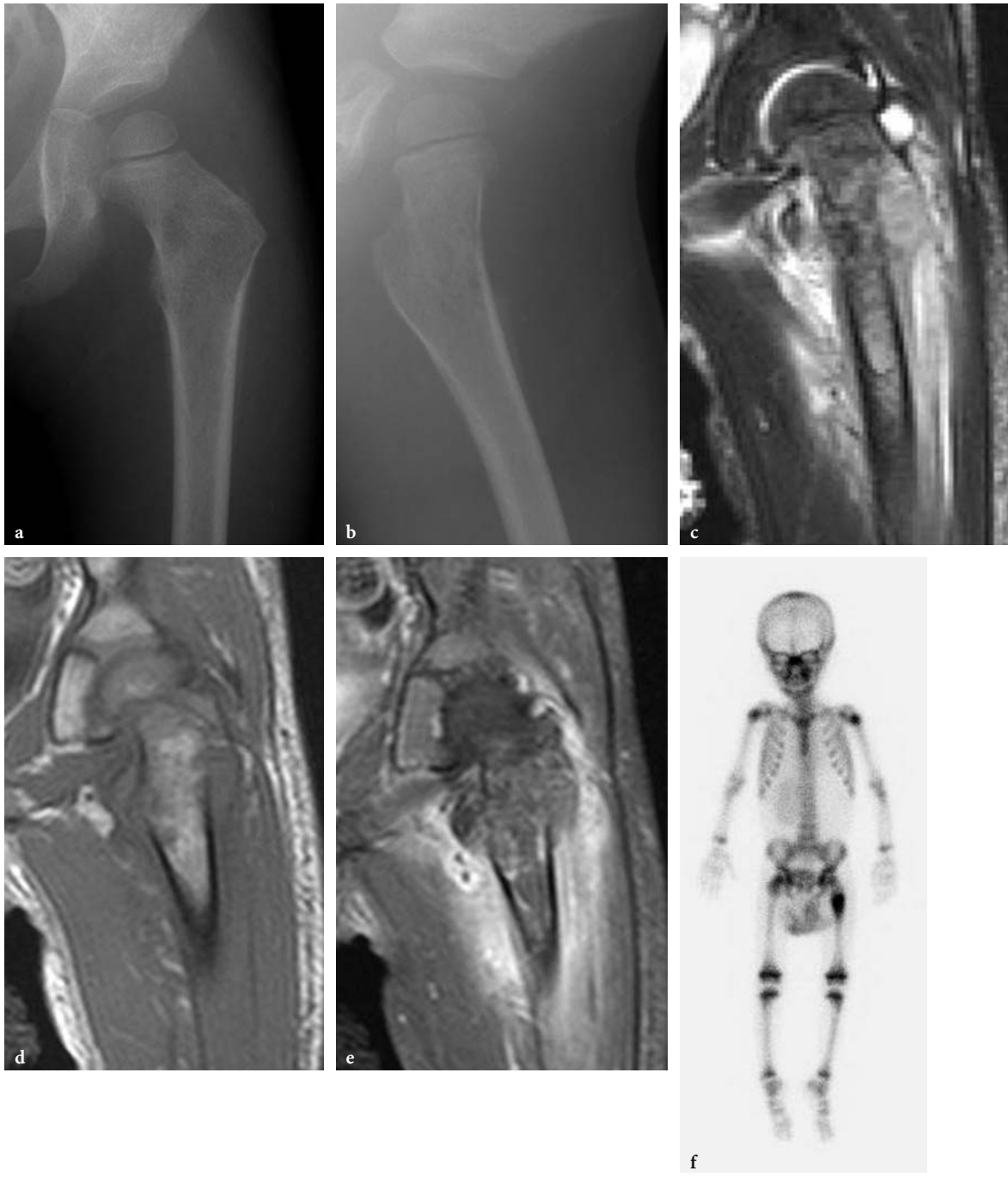

Fig. 17.14a-f. Osteolytic bone metastasis in a 3-year-old girl with clear cell sarcoma of the kidney diagnosed 6 months previously. **a** Anteroposterior and **b** lateral radiographs of the left femur reveal an ill-defined osteolytic lesion at the left proximal femoral metadiaphysis. **c** Coronal fat-suppressed T2-weighted MR image shows cortex destruction and extension of hyperintensity into surrounding muscles. **d** Coronal unenhanced T1-weighted MR image shows an infiltrative hypointense lesion at the left proximal femur. **e** Coronal contrast-enhanced fat-suppressed T1-weighted MR image shows diffuse and heterogeneous enhancement within the lesion and in the surrounding muscles. **f** Anteroposterior whole-body Tc-99m MDP bone scan shows intense focal uptake in the left proximal femur.

et al. 1997). In one series, the radiological aspects of the metastases were variable, with some lytic lesions (Fig. 17.14) as well as violently permeative lesions (Lamego and Zerbini 1983). In other studies, the osseous metastases consisted mainly of multiple lytic lesions (Marsden et al. 1978; Marsden and Lawler 1980). Not much is known about the CT and MR imaging findings of clear cell sarcoma metastasis (Fig. 17.14).

Similar to renal cell carcinoma in adults, skeletal metastases are frequently manifestations of an occult primary tumor (Dorfman and Czerniak 1998). Microscopically, they are described as having a somewhat variable pattern of undifferentiated round-cell and clear-cell features that are negative for epithelial cell markers and that stain with vimentin (Dorfman and Czerniak 1998).

17.5 Conclusion

In conclusion, osseous metastases from renal cell carcinoma are characterized by mainly osteolytic lesions in the metaphysis of, most commonly, the spine, pelvic bone, ribs, and proximal long bones with cortical involvement. Solitary lesions with septa are not uncommon. Both CT and MR imaging may help in defining the extent of the lesion and presence of a periosteal soft tissue mass. The presence of "flow-void" sign on MR imaging may suggest the primary origin of a metastatic bone lesion and also suggest its hypervascular nature, which may also be confirmed by angiography. Bone scanning is still used in detection of metastasis and may help in localization.

Although a rare entity, clear cell sarcoma of the kidney in children metastasizes to the bone readily and is characterized by osteolytic lesions, which may be the first manifestation of a clinically occult tumor.

Acknowledgements
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