Preface

During the past two decades, and even more so in the last five years, radiology has evolved at a tremendous pace, and imaging technology continues to make great advances into morphological, as well as functional, aspects of oncologic diseases. Developments in computed tomography (CT) have led to the introduction to ultrafast, high-resolution single-source and dual-source multislice scanners. Positron emission tomography (PET) has stepped into the clinical limelight with the availability of vastly improved structural co-registration and overall improved diagnostic performance from recently developed PET-CT hybrid scanners. Magnetic resonance imaging (MRI) has become faster and more versatile with high magnetic strength systems, MR spectroscopy, diffusion weighted MRI, and flow mapping. Oncologic imaging guided interventional techniques such as radio frequency ablation, microwave and cryoablation procedures have also progressed immensely.

From an oncologic point of view, these developments have improved patient care. Today, the role of imaging extends beyond traditional detection, localization, characterization, staging, follow-up and treatment of patients with cancer. CT is currently being investigated as a screening tool for colon and lung cancer. MRI has emerged as a modality of choice for imaging many cancers including hepatic, adrenal and most musculoskeletal cancers. Hybrid PET-CT scanners provide combined morphologic and functional information for tumor detection, and assessment of early tumor response to treatment. The growing, dynamic collaboration between the radiologic and oncologic communities is important to foster to ensure cancer patients receive optimal care.

This book, "Imaging in Oncology," describes the current status of imaging techniques in oncology, with the help of specialized contributions from world-renowned oncologic imaging experts.

1
Anatomic, Physiologic and Metabolic Imaging in Neuro-Oncology

Sanjeev Chawla, Harish Poptani, and Elias R. Melhem

1 Introduction

Primary brain tumors arise from various cell types of the brain, including glial cells, neurons, neuroglial precursor cells, pinealocytes, pericytes of the vessels, cells of the hypophysis, lymphocytes and the meninges [1, 2]. The incidence of primary brain tumors varies between subtypes, with the most common primary brain tumors in adults being gliomas and meningiomas.

Gliomas can be histologically classified into astrocytomas, oligodendrogliomas, mixed oligoastrocytomas, ependymal tumors and tumors of the choroid plexus. Tumor malignancy or grade is generally assessed according to the World Health Organization (WHO) criteria, taking into account the presence of nuclear changes, mitotic activity, endothelial proliferation and necrosis [1, 3]. The most fatal and common primary brain neoplasm is the glioblastoma multiforme (GBM), which corresponds to WHO grade IV. Despite aggressive multimodal treatment strategy (surgery, radiation and chemotherapy), median survival of patients with GBM is limited to less than 14 months. A complex series of molecular events occur during tumor growth resulting in dysregulation of the cell cycle, alterations in apoptosis and cell differentiation, neo-vascularization as well as tumor cell migration and invasion into the normal brain parenchyma. Genetic alterations also play an important role in the development of glioma, including a loss, mutation or hypermethylation of the tumor suppressor gene, such as p53 or other genes involved in the regulation of the cell cycle. During progression from low-grade to high-grade, step-wise accumulation of genetic alterations occurs. Growth of certain tumors seems to be related to the presence of viruses and familial diseases that accelerate the progression of molecular alterations, or exposure to environmental chemicals, pesticides, herbicides and fertilizers [4-6].

A better understanding of tumorgenesis is crucial for the development of specific molecular therapies that specifically target the tumor and reduce patient morbidity and mortality. Positron emission tomography (PET), computed tomography (CT) and magnetic resonance imaging (MRI) are generally used for non-invasive diagnosis and

Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania, United States

M.A. Blake and M.K. Kalra (eds.), *Imaging in Oncology.*

understanding of tumor growth mechanism. Cranial CT and MRI, with and without contrast media, are widely used for primary diagnosis of brain tumors. CT is used for detection of calcifications in oligodendrogliomas, meningiomas or craniopharyngiomas, and for tumors that are located at the base of the skull. However, the discrimination of tumor boundaries from normal tissue or vasogenic edema, as well as the evaluation of tissue heterogeneity and tumor grading are often a challenge and are not adequately reflected on CT. Furthermore, the use of ionizing radiation and image acquisition only in the axial plane, limits its applicability.

PET uses various radioactive agents to detect differences in metabolic and chemical activity in the body. PET measures a wide range of physiologic processes critical in understanding the pathophysiology of brain tumors with high sensitivity. It allows for detection of metabolic changes that occur prior to structural changes visible on CT and conventional MR images. However, the major limitation of PET is its relatively poor spatial resolution and a high incidence of false positives.

Continuous developments in MRI provide new insights into the diagnosis, classification and understanding of the biology of brain tumors. MRI offers several advantages compared to CT and PET. MRI offers excellent spatial resolution ($1 \times 1 \times 1\,mm^3$ in humans), very high gray-white matter contrast and acquisition of multiplanar images. MRI is particularly accurate in establishing the intra- or extra-axial origin of tumors. The use of three-dimensional (3-D) image acquisition and reconstruction with MRI is not only limited to diagnosis, but is also useful for pre-surgical planning, stereotactic procedures and radiotherapy. Despite optimization of sequences and protocols, the classification and grading of gliomas with conventional MRI is sometimes unreliable, with the sensitivity for glioma grading ranging from 55.1 percent to 83.3 percent [7]. Integration of diagnostic information from advanced MRI techniques like proton magnetic resonance spectroscopy (^{1}H MRS), diffusion and perfusion-weighted imaging and functional MRI (fMRI) can further improve the classification accuracy of conventional anatomical MRI [8]. Advanced MRI techniques are also being used to gain additional information on metabolic and molecular tumor markers [9, 10]. In selected patients, MRI and PET are being used in conjunction to define the real extent of the tumor [11].

2 Magnetic Resonance Imaging

2.1 Diagnosis and Grading of Brain Tumors

2.1.1 Conventional MRI

General Features of Brain Tumors

Due to the excellent soft tissue contrast and high spatial resolution, MRI provides exquisite anatomical details that aid in diagnosis, classification and understanding the biology of brain tumors. A routine MRI examination of patients with brain

tumors includes long TR/long TE (T2-weighted), short TR/short TE (T1-weighted), fluid-attenuated inversion recovery (FLAIR) and post-contrast T1 sequences. Detection of a tumor is based primarily on the presence of mass effect and signal alteration on these imaging sequences. The three main variables that differentiate tumors from normal tissue are: water content, regressive events and vascular architecture. Most brain tumors exhibit increased water content and, thus, appear hyperintense on T2-weighted and FLAIR images, and hypointense on T1-weighted images (Fig. 1.1 a,b, c and Fig. 1.2a,b, c). This hyperintensity is more pronounced in masses having a low nucleus/cytoplasm ratio (e.g., astrocytoma), than in masses with a high nucleus/cytoplasm ratio (e.g., medulloblastoma). The peritumoral hyperintensity on T2-weighted images is generally nonspecific and is thought to be due to tumor infiltration, vasogenic edema, or both.

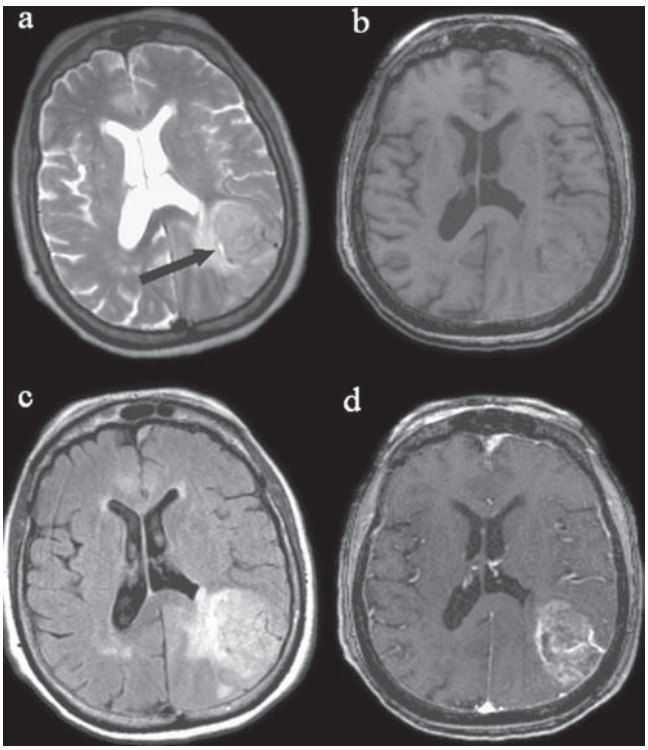

Fig. 1.1 High-grade glioma. Axial T2-weighted image (**a**) demonstrates an ill-defined, hyperintense (compared to gray matter), heterogeneous mass in the left parietal lobe along with vasogenic edema along the white matter tracts. Note the presence of necrotic foci (arrow) within the tumor. This mass appears as iso to hypointense on T1-weighted image (**b**) and hyperintense on FLAIR image (**c**). There is a heterogeneous contrast enhancement within the mass on the corresponding post contrast T1-weighted image (**d**)

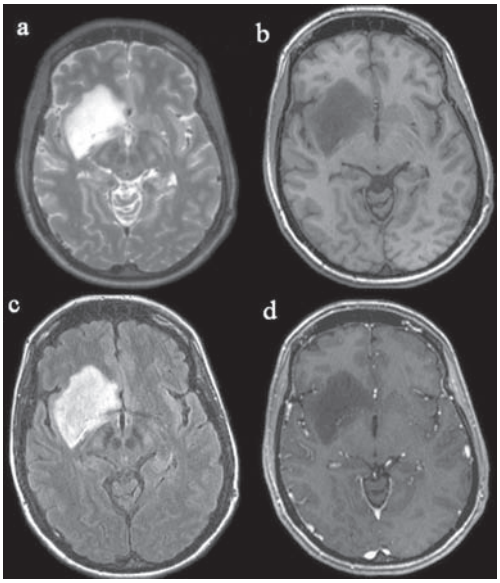

Fig. 1.2 Low-grade glioma. Axial T2-weighted image (**a**) demonstrates a homogenously hyperintense mass in the insular region extending into the right frontal lobe. This mass is well circumscribed with minimal mass effect and edema that appears hypointense on T1-weighted image (**b**) and hyperintense on FLAIR image (**c**). There is no evidence of abnormal contrast enhancement on the post contrast T1-weighted image (**d**)

Regressive events such as cyst formation, necrosis and hemorrhage, calcifications and fatty degenerative areas modulate the MRI appearance of brain tumors. Intratumoral cysts are secondary to focal mucoid degeneration and fluid transudation from cyst walls. Cysts can be filled with water, or contain considerable amounts of protein or other debris from prior hemorrhage. If the cyst contains water only, it has the same signal intensity as cerebrospinal fluid (CSF) on T2- and T1-weighted images. When the protein content increases, protons become bound in a hydration layer adjacent to the protein, significantly decreasing the T1 relaxation time of water, leading to an increase in the signal intensity on FLAIR and T1-weighted images. Necrotic areas result from ischaemic cell damage or intratumoral hemorrhagic events that result in the formation of pseudocystic areas. These areas typically appear hyperintense on T2 and hypointense on T1-weighted images, compared to normal brain parenchyma.

Certain primary intracranial neoplasms and metastatic tumors demonstrate hemorrhage and calcification [12]. Both chronic hemorrhage and calcifications appear hypointense on T2 and T2-weighted images, due to the induction of paramagnetic susceptibilities [13]. Recently, corrected gradient echo phase imaging has been used to differentiate hemorrhage and calcification [14, 15]. An abnormal vascular architecture is a feature that is generally observed in tumors. Stimulation of the formation of new capillaries (neo-vasculature) within the tumor tissue is facilitated

by hypoxia and endothelial growth factor receptors (EGFR). In malignant gliomas, formation of capillaries with fenestrated endothelia is stimulated, which leads to disruption of the blood-brain barrier (BBB) and contrast enhancement [16], as shown on Fig. 1-1d. On the other hand, in some tumors with a functioning BBB, these capillaries exhibit near-normal features, hence, these tumors do not enhance on contrast-enhanced T1-weighted images [16] as shown on Fig. 1.2d.

Metastatic tumors are characterized by the presence of typically leaky, non-central nervous system capillaries similar to their tissue of origin and, hence, exhibit intense enhancement. Extra-axial tumors, like meningiomas, arise from tissue whose capillaries lack tight junctions and, consequently, these tumors also exhibit contrast enhancement [16]. While the extent of a tumor in the brain can be evaluated by contrast enhancement, it is known that invasive tumor cells are also present beyond the enhancing portion of the tumor, particularly in gliomas. Since contrast enhancement on conventional MRI indicates disruption of BBB and not underlying regional vascularity, it cannot be used to predict histological grade [17]. However, Fayed, et al. [18] have reported a significant difference in the contrast-to-noise ratio (CNR) of gadolinium-enhancement between low- and high-grade gliomas. Using a CNR threshold of 35.86, these authors reported a sensitivity of 82.6 percent and a specificity of 91.7 percent for the prediction of malignancy.

Besides primary information on the size and location of the tumor, conventional MRI (T1, T2 and post-contrast T1 images) provides additional information about secondary phenomena such as mass effect, edema, hemorrhage, necrosis and signs of increased intracranial pressure.

General Features that Differentiate Intra-axial from Extra-axial Tumors

Differentiation between intra-axial and extra-axial masses is crucial as clinical management of these tumors is different [19]. This distinction has been made easier by multiplanar capabilities of MRI. Key features that help in identifying an intra-axial mass include gyral expansion, thinning or effacement of the adjacent extra-axial subarachnoid space and peripheral displacement of blood vessels along the pial surface of the brain (best seen on contrast-enhanced images) [19]. Imaging features more characteristic of extra-axial intradural masses include local bony changes such as hyperostosis, or widening of pre-existing foramina or canals; displacement of brain surface vessels away from bone and dura; white matter buckling, and widening of the subarachnoid space adjacent to the mass; central displacement of both the gray-white junction and presence of blood vessels along the pial surface. Extradural masses show similar behavior, but they usually displace the dural sheet centrally [19].

Common Brain Tumors Occurring in Adults

Intra-axial Tumors

The most common tumors of intra-axial location are gliomas and metastases. Gliomas derived from brain cells can, thus, be classified as true brain tumors,

2
Imaging of Spinal Tumors

Izlem Izbudak[1], Aylin Tekes[1], Juan Carlos Baez[2], and Kieran Murphy[3]

Key Points

- Primary spinal tumors are rare, metastasis to spine is common and comprise 90 percent of spinal column tumors.
- The advent of MRI revolutionized the characterization of spinal tumors by providing detailed direct visualization of the bone marrow and spinal cord in multiple planes, allowing earlier detection and treatment for both intradural and extradural tumors.
- Sagittal T1-weighted and STIR images are the most sensitive sequences for the bone marrow lesions, even in the early phase. Contrast-enhanced T1-weighted images are more sensitive when fat-saturation is applied.
- Whole body MRI with STIR sequence is currently possible in a short scan time revealing metastatic disease in both the spine and in solid organs.
- Differentiating osteoporotic acute compression fractures of the vertebra from malignant compression fractures is challenging even with MRI. MR techniques, such as DWI or chemical shift imaging, have been studied and quantitative techniques might be helpful.
- Early signs of cord or cauda equina compression is progressive sharp nerve root pain aggravated by bending or coughing; a limited sagittal T2-weighted MRI of the spine would be enough to evaluate compression.
- Most (90 percent to 95 percent) of the intramedullary tumors are malignant and predominantly composed of glial components. The most common types are ependymomas in adults and astrocytomas in children.
- Advanced imaging techniques such as MR spectroscopy, DWI, MT, and functional studies are currently limited by the strong magnetic field inhomogeneities

[1] Johns Hopkins University, Department of Radiology, Neuroradiology Division.

[2] Johns Hopkins University, School of Medicine.

[3] Johns Hopkins University, Department of Radiology, Neurointerventional Division

Corresponding author:
Izlem Izbudak, MD, 1211 Asquith Pines Place, Saverna Park, Arnold, MD 21012
e-mail: iizbuda1@jhmi.edu

M.A. Blake and M.K. Kalra (eds.), *Imaging in Oncology.*

present in the spinal cord region, respiratory and cardiac movements, and the small size of the spinal cord.
- We recommend the use of vertebroplasty for painful destructive vertebral lesions. The few complications reported have mostly been related to excessive cement injection, underlining the need of excellent imaging conditions to control the cement injection.

Spinal tumors can be grouped into 2 main categories: extradural (bone) and intradural. Intradural tumors are further grouped into intradural/intramedullary and intradural/extramedullary components.

Oncologists more commonly treat extradural malignant spinal tumors. Therefore, we will concentrate more on this group of tumors, complications such as compression fractures or cord compression and the percutaneous therapy with vertebroplasty. Relatively common benign and malignant primary bone tumors of the vertebrae are also briefly discussed, as well as the common intradural extramedullary and intradural intramedullary tumors.

1 Extradural Tumors

1.1 Malignant

1.1.1 Metastasis

The spine is a common site for metastatic disease of the breast, prostate, lung, kidney, thyroid, uterine carcinoma and melanoma. The lumbar spine is the most affected, followed by thoracic, cervical spine and sacrum [1]. Once established in an osseous location, metastatic tumor cells activate osteoclasts, which ultimately lead to bone resorption. [2, 3]. Direct tumor cell bone lyses also ensues.

Conventional radiographs show metastatic bone lesions only after the loss of more than 50 percent of the bone mineral content at the site of the disease. However, they are helpful for characterization of the lesion as lytic, blastic or mixed. Additionally the fracture risk is traditionally determined on plain radiographs [4].

Computed tomography (CT) is valuable as an adjunct in detailing osseous anatomy, character and extent of the specific lesion. Also CT is used for guiding biopsies for previously detected vertebral lesions.

MRI is a sensitive modality for the detection of metastatic disease and sometimes it provides improved specificity in characterization of the lesion. MRI can evaluate the lesion, its intramedullary and extramedullary extent, the degree of cortical involvement, the absence or presence of periosteal involvement and the extent of the soft tissue mass. Another advantage of MRI is to detect compressive myelopathy.

The vertebral metastasis may be focal or diffuse, and diffuse metastasis may show a homogenous or heterogenous signal pattern on MRI. Diffuse inhomogenous metastasis can be differentiated from normal inhomogenous fatty marrow in elderly

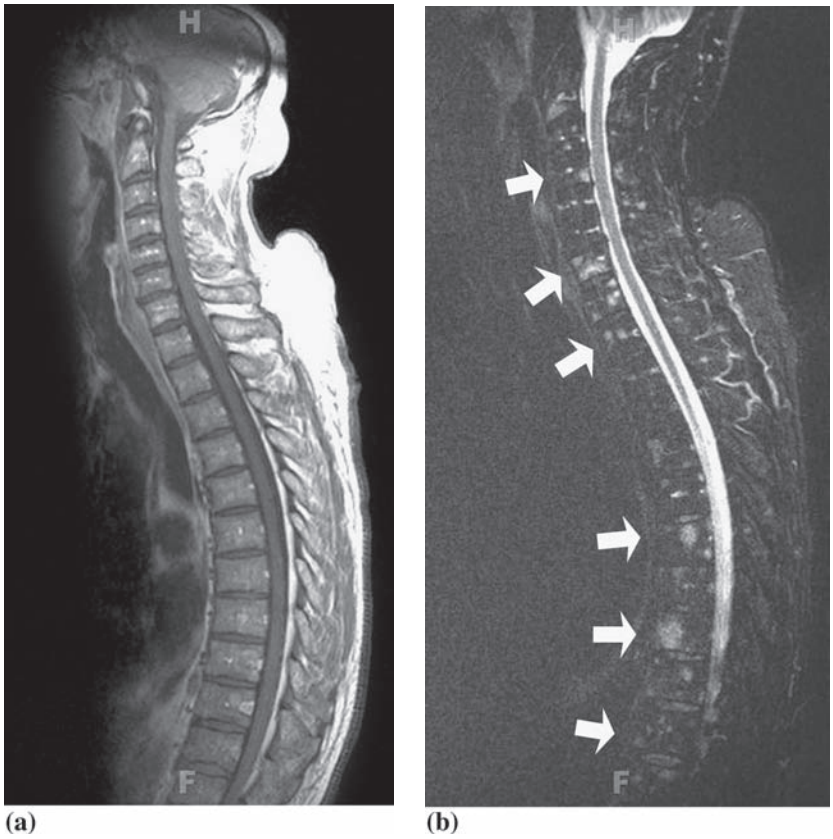

Fig. 2.1 Diffuse prostate cancer metastasis. (**a**) Contrast-enhanced sagittal T1-weighted MR image does not reveal a definite enhancing lesion. (**b**) Sagittal STIR sequence shows multi-level bright tumor deposits (arrows) on the background of suppressed fatty marrow signal

individuals by using a short tau inversion recovery (STIR) sequence which shows multiple bright metastatic deposits within the background of dark patchy fatty marrow (Fig. 2.1).

Lytic lesions may be seen in almost all tumor types. Bone metastases of bladder, kidney and thyroid cancer are invariably lytic. The lytic lesions usually show avid contrast enhancement on fat-saturated T1-weighted images (Fig. 2.2). Blastic lesions are frequently seen in prostate and breast cancer, occasionally in lung, stomach, pancreas and cervix carcinomas, and infrequently in colorectal cancer [5]. MRI shows focal areas of low signal intensity on both T1- and T2 sequences, and high signal intensity on STIR, though less conspicuous than the lytic pattern.

With the recent development of turbo STIR sequences, it is possible to image the whole body in 30 to 40 minutes by using MRI, which also reveals solid organ

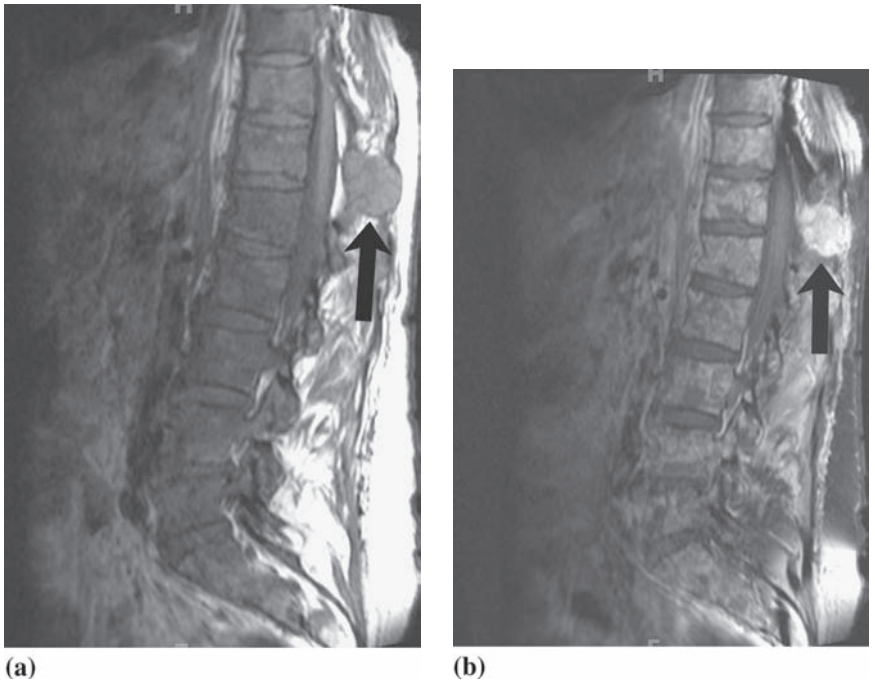

Fig. 2.2 Diffuse breast cancer metastasis with soft tissue component. (**a**) Sagittal T1-weighted MR image shows diffuse decreased signal of the vertebrae that is almost isointense with the intervertebral discs. There is posterior soft tissue mass at T12 level (arrow). (**b**) Contrast-enhanced fat-saturated sagittal T1-weighted image demonstrates heterogenous enhancement of the vertebrae and the metastatic soft tissue mass (arrow)

metastasis such as liver, lung or brain, in addition to axial and peripheral skeleton metastasis [6, 7, 8]. Eustace, et al. [6] compared scintigraphy to whole body turbo STIR MRI in 25 patients with known or suspected skeletal metastasis and found that MRI is 96.5 percent sensitive and 100 percent specific with a positive predictive value (PPV) of 100 percent, whereas scintigraphy is 72 percent sensitive and 98 percent specific with a PPV of 95 percent.

1.1.2 Lymphoma

Primary bone involvement occurs in 3 percent to 5 percent of the patients with Non-Hodgkin's Lymphoma, and 25 percent of them have secondary bone involvement. Primary bone involvement is rare in Hodgkin's disease. Secondary bone involvement occurs in 5 percent to 20 percent of patients with Hodgkin's disease during the course of the disease, but in only 1 percent to 4 percent at presentation. The radiographic and CT findings are nonspecific and represent late manifestations, more commonly osteolytic; ranging from a permeative moth-eaten pattern to a more geographic area of osteolytic destruction [9]. Patchy sclerosis, mixed osteolytic-sclerotic pattern and, rarely, "ivory vertebrae" are seen.

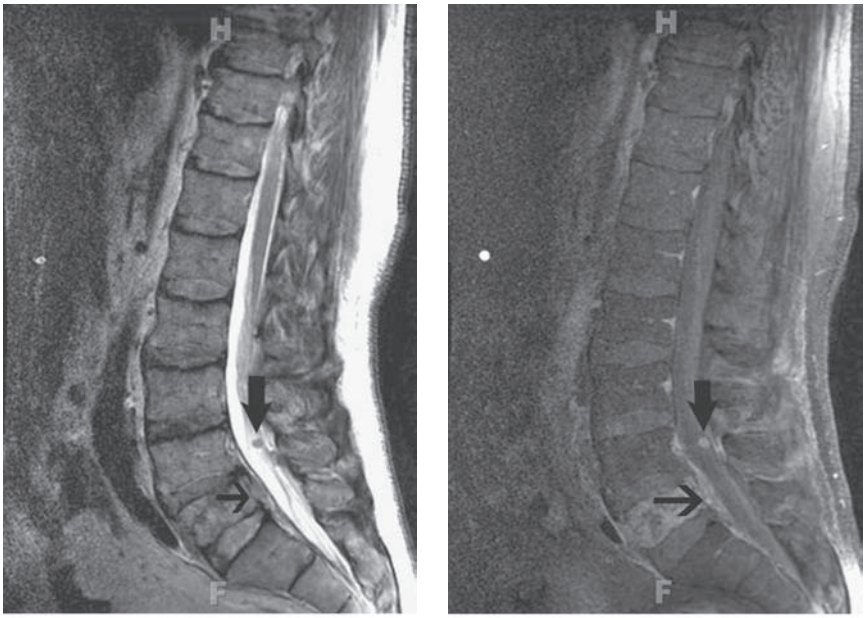

Fig. 2.3 Metastatic B-cell lymphoma. (**a**) Sagittal T2-weighted MR image shows slight heterogenous signal in L5 vertebra, soft tissue mass in the anterior epidural space (thin arrow) and a small hypointense nodule within the thecal sac adjacent to cauda equina roots at L4 level (arrow). (**b**) Contrast-enhanced fat-saturated T1-weighted sagittal image reveals bone marrow metastasis in L5 showing diffuse heterogenous enhancement with an enhancing soft tissue component in the anterior epidural space (thin arrow) and intradural extramedullary metastatic nodule also showing enhancement (arrow)

Lymphoma may produce diffuse infiltration of the bone marrow, usually in the low-grade Non-Hodgkin's type, and it can only be detected on MRI. T1-weighted images demonstrate diffuse hypointensity of the vertebrae and bright signal of the intervertebral discs. The finding of high signal intensity marrow on T2-weighted fat-suppressed images or an obvious contrast enhancement, particularly on fat-saturated contrast-enhanced T1-weighted images, help to differentiate it from normal hypercellular marrow. In Hodgkin's lymphoma, intermediate and high-grade non-Hodgkin's lymphoma, the bone involvement is usually focal. In Non-Hodgkin's lymphoma epidural soft tissue mass can occur alone or as a component of vertebral or paraspinal tumors, and this might be present either at diagnosis or during the disease course (Fig. 2.3).

1.1.3 Leukemia

Leukemia usually shows diffuse bone marrow infiltration, rather than focal disease, and results in a decreased signal on T1-weighted images, presenting diagnostic challenges similar to diffuse lymphoma. In both diseases the decrease in bone marrow signal intensity