CHAPTER

25 Metastatic Disease: Bone, Spinal Cord, Brain, Liver, and Lung

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Local tumor control is now achieved with modern combined modality therapy. Metastatic disease therefore dominates the survival outcomes of patients with cancer. Metastases to the bone commonly cause pain, whereas those to the lung, liver, and brain cause organ dysfunction with substantial changes in quality of life. Metastases to any of these organs can lead to a shorter life. Although palliative care comprises a large part of the clinical practice of oncology, studies show that cancer pain is often inadequately managed.[1,2]

Among painful metastases, osseous metastases[3] remain the most common cause of intractable pain in patients with cancer. Bone is the third most common site of metastases after lung and liver.[4] Metastases usually become apparent after the diagnosis of the primary tumor, but in up to 23% of patients they are the presenting problem. Bone pain results in immobility, anxiety, and depression and severely impacts a patient's quality of life. Thus, treatment of bone pain is a high priority.

Brain metastases are a devastating site of metastatic disease. Most patients with brain metastases succumb to metastatic disease within a few months.[5,6] Relatively few are candidates for open surgery, which can carry the risk of severe sequelae. The advent of radiosurgical techniques and high-quality magnetic resonance imaging (MRI) of the brain has greatly changed the outcomes for some patients with brain metastases. Patients can have improved duration of cognitive performance, with some enjoying prolonged survival.[6] The success of this approach is limited to patients with tumors in favorable regions of the brain. Among patients with lung cancer, the actuarial incidence of brain metastases can exceed 70%.[7,8] Other cancers can also have high rates, including 19% of women with metastatic breast cancer. Regarding therapy, local therapies such as surgery or radiosurgery are often supplemented by elective whole brain irradiation in patients with more than one lesion.[9]

Liver metastases are common in many cancers, and like brain metastases are usually associated with a limited median survival. Liver metastases occur in 40% to 70% of patients with progressive colorectal cancer and in a similar range of patients with progressive breast cancer or progressive lung cancer.[10,11] Treatment for liver disease, like pain, is often difficult and therefore inadequately managed. More recently there has been an effort to treat liver metastases using localized therapies. These include stereotactic radiation techniques, radiofrequency ablation, hyperthermia, and embolic therapy in addition to resection. There has been satisfactory success with many of these treatments, which appear to be improving patient outcomes. International consensus increasingly favors stereotactic liver irradiation as a local treatment for liver metastases.[12,13]

BONE METASTASES

Table 25-1[14] shows the prevalence of skeletal metastases in several autopsy series. The marked variation may be attributed to differences in the thoroughness of the pathologic examination of the skeleton. Bone scintigraphic surveys have, in general, reported higher rates of bone metastases. In a study by Tofe et al,[15] bone scans of 1143 patients with a nonosseous primary tumor were examined; 61% of the patients had an abnormal bone scan finding, and 33% had breast, lung, or prostate primary cancer.

In a prospective series of hospital patients with bone metastases, the tumors carrying the highest risk of bone metastases were those originating in the prostate (32.4%), breast (21.9%), kidney (16.4%), thyroid (11.7%), lung (10.9%), and testes (10.2%).[2] The incidence of patients developing bone metastases by primary site is shown in Table 25-2.[15]

The distribution of skeletal metastases from breast cancer is shown in Table 25-3. Similar distributions have been noted from prostate, lung, and breast primary cancers.[16-19]

Pathophysiology

Tumor cells gain access to the systemic circulation, primarily through the capillary system, but some gain access through the lymphatics; only a few of these cells are able to successfully establish a metastatic focus.[20] Indeed although circulating tumor cells are common,[21,22] they do not reliably portend metastases and when included in American Joint Committee on Cancer (AJCC) staging are considered M0-like in choice of therapy. The process of developing a hematogenous metastasis from a primary tumor includes many steps; steps that are rarely achieved by any individual circulating tumor cell.[23] The tumor must dissociate from the primary mass, gain access to the circulation, survive the immune system and circulatory shear forces, identify a host organ, and develop an exit passage to that organ. Once it enters an organ it must retain reproductive potential, proliferate, generate a vasculature, and grow. The molecular expression profiles that dictate which tumor cells can produce a metastasis, at what frequency, and in which organs are of great research interest.[24]

Cancer cells metastasize to bone mostly via hematogenous spread. Skeletal blood flow accounts for only 4% to 10% of the cardiac output,[25] and some authors believe that the incidence of skeletal metastases is higher than expected based on perfusion alone. A mechanism explaining the high incidence has been described by Weiss.[26] The microstructure of the hematopoietic marrow renders it particularly vulnerable to tumor cell accumulation and ultimate invasion. Nutrient arteries to the bone tend to subdivide into capillaries as they near the endosteal margin of the bone. These capillaries become continuous with a rich venous sinusoidal system, with a capacity six to eight times that of the osseous arterial system. More important, the circulation comes to a near standstill at this point, allowing tumor cells more time to invade the matrix.

To sustain growth, a colony of tumor cells needs to obtain its own vascular supply once it has been established. A hypothesis is that a tumor angiogenesis factor attracts

TABLE 25-1 Prevalence of Skeletal Metastases at Primary Site

Primary Site	Prevalence (%)
Breast	47-85
Prostate	54-85
Thyroid	28-60
Kidney	33-40
Bronchus	32-40
Esophagus	5-7
Other gastrointestinal	3-11
Rectum	8-13
Bladder	42
Cervix	0
Ovaries	9
Liver	16

Data from Galasko CSB: Incidence and distribution of skeletal metastases. Clin Orthop 210:14–22, 1986.

TABLE 25-2 Incidence of Bone Metastases According to Primary Site

Primary Site	No. of Patients	Patients with Bone Metastases (%)
Breast	6423	17
Prostate	144	16
Esophagus	451	6
Lung	589	5
Bladder	172	5
Rectum	274	4
Thyroid	107	4
Uterine cervix	1981	3
Uterine corpus	509	3
Head and neck	2860	2
Ovaries	586	1
Colon	153	1
Stomach	118	1

Data from Tubiana-Hulin M: Incidence, prevalence and distribution of bone mets. Bone 12:S9–S10, 1991.

TABLE 25-3 Distribution of Skeletal Metastases in 212 Breast Cancer Patients

Anatomic Site	At Presentation (%*)	At Any Time (%*)
Lumbar spine	52	59
Thoracic spine	35	57
Pelvis	31	49
Ribs	18	30
Femur	15	24
Skull	12	20
Cervical spine	11	17
Humerus	8	13
Other	3	3
Diffuse	1	12

Data from Tubiana-Hulin M: Incidence, prevalence and distribution of bone mets. Bone 12:S9–S10, 1991.
**Of all patients.*

endothelial cells to a small tumor colony that would otherwise be dependent on local tissue circulation and incapable of further invasion.[27] The production of such tumor angiogenesis factor may be partly blocked by the immune responses, presumably mediated through lymphocytes. Therefore, an established micrometastasis may attract vasculature required for growth several years later. This theory may explain the late appearance of metastases long after definitive treatment of the primary.

Some tumors, notably of breast, prostate, lung, renal, and thyroid, produce and secrete humeral mediators that stimulate osteoclast activity. These include transforming growth factor, platelet-derived growth factor, tumor necrosis factor, prostaglandins, procathepsin D, interleukins, parathyroid hormone-related protein, and granulocyte-macrophage colony-stimulating factors.[28,29]

The distribution of metastases in the skeletal system is not uniform. Bone metastases tend to involve the axial skeleton more often than the appendicular skeleton. Considering the distribution of marrow in the axial and appendicular skeleton, this higher predilection argues for specific bone marrow-derived growth factors that fertilize the soil of the bone for tumor growth.[25]

Diagnosis

Laboratory

The biochemical parameters include alkaline phosphatase, urinary hydroxyproline, and the urinary hydroxyproline-creatinine ratio lack specificity, and are of no value in the diagnosis of skeletal metastases.[30,31]

Imaging

Skeletal scintigraphy is usually the first-line imaging technique used for detecting skeletal metastases. A bone scan is more sensitive than plain radiographs and has the advantage of examining the entire skeleton. Most lesions evoke an osteoblastic response, which shows up as an increased tracer uptake.[32] Occasionally, metastases may show up as areas of decreased uptake. This may be observed in rapidly growing lesions, when bone destruction far exceeds new bone formation, or secondary to an infarction. Highly vascular metastases, such as those from a renal primary cancer, may be seen on the early vascular phase of the bone scan. Metastases not detected by a bone scan include tumors that do not evoke an osteoblastic response such as myeloma, some lymphomas, and very small deposits.[33]

Widespread metastatic disease may be misinterpreted as a normal scan with symmetric uptake. In these situations, a reduction in urinary excretion of isotope and faint or absent renal uptake with decreased bladder activity are clues of an abnormal scan.[34]

Most skeletal metastases develop in the medulla and involve the cortex later on; therefore, plain radiographs are generally insensitive.[34] Within the spine, the vertebral body is affected first, although the radiologic findings of pedicle destruction are noted first.[35]

Computed tomography (CT) scanning has been found to differentiate between metastases and degenerative joint disease, even though the two coexist, and the latter is a common cause of increased uptake on a bone scan. Muindi et al[36] reported that 50% of patients with breast cancer with a positive bone scan and a normal radiograph had obvious skeletal metastases on a CT scan, 25% had a benign cause, and 25% had a negative CT. None of the patients with a CT scan that was negative for metastases subsequently experienced metastases. CT scan is also valuable in evaluating soft-tissue involvement and can be combined with myelography for

detecting extradural tumor spread in patients unable to undergo MRI.

More recently, MRI has been described as the method of choice for examining the spine. It is more sensitive than a bone scan for detecting early metastases within the medulla, but both T1- and T2-weighted images are required.[37] It is the procedure of choice when neural compression is suspected[31] because it is less invasive than CT myelography, and a small incidence of acute deterioration of neurologic function has been reported by CT myelography.[38] When cord impingement is suspected, imaging of the entire spine should be considered because approximately 10% of patients have multiple levels of cord impingement.[39] It is also used in discriminating between benign and malignant vertebral collapse. In the future whole-body MRI could emerge for metastasis screening.[40] Disadvantages of an MRI include its high cost, exclusion of patients with metal implants, patients with severe claustrophobia, and inferior visualization of the cortex compared with a CT scan. Treatment response using MRI and CT can be difficult to evaluate.

Positron emission tomography (PET) with 18F-fluoride or 2-fluoro-deoxy-D-glucose (FDG) is used for the initial staging of many malignancies and is helpful in the diagnosis of bony metastasis. 18F-fluoride is a bone-imaging agent and forms fluoroapatite in osteoblastic cells. Uptake of 18F-fluoride is higher than for 99Tc used for bone scintigraphy.[41] This sensitivity can lead to inadvertant overdiagnosis of bone metastases, but can be useful for diagnosis, tumor localization, and assessment of treatment response. FDG is a tumor-imaging agent that uses the higher glycolysis activity in the tumor cells.[42] FDG-PET scan compared to bone scintigraphy shows a similar high sensitivity (range from 74% to 95%) but a higher specificity (range of 90% to 97%).[43-47] Limitations include traumatic, infectious, and inflammatory processes that can also accumulate glucose. Accumulation of FDG requires the tumor to have an adequate metabolic rate. Neoplasms, like prostate adenocarcinoma, are not consistently seen using PET scans.[48,49] PET images provide poor anatomic imaging but are extremely useful when employed with a concurrent CT or fused MRI image.[41,50,51]

Biopsy

Bone biopsy is not necessary routine. It is helpful in patients with no history of malignancy, in patients with a solitary lesion (in whom a more aggressive treatment approach may be indicated), and in patients with more than one suspected primary lesion.

Treatment

The primary goal of therapy is to improve quality of life. To achieve this goal, we need to decrease or eliminate pain and improve or maintain skeletal function. The complexity, duration, and cost of therapy should be low, and complications should be avoided.

Treatment recommendations must be individualized. A key consideration is patients' overall prognosis. This assessment should be based on an understanding of the natural course of the specific disease. Although the survival of patients with bone metastases is generally poor, potential long-term survivors must be identified. Long-term survivors require a more durable relief of pain, but they are also at more risk for a late, treatment-related complication. The Radiation Therapy Oncology Group (RTOG) trial[52] studied longevity among patients with bone metastases. The median survival in patients with solitary and multiple bone metastases was 36 and 24 weeks, respectively. Patients with breast and prostate primaries survived significantly longer (30 weeks to 73 weeks), whereas patients with lung cancer died within a median of 12 weeks to 14 weeks. Patients with renal cell carcinoma with solitary metastasis are also likely to be long-term survivors. Kjaer[53] monitored 25 such patients for 10 years to 14 years. The median survival was 4.3 years, with 5-year overall survival (OS) of 36%, and 10-year OS of 16%.

Pharmacologic Treatment

Systemic therapy remains the mainstay of treatment for metastatic disease, including bone metastases. For asymptomatic bone metastases not at immediate risk of fracture, disease-appropriate systemic therapy including chemotherapy, hormonal therapy, and biologic therapy is indicated. Patients may also benefit from bisphosphonate therapy.

Bisphosphonates

The discovery of compounds inhibiting calcium phosphate precipitation in plasma and urine led to an interest in the use of bisphosphonates as therapeutic agents. The inhibitory activity was attributed to inorganic pyrophosphate, but the use of this agent was limited because of its rapid hydrolysis when given parenterally. Subsequent research led to the development of pyrophosphate analogs resistant to endogenous phosphatases, now known as bisphosphonates.

Bisphosphonates inhibit osteoclast-mediated bone resorption. The exact mechanism is likely multifactorial, including direct biochemical effects on the osteoclast, prevention of osteoclast attachment to the bone matrix, and inhibition of differentiation of osteoclast precursors and recruitment.

Four Phase II trials of intravenous pamidronate every 2 weeks to 4 weeks as the sole treatment of osteolytic bone metastases in breast cancer reported similar results.[54-57] Relief of pain was noted in approximately 50% of patients, and approximately 25% showed radiographic evidence of bone healing. Similar results for bone pain have also been reported in patients with prostate cancer.

In more recent studies, one Phase II[58] and one Phase III[59] showed equivalence between zoledronic acid and pamidronate. Rosen conducted a three-arm study for patients with bone lytic or mixed disease from either breast cancer or multiple myeloma.[59] One thousand six hundred forty-eight patients received intravenous pamidronate 90-mg zoledronate in 4 mg or 8 mg every 3 weeks for 13 months. The primary endpoint was the incidence of a skeletal event and secondary endpoints were pain relief and performance status (ECOG). All treatment groups showed equivalence with a similar frequency of skeletal events at 12 months and with pain scores decreased by an average of 0.5 on a scale of 5. This randomized trial led to modification of the ASCO 2003 and the Cochrane Breast Cancer Review Group update recommendations on the use of bisphosphonates in breast cancer.[60,61] Both boards now recommend either pamidronate 90 mg intravenously (IV) over 2 hours or zoledronate acid 4 mg IV over 15 minutes for patients with an abnormal bone scan and abnormal imaging by plain radiographs on CT scan or MRI. Bisphosphonates have not yet been formally tested in patients with early, asymptomatic bone metastasis.

Zoledronic acid has also been used in prostate cancer to treat blastic metastasis.[62] Saad et al randomized 643 patients to placebo or to zometa 4 or 8 mg IV infusion every 3 weeks for 15 months. Results show a reduction in skeletal-related events from 44% to 33% with a significant p value of 0.021. Pathological fractures were reduced from 22% to 13% (p = 0.015). Onset of the events occurred at a median time of >420 days (median not reached) in the group receiving zometa and at 321 days in the placebo group. Time to disease progression or survival was similar in both groups. The need for local field radiation was not significantly different in the two groups.

Zometa has also been evaluated for the treatment of bone metastases from other disease sites; 773 patients with lung, renal, head and neck, thyroid, and unknown primaries received either a placebo or zometa 4 or 8 mg.[63] Skeletal events including hypercalcemia were significantly reduced from 47% to 38% ($p = 0.039$) and the median time to the first event was longer in the zometa group (225 days versus 155 days, $p = 0.023$).

Although zoledronic acid is well tolerated, the treating physician is advised to monitor serum creatinine before each administration. Caution is also advised for patients receiving concomitant aminoglycoside or loop diuretic because of an increased risk of hypocalcemia. Ruggiero published a retrospective review of 63 patients on bisphosphonates who suffered osteonecrosis of the jaw[64]; 57% received pamidronate and 21% zoledronic acid. Surgical treatment was required. Oral agents, such as clodronate, have low bioavailability (2%) and produce gastrointestinal side effects.

Analgesics

The optimal management of pain begins with careful assessment of the degree of pain, site, functional limitations, and concurrent neurologic symptoms.[65] The World Health Organization (WHO) analgesic ladder for cancer pain management provides guidelines for analgesic use.[66]

Step I. Nonopioid with or without adjuvant therapy
Step II. Opioid for mild to moderate pain plus nonopioid with or without adjuvant therapy
Step III. Opioid for moderate to severe pain with or without nonopioid with or without adjuvant therapy

Step I nonopioid analgesics include acetaminophen, aspirin, and other nonsteroidal antiinflammatory drugs (NSAIDs). The dose of acetaminophen should not exceed 4 g/day. Step II opioids include codeine, dihydrocodeine, hydrocodone, oxycodone, and propoxyphene. Step III opioids include morphine, oxycodone, hydromorphone, and fentanyl.

Attention should be paid to selecting the appropriate analgesic, dose, route, and schedule. Continuous, slow-release medications are generally preferred over short-acting medications. The latter can be effectively used for breakthrough pain. Allowing pain to recur between doses causes unnecessary suffering and may allow tolerance to develop. When prescribing oral opioids, the dose is about two times that of the subcutaneous dose and three times that of the intravenous dose. For patients unable to take oral medications, suppositories and transdermal patches are good options. When combining drugs, it is important to use drugs that act at different levels of the pain pathway (Figure 25-1). The combined effect can be additive and at times synergistic.

The pain of bone metastases is generally only partially responsive to opioids.[67] Many osseous metastases produce prostaglandins that induce osteolysis. NSAIDs alleviate pain by inhibiting the synthesis of prostaglandins. Corticosteroids prevent the formation of arachidonic acid (the precursor of prostaglandins) from cell membrane phospholipids. The use of NSAIDs or corticosteroids combined with morphine is usually effective.

Corticosteroids can be used when pain is caused by nerve compression. They decrease edema and reduce the pressure on the nerve. Pain relief can be achieved within 48 hours. Corticosteroids can be used as a temporary measure before a more definitive decompression is achieved with radiotherapy or surgery.

Side effects associated with the use of opioids include nausea, vomiting, constipation, urinary retention, dysphoria, mental clouding, tolerance, and addiction. Nausea and vomiting are usually self-limiting and resolve during the first week. Side effects should be anticipated, prevented, and managed aggressively.

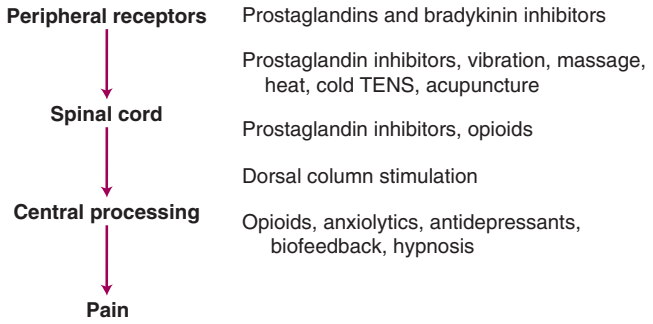

Figure 25-1 Pain pathway and analgesia interventions. *TENS*, Transcutaneous electrical nerve stimulation.

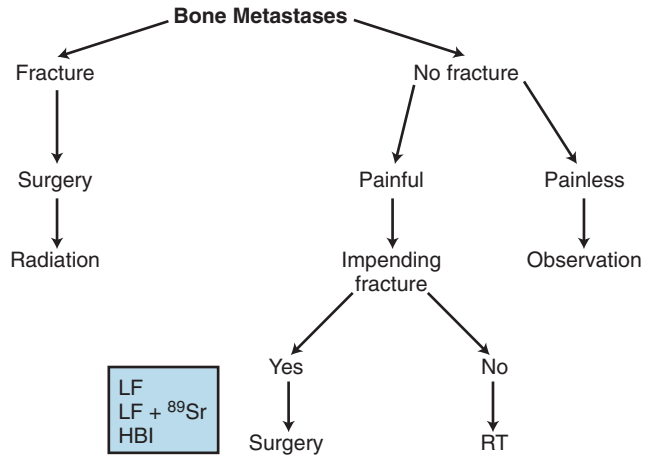

Figure 25-2 **Treatment algorithm for bone metastases.** *LF*, Local field; *LF + ^{89}Sr*, Local field plus strontium-89; *HBI*, hemibody irradiation; *RT*, radiation therapy.

Surgery

Surgery should be considered for patients with pathologic fractures or impending fractures (Figure 25-2). In the former situation, fixation can reduce pain and expedite healing. In the latter, prophylactic fixation may prevent a fracture, thereby eliminating the functional loss and reducing the risk of nonunion of a fracture.

To understand the role of surgery better, we need first to elaborate on the biomechanics of pathologic fractures. Cortical defects weaken bone, especially in the setting of torsional stress. The two general categories of cortical defects are (1) stress riser, a defect with dimensions less than the diameter of the bone, and (2) open-section defect, a discontinuity of dimensions greater than the diameter of the bone.[68] By creating a nonuniform distribution of stresses in bone, stress risers can decrease bone strength by 60% to 70%.[69] An open-section defect has a greater impact on decreasing shear and torque-loading resistance. The volume of bone able to resist the load is significantly decreased compared with a closed section. A 90% reduction in load to failure and energy storage to failure is noted in torsion testing of the human adult tibia with open section.[70] Torsional or rotational forces occur in various daily movements such as getting out of a chair. Bone is weakest during torsion. A single quarter-inch hole made for a bone biopsy can decrease torsional strength by 50%.[71]

The nature of the metastatic lesion affects the overall bone strength. Both lytic and blastic lesions dramatically alter bone elasticity; lytic lesions reduce bone strength more than blastic lesions. Irregular lesions are not necessarily more detrimental to the bone than smooth lesions, but elongated lesions drastically reduce bone strength.[72]

The distribution of pathologic fractures is shown in Table 25-4. Several series have examined various criteria predicting the risk of a pathologic fracture. Keene et al[73] evaluated 2673 patients with breast cancer in an attempt to predict pathologic fracture of the femur using clinical and radiologic criteria. Only 26 (13%) of 203 patients with evaluable proximal femur metastasis had pathologic fractures. They were unable to correlate lesion size and risk of pathologic fracture. No other risk factor was identified. The authors concluded that plains radiographs are insufficient diagnostic tools for identifying high-risk lesions. Of note is that this study was limited to single anteroposterior (AP) films.

Mirels[75] designed a score system to predict the risk of a pathologic fracture (Tables 25-5 and 25-6). Of 78 patients, 51 experienced a fracture and 27 did not. The mean score for the nonfracture group was 7 versus 10 for the fracture group. This system provides a useful tool to evaluate patients for prophylactic fixation. Patients with a score of 10 to 12 should undergo surgery. Patients with scores of 7 or less are not likely to benefit from such therapy. In patients with a "gray zone" score, the status of surrounding bone and lifestyle (old, osteoporotic woman vs young athlete) should be considered.

TABLE 25-4 Distribution of Pathologic Fractures[74]

Location	No.	%
Femur	258	65.0
Femoral neck	69	17.0
Peritrochanteric	50	13.0
Subtrochanteric	84	21.0
Femoral shaft	38	10.0
Supracondylar	17	4.0
Acetabulum	34	8.5
Tibia	31	7.5
Humerus	68	17.0
Forearm	8	2.0
Total	399	100.00

From Mirels H: Metastatic disease in long bones: A proposed scoring system. Clin Orthop 249:256, 1989.

TABLE 25-5 Scoring System by Mirels

	Points		
Variable	**1**	**2**	**3**
Site	Upper extremity	Lower extremity	Peritrochanteric
Pain	Mild	Moderate	Mechanical
Radiograph	Blastic	Mixed	Lytic
Size (% of shaft)	0-3	34-67	68-100

From Mirels H: Metastatic disease in long bones: A proposed scoring system. Clin Orthop 249:256, 1989.

TABLE 25-6 Pathologic Fracture Rate

Score	No. of Patients	Fracture Rate (%)
0-6	11	0
7	19	5
8	12	33
9	7	57
10-12	18	100

From Mirels H: Metastatic disease in long bones: A proposed scoring system. Clin Orthop 249:256, 1989.

The following guidelines may help make a decision regarding prophylactic fixation. Because each patient has unique circumstances, these guidelines cannot replace sound clinical judgment on the part of the attending physician.

1. Life expectancy is longer than 3 months.
2. Patient is medically fit to tolerate major surgery.
3. Procedure planned is expected to expedite mobilization.
4. Quality of bone both proximal and distal to the lesion is adequate to support any fixation device.
5. There is cortical bone destruction of 50% or more.
6. Lesion measuring 2.5 cm or larger is located in the proximal femur.
7. There is pathologic avulsion fracture of the lesser trochanter.
8. Stress pain persists after irradiation.

The following principles govern the surgery of impending fractures:

1. Maximum effort is made to avoid disrupting the surrounding soft tissue to preserve the periosteal blood supply. This is of particular importance in these patients because the endosteal circulation has usually been disrupted by the metastatic deposits.
2. Highly vascular lesions (metastasis from renal cell carcinoma, for instance) should be considered for possible embolization before open curettage.
3. Defects that include the entire circumference of the cortex should be plugged by acrylic cement at fixation to reduce the biomechanical risks associated with stress risers or open-section defects.
4. When large, thin-walled lesions exist, the intramedullary nailing techniques should be augmented by direct reinforcement of the lesion using methyl methacrylate. This will enhance fixation of the distal long bone, particularly with regard to the torsional stability, and will also prevent shortening of the bone.

Pathologic fractures of the humerus commonly occur in the diaphysis followed by the proximal humerus. Fractures of the diaphysis can be fixed using an intramedullary interlocking device, such as a Brooker-Wills nail, which provides excellent strength and effective resistance against varus, torque, and distraction forces.[76] Proximal humerus fractures commonly require a prosthesis. These patients usually achieve a limited flexion and abduction of about 90 degree to 100 degree and enjoy good overall function, joint stability, and pain relief.[68]

Fixation of the femoral neck–intertrochanteric area can be achieved with the use of a compression hip screw and side plate. Fractures involving the femoral neck may be better treated with prosthetic replacement because they are rarely amenable to internal fixation.[77] Subtrochanteric, femoral shaft, and supracondylar femoral lesions are amenable to internal fixation, but large cortical lesions may benefit from an intramedullary acrylic cement filling.

The common problem encountered in acetabular lesions is the failure to appreciate the extent of bone lysis radiographically. Extensive destruction of bone may render efforts to reinforce such lesions with bone graft fruitless. Pathologic fractures of the acetabulum should be managed by total hip arthroplasty.

The spine is the most common site of skeletal metastases. The vertebral body is typically affected first, although pedicle destruction is noted first radiographically. In the absence of a

blastic lesion, 30% to 50% of the vertebral body needs to be destroyed before any destruction can be noted on a radiograph. Vertebral metastases are often asymptomatic. Symptoms are usually a result of one of the following: (1) an enlarging mass within the vertebral body that breaks through the cortex and invades the paravertebral soft tissues, (2) a mass compressing or invading local nerve roots, (3) a pathologic fracture, (4) spinal instability secondary to a pathologic fracture (in particular when the posterior elements are involved), and (5) spinal cord compression.

An aggressive surgical approach to spine metastases is usually not warranted.[78] Spinal stabilization is a major surgery involving multiple risks and prolonged recovery. Most patients with spinal metastases do not have progressive spinal instability or neurologic involvement and can be treated with radiation, hormones, chemotherapy, or temporary bracing. Even patients with vertebral body compression fractures can be treated with temporary bed rest and soft bracing. Indications for surgical intervention include (1) progressive spinal canal impingement and cord compression by a radioresistant tumor or a recurrence after maximum tolerable radiation dose to the intended area; (2) bone or soft-tissue detritus extruded into the canal as a result of progressive spinal deformity, with or without spinal instability; (3) progressive spinal deformity; (4) progressive kyphotic deformity associated with posterior disruption and shear deformity; and (5) solitary metastases of a histology that is unlikely to be controlled long term with tolerable doses of irradiation.

Vertebroplasty of bone metastasis was first described in 1987 and consists of direct injection of the affected vertebra with cement. Polymethylmethacrylate (PMMA) is active through several pathways and produces pain relief in 80% of the patients.[79] The procedure is done under intravenous sedation or general anesthesia. Pain-receptors destruction is achieved with exothermic reaction of the polymonomer and compressive effect on small nerves. Vertebroplasty effects are not modified by external-beam radiation (EBRT) and PMMA conserves its properties despite radiation[79] Vertebroplasty and radiation are complementary, both providing pain relief, the former providing more structural benefit of weak bones, and the later offering more durable tumor control of larger tumors.

Radiotherapy

Local Field Radiotherapy

The vast majority of patients can be managed successfully with EBRT. A large body of clinical evidence documents the effectiveness of such therapy.[80] The optimal dose and fractionation schedule is still not resolved. A summary of the major prospective clinical trials that addressed these issues is provided in Table 25-7. The results of these studies should be interpreted with caution because the inherent heterogeneity within the randomization groups may have precluded detection of significant differences, even when such differences could have existed. The use of different pain scoring systems (physician based versus patient based) and different handling of concomitant use of analgesics, chemotherapy, or hormonal therapy precludes meaningful comparison of the results of these studies.

Between 1974 and 1980, the RTOG conducted a large national study to determine the effectiveness of five different dose fractionation schedules.[52] A total of 1016 patients were entered, 266 into a solitary metastasis stratum and 750 into a multiple metastasis stratum. The former were randomly assigned to treatment with 40.5 Gy in 15 fractions or 20 Gy in 5 fractions. The latter were assigned to 30 Gy in 10 fractions, 15 Gy in 5 fractions, 20 Gy in 5 fractions, or 25 Gy in 5 fractions. A quantitative measure of pain, based on severity and frequency of pain and the type and frequency of pain medications used, was devised to evaluate response. Overall, 89% of patients experienced at least minimal relief, 83% achieved partial relief, and 54% obtained complete relief. There were no significant differences between the treatment arms in both strata. The initial pain score was found to be a useful predictor; patients with high scores were less likely to respond and less likely to experience a complete response. Patients with breast and prostate cancer were significantly more likely to respond than those with lung or other primary lesions. Patients completing their treatment as planned had a significantly higher rate of complete response than those who did not. Although some pain relief was experienced almost invariably within the first 4 weeks, complete relief was first reported later than 4 weeks after the start of treatment in about 50% of patients. The

TABLE 25-7 Summary of Prospective Clinical Trials of Radiotherapy for Painful Osseous Metastases

Study	No. of Patients	Total Dose (Gy)	No. of Fractions	Overall Response (%)	Complete Response (%)
Tong et al[52]	1016	40.5	15	85*	61*
		20.0	5	82*	53*
		30.0	10	87	57
		15.0	5	85	49
		20.0	5	83	56
		25.0	5	78	49
Price et al[81]	288	8.0	1	82	45
		30.0	10	71	28
Hoskin et al[82]	270	4.0	1	44	36
		8.0	1	69	39
Okawa et al[83]	92	30.0	15	76	—
		22.5	5	75	—
		20.0	10 (bid)	78	—
Madsen et al[84]	57	24.0	6	47	—
		20.0	2	48	—
Steenland et al[85]	1157	8.0	1	71	—
		24.0	6		—
Sze et al[86] (review)	3621	Varies	1	60	34
			>1	90	32

median duration of minimal and complete pain relief was 20 and 12 weeks, respectively. There were no significant differences in the duration of pain relief between the different arms. The authors concluded that all treatment dose schedules were equally effective.

Blitzer[87] performed a reanalysis of the RTOG study. Using a stepwise logistic regression, he examined the effect of the number of fractions, the dose per fraction, and solitary versus multiple metastases on the probability of attaining complete pain relief and the need for retreatment. This multivariate technique allowed patients with solitary and multiple metastases to be analyzed together. The number of fractions was the only variable that was significantly associated with outcome. There was no correlation of the time-dose factor (TDF)[88] with outcome. It was concluded that the more protracted schedules resulted in improved pain relief.

The concept of TDF has long been replaced by the linear quadratic model. Using this model, and assuming an α/β of 10 for tumor, we calculated the biologically effective dose (BED) for the various schedules tested by the RTOG. Figures 25-3 and 25-4 depict pain response and freedom from retreatment as a function of BED, respectively. The solid lines are the regression functions, and the dotted lines represent the 95% confidence intervals. The results suggest that schedules with higher BED resulted in better pain relief and reduced the need for retreatment.

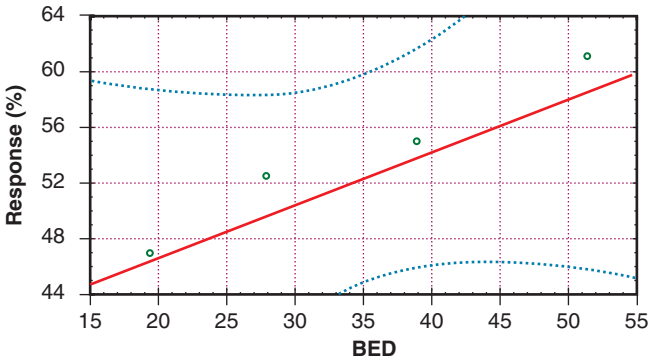

Figure 25-3 Pain response as a function of biologically effective dose (BED) by means of linear regression analysis. Response = 39.1 + 0.38 × BED; $r = 0.74$; $P = 0.15$. The *solid red line* indicates the regression function, and the dotted blue lines indicate 95% confidence intervals.

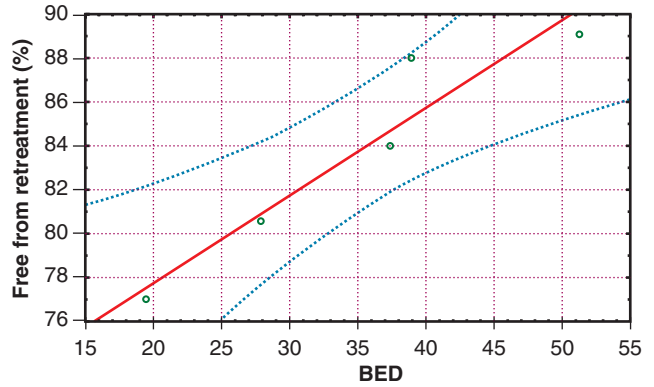

Figure 25-4 Freedom from retreatment as a function of biologically effective dose (BED) by means of linear regression analysis. Response = 69.7 + 0.4 × BED; $r = 0.95$; $P = 0.05$. The *solid red line* indicates the regression function, and the dotted blue lines indicate 95% confidence intervals.

Price et al[81] randomized 288 patients to receive either 8 Gy in one fraction or 30 Gy in 10 daily fractions. Pain was assessed using a daily questionnaire completed by the patient at home. No differences were found in the probability of attaining pain relief, speed of relief, or duration of relief between the two arms.

Hoskin et al[82] randomized 270 patients to receive either 4 Gy or 8 Gy in one fraction. Pain (assessed by the patient) and analgesic usage were recorded before treatment and at 2, 4, 8, and 12 weeks. At 4 weeks, the response rates were 69% for 8 Gy and 44% for 4 Gy ($p < 0.001$). The duration of the effect was independent of dose.

Additional studies have evaluated single- and multiple-fraction regimens. A Danish randomized trial of 241 patients showed no significant difference with regard to pain relief or quality of life after receiving either 8 Gy in a single fraction or 20 Gy in five fractions.[89] Wu et al performed a meta-analysis of 16 trials including 5455 patients[90] and proclaimed equivalence between single and multiple fractions. Van der Linden et al recently published a reanalysis of a Dutch Bone Metastasis Study that included 1171 patients.[91] This study randomized patients to either single 8 Gy or 24 Gy in six fractions. Mean time to retreatment was shorter (13 weeks versus 21 weeks) with a single fraction. It was also more frequent: 24% after a single fraction and 6% after 6 fractions ($p = 0.001$). An initial high pain score also influenced the need for retreatment.

Treatment Techniques

The target volumes for EBRT should be defined after review of all appropriate diagnostic studies. Attention should be paid to soft-tissue masses, which are often associated with bone metastases and at times responsible for the observed symptoms. Such lesions are best assessed by CT or MRI. The target volumes are treated with appropriate margins. Depending on the treatment site and volume, suppression of the bone marrow should be anticipated. In patients for whom chemotherapy is planned, treatment volumes should be kept to a minimum to preserve marrow reserves. Because many patients have repeated courses of therapy, all previous ports and radiation records must be reviewed. To minimize late radiation damage, overlap of radiation fields should be avoided. Depending on the clinical circumstances, overlapping retreatment may be appropriate in patients with short life expectancy.

Hemibody Irradiation

Most patients with bone metastases have multiple sites of involvement. As many as 76% of patients receiving therapy to a local field require additional treatment for pain at other sites within 1 year.[92] Historically, wide-field radiotherapy was used to address this problem. Although large-field radiation is less commonly used is the era of systemic therapy, it remains a treatment option. A summary of results of this form of therapy is provided in Table 25-8. Response rates are similar to those observed with local-field radiotherapy, but the onset of relief is more rapid, occurring often within 24 hours of treatment. Hemibody irradiation (HBI) is mentioned here for completeness but is rarely employed. It may require hospitalization for hydration and premedication with steroids and antiemetics and tends to be associated with substantial morbidity. Most patients experience acute gastrointestinal toxicity, with nausea, vomiting, and diarrhea persisting for 24 to 48 hours. Myelosuppression is commonly observed but is rarely of clinical significance. Radiation pneumonitis is rare at doses below 7 Gy to the lungs.

The RTOG conducted a Phase III study to evaluate the efficacy of HBI in addition to local-field irradiation.[92] A total of 499 patients were randomized to receive either HBI or no

TABLE 25-8 Wide-Field Radiotherapy for Painful Osseous Metastases

Study	No. Fields Treated	Dose (Gy)		Response (%)
		Upper	*Lower*	
Fitzpatrick[93]	570	3-6	10	55-72
Rowland et al[94]	96	7.5	10	80
Qasim[95]	129	7-8*	7-8*	76
Salazar et al[96]	168	6	8	73
Wilkins et al[97]	141	6	8	82
Poulter et al[92]	229	8	8	93

**3 Gy to 4 Gy in multiple myeloma patients.*

further therapy after completion of local-field irradiation to a symptomatic site. Entry was stratified by extent of metastatic disease (solitary or multiple) and the targeted hemibody area (upper, middle, or lower). Local-field irradiation consisted of 30 Gy in 10 fractions. HBI consisted of 8 Gy in 1 fraction given within 7 days of completion of the local field. Partial transmission blocks were used to reduce the dose to the lungs to 7 Gy. Time to disease progression, time to new disease, and time to new course of therapy were significantly longer in the HBI arm. Progression of disease was faster in patients with involvement of the upper and middle hemibody (compared with lower hemibody) and in patients with multiple metastases (compared with solitary tumor). As expected, toxicity was significantly higher in the HBI arm, but there were no fatalities and no occurrences of radiation pneumonitis. Although an impact of HBI on clinically occult metastatic disease was demonstrated, the long-term benefit was relatively small. The ultimate progression rates were not significantly different between the arms, and at 1 year 60% of the patients in the HBI arm had to be retreated.

Stereotactic Radiosurgery of the Spine

The spinal column is a common site of metastatic spread where pernicious disease progression threatens the spinal cord. Although conventional palliative fractionated radiotherapy has proven to be effective in both pain relief and short-term local control, the dose is limited by the close proximity of the spinal cord. As treatment improves and metastatic patients survive longer, progression of spine disease after fractionated radiation therapy becomes a serious issue. Stereotactic radiosurgery (SRS) allows for the delivery of a single, ablative dose fraction of radiation using highly conformal techniques with enhanced targeting accuracy. Generally, the delivery of two to five fractions of radiation, using the same techniques, is referred to as stereotactic body radiation therapy (SBRT). SBRT and SRS offer advantages over traditional fractionated therapy. Including the convenience of one to five treatments versus several days of treatment for patients with limited life expectancy in significant pain, improved long-term local control that is less histology dependent, and a safe effective radiation retreatment modality.

The ability to safely deliver ablative doses of radiation depends on accurate localization and immobilization. Using MRI imaging, a planning CT scan, and in some situations spinal myelogram and PET scan, accurate identification of anatomical dosing gradients is achieved. During treatment, image guidance using the bony vertebra as a high fidelity fiducial for both the lesion and the spinal cord may be used. Immobilization of the bony vertebral body structure may be achieved using gravity in the supine position, usually combined with a variety of other immobilization techniques. Modern treatment planning achieves a sharp dose gradient that allows the technique to achieve an ablative dose of radiation to the PTV while reducing significant dose delivery to critical structures, most importantly the spinal cord, but also the esophagus, lungs, kidney, bowel, and bone marrow of adjacent vertebral bodies.

SBRT or SRS technique can be used as the sole initial treatment for spinal metastatic disease, particularly in tumor histologies that are known to have a poor response to traditional fractionated palliative radiation technique, patients with oligometastatic disease, and patients with a long life expectancy. SRS can also be used as a boost treatment after the delivery of conventional radiation (generally prescribed to 20 Gy to 40 Gy in 2.5 Gy fractions to 4 Gy fractions), postoperatively as adjuvant treatment,[98] and as salvage treatment in patients previously irradiated (generally >3 to 6 months prior) for spine metastases.

Spinal SRS is most ideally performed on intravetebral body lesions without extension into the canal allowing for distance between the PTV and the spinal cord. If there is posterior cortical compromise of the vertebral body by the lesion, conventional fractionated radiation therapy should be considered in radiosensitive histologies. Radioresistant histology patients with limited systemic disease should be considered for surgery followed by radiation.

Generally with SRS/SBRT technique, the pain control and local tumor control is on the order of 85%.[99-104] Garg et al[105] showed local control for single fraction SRS in previously unirradiated tumors to be 88% at 18 months. There appears to be a dose response, with greater palliation with prescribed isocenter doses of ≥14 Gy.[106] Although traditional palliative spine radiation fields encompass the involved vertebral body plus a vertebral body above and below, SRS and SBRT generally treat only the involved vertebral body or a portion of the involved vertebral body. This typically equates to the anterior vertebral body with or without the posterior elements and pedicles in those with more posterior extension. In a study from Henry Ford Hospital (Detroit, MI), subsequent metastases to adjoining vertebral bodies after SRS was rare (~5%) and associated with progression of disease elsewhere.[100] In a study from M. D. Anderson Cancer Center (Houston, TX), in-field failures occurred in ~25% of recurrences, and roughly half of the recurrences were in the epidural space, which was attributed to underdosing this region to maintain spinal cord dose constraints. Patients also failed in other regions not included in the treatment volume (of any given patient) including the pedicles, posterior elements, and pre- and paravertebral regions.[98] The presence of paraspinal disease and using SRS doses <16 Gy increased risk of marginal recurrence is discussed in a paper by Koyfman el al.[107] Recent clinical data has shown spine SRS and SBRT to be tolerable, albeit with limited patient follow-up,[108] because patients with spine metastases generally have a poor survival, even those with solitary spine metastases.[109] It appears that myelopathy and radiculopathy rarely occur.[63,108] For single-fraction SRS, most institutions try to achieve a spinal cord maximum dose below 10 Gy.[57] In the University of Pittsburgh experience of spine SRS in 393 patients with 500 lesions, for which the cord maximum was kept below 8 Gy, no acute or late neurotoxicity was observed, and no late toxicity was reported after a follow-up of 3 to 53 months (median, 21 months).[100] In Garg et al[105] the dose to the spinal cord was limited to no greater than 0.01 cm^3 of the spinal cord receiving >10 Gy and the spinal cord plus 2 mm was limited to receiving 12 Gy. These constraints yielded limited toxicity with only 3% of patients suffering grade-3 neurotoxicity with some patients' prescription doses as high as 24 Gy. Sahgal et al[110] looked at dose-volume histogram results for nine cases of spine SBRT, treated at multiple institutions, where radiation myelopathy was

reported and compared them with a cohort of 66 spine SBRT patients without radiation myelopathy. They found a risk of radiation myelopathy of 5% or less when limiting the thecal sac Pmax volume to 12.4 Gy in a single fraction, 17.0 Gy in two fractions, 20.3 Gy in three fractions, 23.0 Gy in four fractions, and 25.3 Gy in five fractions. Several institutions have demonstrated that spinal cord maxima of 12 Gy[102] to 20 Gy[108,111] are tolerated in some patients, though from a multiinstitutional pooled analysis, radiation myelopathy has only been documented to occur after exceeding a fractional dose maximum of 10 Gy to the spinal cord.[112] From this study, dose-volume parameters such as maximal dose and mean and median dose to 0.1 mL to 5 mL of spinal cord significantly correlated with the risk of radiation myelopathy. From the RTOG 0631 study (which is a randomization of spine SRS delivered with 16 Gy versus conventional radiation delivered in one fraction of 8 Gy), spinal cord dose constraints are: 10% and 0.35 mL of spinal cord <10 Gy, and 0.035 mL <14 Gy, with the spinal cord volume defined as 5 mm to 6 mm above and below the target, based on T2- and T1-weighted MRI.

The use of SRS is attractive in the setting of progression after conventional fractionated radiation for spine metastases. With a repeated course of standard fractionated radiation, there is concern about exceeding residual cord tolerance, while affording inferior local control versus SRS. A study of spinal cord tolerance in a rhesus monkey model by Ang et al[113] suggested that the spinal cord has remarkable ability to recovery from previous radiation when treated 1 to 3 years later. Mahadevan et al[114] showed SBRT salvage after normal fractionated palliative radiation was effective. The dose used was 8 Gy × 3 = 24 Gy when the tumor did not touch the spinal cord and 5 Gy to 6 Gy × 5 = 25 Gy to 30 Gy when the tumor abutted the cord. The cord surface received up to the prescription dose. In this group, 93% of patients had stable or improved disease, whereas 7% of patients showed disease progression. With 65% of patients gaining significant pain relief, there was no significant toxicity other than fatigue. A spine SRS/SBRT retreatment study by Sahgal et al[110] looked at patients from multiple institutions, given salvage SRS/SBRT, with one to five fractions, at least 5 months after conventional palliative radiotherapy. They compared dose volume histograms of patients who developed radiation myelopathy to patients who did not develop radiation myelopathy. They found that a thecal sac Pmax nBED of 20 Gy to 25 Gy 2/2 appears to be safe provided the total Pmax nBED does not exceed approximately 70 Gy 2/2, and the SBRT thecal sac Pmax nBED comprises no more than approximately 50% of the total nBED.

The use of SRS/SBRT for spinal metastatic tumors is increasing. Standard field palliative radiation has been a standard option in the treatment of spinal metastatic lesions where the dose delivered was limited by the sensitivity of the spinal cord and surrounding critical structures. Spinal SRS emerged with modern techniques of improved localization, immobilization, and dose gradients within a treatment plan. This relatively new radiation modality affords patients with metastatic spine lesions a safe, effective, and convenient therapy.

Systemic Radionuclide Therapy

The first report on the use of systemic radionuclides for the treatment of bone metastases was published by Pecher more than 50 years ago.[115] Using this modality, all involved osseous sites can be addressed simultaneously. Selective absorption into bone metastases limits irradiation of normal tissues and increases the therapeutic ratio. Administration as a single intravenous injection in the outpatient clinic is a further advantage for many patients.

Systemic radionuclides should be considered in the following circumstances:

1. In patients with widely metastatic disease, as adjuvant to EBRT
2. In patients with pain but without a predominantly painful site, as a first-line therapy
3. There is no evidence of imminent epidural cord compression, pathologic fracture, or mechanical instability
4. In patients with good marrow reserve with a white blood cell count of greater than 2400 and a platelet count of greater than 100,000
5. Patients for whom the value of future marrow toxic chemotherapy is limited.

Historically, phosphorus-32 was the first radionuclide to be widely used in the treatment of bone metastases,[116] although this isotope is now rarely used for bone disease as a result in part of myelosuppression with pancytopenia and an increased incidence of acute leukemia.[92] Phosphorus-32 has since been replaced by newer, less toxic radionuclides (Tables 25-9 and 25-10).

Strontium 89. Strontium 89 decays by beta emission to yttrium 89 with a half-life of 50.6 days. The average beta energy is 1.46 MeV. Chemically similar to calcium, strontium 89 is quickly taken up into the mineral matrix of bone. The fraction of strontium 89 retained is proportional to the metastatic tumor burden and varies between 20% and 80% of the administered dose.[126] Accumulation is preferred in and around metastatic deposits, where active bone formation takes place, which is likely adjacent to but not in the site of malignancy.[126-128] Once incorporated into the metastatic lesion, strontium 89 is not removed metabolically and remains deposited for as long as 100 days.[126] Accurate tumor dosimetry is difficult and usually based primarily on the location of tracer accumulation. Estimates of the total dose absorbed within the metastatic lesion vary between 0.9 cGy and 231 cGy per megabecquerel (MBq), with the typical mean total dose at 23 cGy/MBq and high doses usually corresponding to superscans.[127-130] Typical doses are 1.5 MBq/kg, leading to a nominal tumor dose of 20 Gy to 25 Gy. Elimination is through the kidneys, and careful disposal of urine is needed for 7 days to 10 days after administration. Extra care is advised for incontinent patients. Because strontium 89 emits extremely little gamma radiation, the patient is not a radiation hazard to family members or hospital staff.

The efficacy of strontium 89 has been well documented in dose-seeking studies.[118,119,126,130-134] Laing et al[118] reported on the

TABLE 25-9 Physical Characteristics of Various Radionuclides

Radionuclide	Physical Half-Life	Beta Energy (MeV)	Gamma Energy (keV)	Chelate
Phosphorus-32	14.3 d	1.71	—	Orthophosphate
Strontium 89	50.6 d	1.46	—	Chloride
Rhenium 186	90.6 h	1.07	137	HEDP
Samarium 153	46.3 h	0.84	103	EDTMP

EDTMP, *Ethylenediaminetetramethylene phosphonate;* HEDP, *hydroxyethylenediphosphonic acid.*

TABLE 25-10 Summary of Clinical Trials with Systemic Radionuclides

Radionuclide	Response Rate (%)	Complete Response (%)	Response Duration
Phosphorus-32[117]	60-80	—	–5 mo
Strontium 89			
Laing et al[118]	75	22	6 mo
Robinson et al[119]	80	11	NA
Quilty et al[120]	65-70	30*	NA
Rhenium 186			
Maxon[121-123]	77	21	5 wk
Samarium 153			
Collins et al[124]	76	NA	2.6
Ahonen et al[125]	80	54	2-17 wk

NA, *Not applicable.*
**Substantial or dramatic response, estimated from a graph.*

results of a dose-escalation study. The optimal dose was found to be 1.5 MBq/kg with no appreciable increment in efficacy above this dose. Of 83 patients treated with at least 1.5 MBq/Kg, 75% had partial relief of pain and 22% were rendered pain free. Pain relief began 10 days to 20 days after treatment and peaked at 6 weeks. Response was maintained for a median of 6 months (range, 4 months to 15 months). The RTOG conducted a dose escalation study and concluded that the maximum tolerated dose of strontium 89 is 6.5 mCi (approximately 3.4 MBq/kg).

Toxicity of strontium 89 is mainly hematologic. Platelet depression is dose dependent and can be prolonged. Most patients have a 20% to 50% drop in their counts after doses of 3 mCi to 4 mCi (1.5 MBq/kg to 2 MBq/kg). Grade 3 toxicity is rare. Other adverse effects include a transient increase in bone pain in up to 10% of patients and rarely facial flushing. The pain flare occurs 1 week to 2 weeks after treatment, may last a few days, and usually heralds a favorable response.

Porter et al[135] reported the results of the Trans-Canada study. This trial evaluated the efficacy of strontium 89 adjuvant to local-field EBRT in patients with hormone-refractory prostate cancer. A total of 126 patients were randomized to local-field radiotherapy (20 Gy in 5 fractions or 30 Gy in 10 fractions) followed by placebo or by strontium 89 (10.8 mCi). Overall and complete responses (relief of pain at the index site) were higher in the treatment arm, but the differences did not reach statistical significance. At 3 months after treatment, 58.7% and 34% of patients in the treatment arm and control arm, respectively, were free of new painful metastases. The median time to further radiotherapy was 35.3 weeks and 20.3 weeks in the treatment and control arms, respectively. Hematologic toxicity was, as expected, higher in patients treated with strontium 89.

Samarium 153. Samarium 153 is a man-made radionuclide that emits beta particles of 0.81 MeV (20%), 0.71 MeV (30%), and 0.64 MeV (50%) and gamma photons of 103 keV (28%). It has a relatively short half-life of 46.3 hours and, consequently, a relatively high dose-rate. Samarium 153 has been chelated to a phosphonate, ethylenediaminetetramethylene (EDTMP), to produce a bone-seeking complex. About 50% of an intravenously administered dose is retained in bone.[136,137] Absorbed dose in bone and red marrow has been estimated at 2.5 cGy/MBq and 0.57 cGy/MBq, respectively.[137] In a Phase I/II clinical trial,[124] the maximally tolerated dose (MTD) was determined to be 2.5 mCi/kg. The principal toxicity observed was hematologic; maximum myelosuppression occurred at 3 weeks to 4 weeks. A flare of bone pain occurred in 12% of patients. The overall pain relief rate was 74%, with a median duration of palliation of 2.6 months. In responders, relief was obtained promptly within 7 days to 14 days of treatment. Response rates were significantly higher with 2.5 mCi/kg than with 1.0 mCi/kg.

Rhenium 186. Rhenium 186 emits beta particles of 1.07 MeV and a 137-keV gamma ray and has a short half-life of 3.8 days. Like samarium 153, it has been complexed to a bone-seeking phosphonate, hydroxyethylenediphosphonic acid (HEDP). Retention in bone is about 50% of the injected dose; the rest is excreted through the kidneys into the urine.[121] Rhenium 186 has been studied in a small number of patients with metastatic cancer of the prostate, breast, colon, and lung.[122] After administration of 33 mCi to 35 mCi, 75% to 80% of patients experienced pain relief, most often within 2 weeks.[121-123] The therapeutic efficacy of rhenium 186 has been confirmed in a double-blind, crossover comparison with placebo.[123] Myelosuppression begins 2 weeks after treatment, peaks at 4 to 6 weeks, and resolves by 8 weeks.[122] A pain flare occurs in 10% of patients 2 days to 3 days after treatment and resolves within 1 week.

Choice of Radiotherapeutic Approaches

In the United States, the usual approach to painful osseous metastases includes fractionated EBRT to index painful sites. Asymptomatic sites are less commonly irradiated. Patients with multiple lesions will commonly receive radionuclides in addition to EBRT to cytoreduce occult metastases and reduce the need for future local radiation. Radionuclides alone and hemibody radiation are less common in the United States, although the latter is often used in Europe and Canada. The advent of improved external-beam targeting technologies and the earlier discovery of patients with limited metastases have spawned efforts for local targeting of bone metastases. The utility of these high-dose treatments to achieve improved tumor control with reduced marrow and other toxicity is under investigation.[138]

SPINAL CORD COMPRESSION

Malignant spinal cord compression occurs in 5% of all patients with malignant disease and in approximately 20% of patients with metastases to the vertebral column.[139] More than 95% of spinal cord compressions are the result of extramedullary malignancy, most commonly secondary to involvement of the vertebral column anterior to the spinal cord, less frequently by tumors posterior to the spinal cord, and occasionally by invasion of the epidural space. Thankfully, the frequency of severe spinal cord compressions leading to paralysis and incontinence is decreasing with the availability of high-quality MRI technologies.[140]

Any tumor that metastasizes to the bone can eventually result in a cord compression. Most commonly seen primaries include lung, breast, prostate, kidney, lymphoma, myeloma, sarcoma, and unknown primaries.

Clinical Manifestation and Patient Evaluation

The majority of patients present with pain, motor loss, autonomic dysfunction, and sensory loss.[141] Pain is often radicular for weeks or months before the onset of neurologic symptoms, offering ample time for early diagnosis. Autonomic dysfunction may occur early and manifest as hesitancy and urgency. Weakness usually precedes sensory loss; incontinence, paraplegia, and paralysis are late effects. Pain was the initial symptom in 96% of the patients but is a poor indicator of spinal-epidural involvement.[142] In contrast, 75% of patients with major neurologic involvement have involvement of the epidural space.

Diagnosis

Early diagnosis is essential because recovery of neurologic function is related to the degree of loss. A careful history and physical examination focusing on neurologic assessment with a high index of suspicion in patients with known malignancy is key to early diagnosis. MRI is the diagnostic study of choice. Distortion of the theca by extradural lesions and soft-tissue abnormalities can be easily identified.[142,143] In case of compression fracture, protrusion of the vertebral body or tumor into the spinal canal is seen clearly, as is the impingement of nerve roots and neural foramina.[144] Approximately 10% of patients have multiple sites of cord compression and perhaps benefit from imaging of the entire spine.

Treatment

A multidisciplinary approach is recommended to treat spinal cord compression. High-dose steroids should be administered after a clinical diagnosis. An initial dose of 20 mg of dexamethasone (Decadron) followed by 4 mg four times daily improves pain and neurologic symptoms in most patients. Steroids should be tapered gradually after completion of radiation. Patients receiving dexamethasone should be placed on H_2 blockers and monitored for hyperglycemia, hypertension, and electrolyte imbalances.

A randomized trial comparing laminectomy followed by radiation versus radiation alone in the treatment of spinal epidural metastasis showed no significant difference in the effectiveness of treatment in regard to pain relief, improved ambulation, and improved sphincter function.[145] Although most cases of spinal cord compression can be managed with steroids and radiotherapy, patients without a histologically proven cancer, radioresistant tumors, previously radiated sites, or mechanical instability should be seen by a neurosurgeon for a laminectomy (Figure 25-5).

In a multiinstitutional randomized study[146] of patients with symptomatic spinal cord compression from vertebral metastases, 50 patients were randomized to receive decompressive surgery followed by radiation and 51 were randomized to receive radiation alone (30 Gy in three Gy fractions for both arms). The study was closed early because of the superiority in outcomes of surgery plus radiation versus radiation alone. Compared to patients receiving radiation alone, following surgery and radiation, significantly more patients were able to walk, patients retained the ability to walk significantly longer, significantly more patients regained the ability to walk, and the need for corticosteroids and analgesics was significantly reduced. Patients undergoing surgery also had a significantly longer survival time. Table 25-11 summarizes the results from this landmark study.

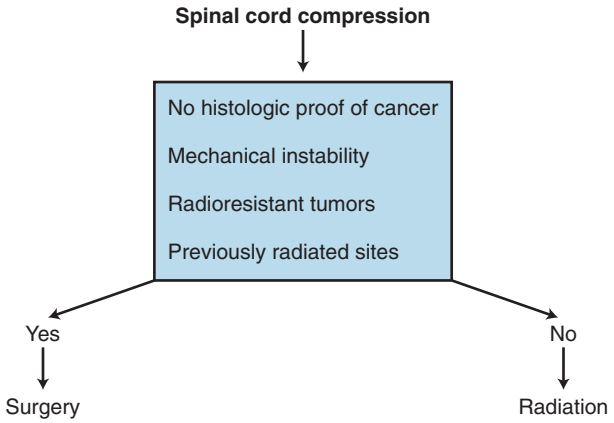

Figure 25-5 Treatment algorithm for spinal cord compression.

TABLE 25-11 Treatment Results for Spinal Cord Compression

Variable	Radiation Alone	Radiation and Surgery	*p* Values
All patients			
Able to walk after treatment	29/51 (57%)	42/50 (84%)	0.001
Retained ability to walk	median 13 days	median 122 days	0.003
Maintenance of continence	median 17 days	median 156 days	0.016
Maintenance of muscle strength	median 72 days	median 566 days	0.001
Dexamethasone dose	median 4.2 mg	median 1.6 mg	0.0093
Morphine dose	median 4.8 mg	median 0.4 mg	0.002
Survival time	median 100 days	median 126 days	0.033
Initial ambulatory patients			
Maintained ability to walk	26/35 (74%)	32/34 (94%)	0.024
Retained ability to walk	median 54 days	median 153 days	0.024
Initial nonambulatory patients			
Regained ability to walk	3/16 (19%)	10/16 (62%)	0.010
Retained ability to walk	median 0 days	median 59 days	0.024

Treatment outcome is dependent on pretreatment function. In a study of 137 patients with malignant spinal cord compression, 81% of patients who were ambulatory pretreatment remained ambulant, whereas only 16.5% of those who were nonambulant before treatment became ambulant after treatment. Pain improved after treatment in 73% of the patients regardless of their ambulatory status.[139] This was confirmed by Zelefsky et al in a retrospective review of 42 patients.[147] They also reported that the presence of a compression fracture of greater than 50% at the level of the spinal cord compression was associated with poor response on refluoromyelography (RFM). Sixty-seven percent with severe compression fractures had no response on RFM versus 11% without compression fracture ($p = 0.01$).

Irradiation Technique and Doses

The depth of the tumor mass can be determined by MRI. If the MRI is unavailable at the time of simulation, a lateral film taken at simulation can help determine the prescription depth. The width of the field is dependent on the extent of the soft-tissue mass as determined by the MRI.

Treatment fields are dependent on the site of involved spinal cord. The cervical spine is usually treated using opposed laterals to avoid the oral cavity. For the thoracic spine, a posterior field alone can be used. When treating the lumbar spine or when the target appears to be more midline, a parallel opposed anteroposterior/posterior-anterior (AP/PA) beam arrangement may be preferred. For either the thoracic or lumbar spine, acceptable alternative techniques include paired posterior obliques or PA and paired laterals. For nonemergent cases, wherein there is sufficient time for treatment planing, IMRT or arcing technique can produce reduced normal tissue consequences, particularly in the neck and thoracic regions where esophageal irradiation can be symptomatic.

The dose of irradiation used for the treatment of spinal cord compression is dependent on both the histopathologic findings and the clinical situation (ambulatory versus nonambulatory, solitary versus multiple metastases, systemic therapy options and efficacy, etc.). The typical dose is 30 Gy in 10 fractions over 2 weeks or 20 Gy in 5 fractions. If life expectancy exceeds a few months, a more protracted regimen (35 Gy to 40 Gy in 3 to 4 weeks) is reasonable with regard to the issue of spinal cord tolerance.

BRAIN METASTASES

Brain metastases are the most common intracranial brain tumor and a common complication of systemic cancer. The incidence ranges from 20% to 40% of all patients diagnosed with cancer.[148] Cancers known to generate systemic disease are the most common primary tumors involved: lung, breast, colon, and melanoma. Current improvements in systemic therapy have improved survival significantly for several cancers but may leave untreated tumor cells beyond the blood-brain barrier and increasing the incidence of brain metastasis in some solid tumors. More precise diagnostic tools, such as MRI, also have an impact on the increasing discovery of brain metastases.

The prognosis of brain metastases is poor and the impact on the patient's quality of life is important as a result of the functional neurologic deficits associated. Symptom management is successful in most patients and efforts can be concentrated on improving the outcome of the patients.[148]

Arterial hematogenous spread results in tumor emboli growth at the gray-white junction[149]; the most common neuroanatomical sites are the cerebral hemispheres (80%), the cerebellum (15%), and the brainstem (5%),[150] with this distribution approximately mirroring blood flow volumes. However, data shows that the distribution of intracranial metastases based solely on the model of arterial embolization and blood volume does not likely depict the full biological basis of spatial distribution of brain metastases. It has been found that patients with non–small cell lung cancer lesions are more likely to be located in the parieto-occipital lobes and cerebellum. Breast cancer lesions have a greater probability to be located in the cerebellum.[151] Multiple metastases are more common than single metastasis and the contribution of MRI to this statistic has reached 80% to 90%.[148]

Presenting symptoms are various and require that any new neurologic symptom be investigated in a patient known to have cancer. Symptoms reflect increasing intracranial pressure and focal neurologic deficit—headache, nausea, lateralized weakness, seizures, modified higher neurologic function. In most patients, the cancer is already diagnosed, but in as many as 20%, it may be the first manifestation; histologic confirmation is then necessary.

Contrast-enhanced MRI is the diagnostic modality of choice. The radiologic differential diagnosis includes primary brain tumor, inflammatory lesion, abscess, and brain infarction or hemorrhage. CT may also be used, but it is less specific and warrants MRI confirmation in the case of a single metastasis. Patchell et al[152] reported a false-positive rate of MRI of 11%, confirmed by histology.

Treatment

Palliative treatment of brain metastases requires rapid control of the symptoms, which are decreasing the patient's quality of life. Collaboration with colleagues in neurology is preferable. Pharmacologic treatment includes corticosteroids and antiepileptic drugs, although antiepileptic drugs should not be used prophylactically in patients without prior seizure.[153] Rapid regression of cerebral edema is the first step and can be achieved with intravenous corticosteroids. Optimal dosage is unknown, but the general practice is to administer a loading dose of Decadron (8 mg to 32 mg) followed by oral medication (4 mg four times a day).[154] Side effects are numerous, and a tapering dose schedule should be planned as symptoms improve. As a single modality, corticosteroids achieve poor survival results of 1 month to 3 months.

Treatment depends on several prognostic factors; Gaspar et al[155] have evaluated results of RTOG trials to produce a recursive partitioning analysis. Pretreatment and treatment-related variables were analyzed. Class 1 (Karnofsky Performance Status [KPS] >70, age <65 years, and controlled primary tumor) patients have a better median prognosis of 7 months. Class 2 (KPS <70, age >65 years, or uncontrolled primary tumor) patients have a median prognosis of 4 months. Class 3 (KPS <70, age >65 years, and uncontrolled primary tumor) patients have a median of 2 months. Other factors, such as histology of the tumor and the number and size of metastases, are important in the initial evaluation. Treatment options are evolving and now include whole brain radiotherapy (WBRT), surgical resection, and radiosurgery (linear accelerator or gamma knife).

Patients with a single brain metastasis in recursive partitioning analysis (RPA) Class 1 are treated aggressively with either surgical resection or SRS with or without WBRT. Multiple metastases from any RPA class receive standard WBRT alone. Patients with up to three metastases in Class 1 or 2 may be considered for local modality surgery or SRS.

Whole Brain Radiotherapy

WBRT is the treatment of choice for many patients because of the high incidence of multiple metastatic brain sites.[148,154,155] The goal of WBRT is to limit tumor progression, sterilize

microscopic disease preventing future brain metastasis[156] and to limit corticosteroid dependency. Classically, WBRT is thought to have some response in around 50% of patients and is histology dependent with small cell and breast cancers being the most sensitive. Renal cell and melanoma histologies are thought to be the most resistant. A study by Nieder et al[157] showed complete remission was observed in 37% of metastases from small-cell carcinoma, 35% of those from breast cancer, 25% of those from squamous-cell carcinoma, and 14% of those from nonbreast adenocarcinoma. The rate was 52% for metastases <0.5 cm^3 and 0% for those >10 cm^3. Sneed et al[158] showed WBRT for patients with unresected brain metastases results in symptomatic response in about 50% of patients and improvement in median survival from 3 months to 6 months compared to historical controls. The optimal dose of radiation is unknown, but in clinical practice, the range is 20 Gy in 5 fractions over 1 week to 40 Gy in 20 fractions over 4 weeks.[148]

Complications of treatment include alopecia, transient worsening of neurologic symptoms, and otitis. Continuing use of corticosteroids during WBRT may limit the incidence of most side effects. Long-term side effects such as memory loss, dementia, and decreased concentration are possible in survivors but are not expected to materialize in the majority of poor prognosis patients.

At our institutions, WBRT is becoming less commonly employed in patients with one to three metastatic lesions. Studies by Aoyama et al[156] and Chang et al[159] have shown that WBRT does not add to survival in this subset of patients and may even be detrimental, compared to SRS alone as shown in the study by Chang et al. The authors attributed this finding to patients treated with WBRT receiving less salvage treatment and less systemic therapy. In the Chang et al[159] study, there was a greater risk of significant decline in learning and memory function at 4 months in the SRS with whole brain group compared to SRS alone.

Because of this association of WBRT and cognitive decline, RTOG 0933, a single-arm Phase II study, looked at hippocampal sparring WBRT, using IMRT technique, compared to a historical control of WBRT without hippocampal avoidance. The dose received by the entirety of the hippocampus did not exceed 10 Gy, and the maximum dose did not exceed 17 Gy. The results showed that avoidance of the hippocampus during WBRT is associated with memory preservation at 4 months and 6 months. Only 4.5% of patients had progression in the hippocampal avoidance region.[160] The RTOG is planning a study of hippocampal sparing prophylactic cranial irradiation in patients with small cell lung cancer. Further study is needed to define the role and optimization of WBRT in the modern era.

Technique of WBRT

The patient is undergoing simulation for palliative treatment and therefore should be conscious and cooperative. Agitated or unresponsive patients should be stabilized before this step to decrease the risk of injury. Simulation is done in a supine position with a head rest, and immobilization is achieved with a custom mask or at least tape between the forehead and table. CT simulation requires the use of a mask.

Portal films with the gantry at 90 degrees and 270 degrees will give parallel-opposed lateral fields. The collimator should be rotated to allow the inferior border to parallel the base of skull. The field borders should go beyond the skull anterior, superior, and posterior bony limits by 2 cm to allow dosimetric homogeneity. The inferior border can be set from the bony canthus to the C1 to C2 intervertebral space and should cover the base of skull with a 1-cm margin. CT simulation is now commonly used with the same parameter but allows for a custom-block design to avoid irradiation of the lens and facial structures. All fields are treated daily. Megavoltage energy of 4 MV to 6 MV is used.

Surgical Resection

The role of surgery has evolved over the past decade. Three randomized controlled trials comparing WBRT alone versus surgery plus WBRT in patients with a single brain metastasis have been published.[152,161,162] Two demonstrated a survival advantage of the combined modalities over WBRT alone (Table 25-12). All three trials addressed the issue of single metastasis, and one cannot extrapolate the results to multiple lesions. The negative results of Mintz contradict those of others, but this trial also contained a large crossover rate, poor KPS patients, lower complete surgical resection rate, and lower WBRT dose.[162] These trials established the increased effectiveness of combination therapy of WBRT and surgical resection. Patchell et al[163] examined the effectiveness of postoperative WBRT after complete resection in patients with a single brain metastasis. They found that although whole brain did not improve survival in this group of patients it did improve local control at the site of resection, decreased the risk of general brain recurrence and decreased the risk of dying from neurological causes.

Radiosurgery

Numerous papers have been published showing the efficacy of SRS with excellent survival and local control in patients with one to three brain metastases. SRS does not require WBRT[163] to achieve excellent local control at the metastatic site, likely because of the penumbra dose beyond the periphery of the metastatic lesion sterilizing microscopic disease. In our institution, surgical resection of a single brain metastasis is trending toward being reserved for symptomatic tumors resistant to steroid treatment, larger lesions more than 4 cm where giving an ablative dose of radiation using a stereotactic technique would be deleterious and establishing diagnosis of metastatic disease when indicated.

Stereotactic radiosurgery is an accepted alternative to resection in patients with limited metastatic lesions that meet size criteria. SRS may be offered to patients with one to three brain metastases and 4 cm or less in size.[164-179]

TABLE 25-12 WBRT Alone or Plus Surgical Resection in the Management of Brain Metastases

Trial	Treatment	Radiotherapy Schedule	*n*	Median Survival (mo)	*p* Value
Patchell[152]	Biopsy + WBRT	36 Gy/12	23	4.2	<0.01
	S + WBRT	36 Gy/12	25	10	
Vecht[161]	WBRT	40 Gy/10 bid	31	6.5	NA
	S + WBRT	40 Gy/10 bid	32	10.8	
Mintz[162]	WBRT	30 Gy/10	43	6.3	0.24
	S + WBRT	30 Gy/10	41	5.9	

S, *Surgery;* WBRT, *Whole brain radiotherapy.*

RTOG 9508 study randomized 333 patients with 1 to 3 brain metastases to WBRT (37.5 Gy in 2.5 Gy fractions) versus WBRT plus SRS within 1 week of completing WBRT.[168] All metastases were ≤4 cm in size and only one metastasis could be >3 cm. The dose was dependent on the lesion size based on the RTOG 9005 Phase I study 2: 24 Gy to lesions ≤2 cm, 18 Gy for lesions >2 to ≤3 cm, and 15 Gy to lesions >3 Gy to ≤4 cm. In both RTOG 9005 and RTOG 9508, the prescription dose covering the gross tumor was the 50% to 90% isodose line, equating to central doses of 1.1 to 2 times the prescription dose. The RTOG 9508 trial demonstrated a significant survival advantage with the use of SRS in patients with a single unresectable metastasis, with a median survival of 4.9 months versus 6.5 months ($p = 0.0393$). The addition of SRS resulted in improved performance status and reduced extent of steroid use. The authors conclude that SRS should be used for patients with an unresectable solitary metastasis and considered for patients with one to three metastases.

SRS alone (without WBRT) in patients with one to three unresectable brain metastases is an alternative approach that remains actively investigated.[180,181] In retrospective studies, the 1-year local control rate is generally on the order of 80% to 95% with WBRT with SRS,[165,170,172,174,175,177] versus 80% to 90% with SRS alone.[172,177-179] At 2 years, the local control is on the order of 80% to 85% versus 50% to 70%. Thus, WBRT does lower the risk of brain failure, and the equivalence in survival likely reflects the need for more salvage therapy in the patients who underwent SRS only. In a study published by the University of Alabama (Birmingham, AL), the risk of new brain metastases in 100 patients treated with SRS alone was significantly correlated to the number of brain metastases (hazard ratio [HR] of 3.3 in patients with >3 metastases, $p = 0.004$), poorly controlled extracranial disease (HR of 2.16, $p = 0.04$), and melanoma histology ($p = 2.14$, $p = 0.02$).[182] Retrospective data suggest similar local control, overall survival, and neurologic death with SRS alone versus resection with WBRT.[183,184] Interestingly, in some series the reported local control with SRS is greater than that after resection,[185,186] probably reflecting the radiosurgical penumbra dose around the tumor periphery that treats microscopic disease.[187]

A multiinstitutional, pooled retrospective analysis examined 569 patients treated with SRS alone compared to SRS with WBRT.[167] Among the patients treated with SRS alone, 37% underwent salvage therapy at a median of 5.7 months after SRS versus 7% after a median of 8 months following WBRT with SRS. This study did not differentiate between salvage for local failures and distant central nervous system (CNS) failures. Survival was not significantly different (~8 month median survival in both arms). In a randomized study from M. D. Anderson Cancer Center (MDACC; Houston, TX), 58 patients were randomized to receive SRS alone versus SRS plus WBRT.[159] Patients treated with SRS alone had a significantly inferior 1-year tumor control (67% versus 100%, $p = 0.012$) and distant brain tumor control (45% versus 73%, $p = 0.020$), but had a significantly improved 1-year survival (63% versus 21%, $p = 0.003$), with a >2 HR of death from neurologic causes as well as systemic causes. Postulated reasons for the improved survival of the SRS-only group is the earlier administration of systemic therapy as well as the high rate of salvage therapy (87%) for brain metastases.

Avoiding WBRT can potentially prevent acute and late toxicity from WBRT and allow WBRT to be used as salvage therapy if needed. During WBRT, patients acutely experience alopecia and may develop skin erythema and mild desquamation. Less commonly, otitis media may develop. More concerning is the late toxicity from WBRT, occurring months to years after radiation, which may be relevant in the population of patients with a solitary metastasis who have a potential for cure. Late toxicity includes cataract formation, dry eye, and neurocognitive defects such as memory loss and dementia.[188-190] The extent to which WBRT causes neurocognitive defects is not well reported.[191] Neurocognitive decline may in part be because of the poor function of many patients who present with brain metastases and the general deterioration of patients whose cancer progresses.[192,193] In the randomized study of SRS versus WBRT with SRS from Japan, there was not a significant difference in the posttreatment change in neurocognitive function between the two study groups, although those patients in the SRS-alone group experienced a more rapid decline in neurocognitive function, presumably as a consequence of brain failure (local failure or distant brain failure).[194] Patients treated with WBRT did experience a continued decline in neurocognitive function, as a result of tumor recurrence or effects from WBRT. In the previously discussed trial from MDACC, Chang et al employed the most sophisticated cognitive testing to date in a randomized trial. The trial was prematurely closed because of the significantly greater likelihood of decline in learning and memory function for patients undergoing WBRT with SRS versus SRS alone.

LIVER METASTASES

Liver metastases are a common cause of morbidity and mortality. They can occur in patients with tumors of many common cancer types, are difficult to treat, and often lead to short survival periods. The liver is also protected from some cytotoxic agents because of its natural detoxification function and its relative hypoxic state. In contrast to the 80% perfusion of the normal liver by the portal venous system, most liver tumors obtain blood flow almost exclusively through the hepatic arterial system. This phenomenon necessitates novel interventional radiological techniques. Likewise, advances in imaging have allowed for more definitive anatomic localization of liver metastases, leading to new minimally or noninvasive treatments for these tumors.

Clinical Manifestations and Patient Evaluation

Common symptoms of liver metastasis include nausea, vomiting, changes in bowel habits, distension, and bloating associated with ascites, jaundice, and pain as a result of distension of the liver capsule. Some patients experience petechia, night sweats, and weight loss.

Diagnosis

Most liver metastases are discovered with routine metastatic surveys. Biphasic and triphasic helical CT is the optimal method for the detection of liver metastases. During the portal venous phase of the scan, the tumor is hypointense because of its dependence on hepatic arterial perfusion, while tumors can be enhanced on arterial phase images. Approximately 90% of lesions greater than 1 cm are detected by portal phase images alone; approximately 10% more lesions are detected when the arterial images are used in combination.[195] These imaging characteristics are also useful for distinguishing metastatic disease from many other benign small lesions commonly seen in the liver, including cysts and hemangiomas.[196] An MRI can also help detect liver metastases; however, MRIs are expensive, can have motion artifacts, and have less well-defined tumor borders. They are generally employed when a patient has a contraindication to a contrast CT scan, or when a CT is inconclusive. MRI can distinguish solid hepatic metastasis from fatty change, cysts, and hemangiomas. On T1-weighted images, hepatic metastases have low-signal intensity, whereas on T2-weighted images tumors have inhomogeneously

high-signal intensity. Other methods of tumor detection include ultrasound and incidental detection during procedures done for benign diagnoses.

Treatment

Most treatments for liver metastases are systemic. Liver metastasis can respond well to chemotherapy and hormone therapy, but most remissions are short-lived. The response to these treatments can be mixed, with some tumors progressing while others subside. Aggressive local treatments for liver metastases can also provide substantial benefits. Although liver transplantation is not recommended, resection of lesions can lead to long-term survival, particularly among patients who respond to chemotherapy.[197,198] Benefits for patients who respond to chemotherapy occur even among those who were initially unresectable because of nodes, number or location of lesions, or lesion size.[198] Generally, resections are limited to patients with disease in a single lobe peripheral to the portal region. This limitation is also true for many other localized techniques, including radiofrequency ablation and cryotherapy.

Chemoablation has arisen as an effective form of therapy. In this invasive radiological technique, the artery feeding the tumor is infused with chemotherapy, usually after an injection of contrast material defined by the tumor vasculature, followed by vascular ablation to trap the drug and asphyxiate the tumor.[199-203] Chemoablation is suitable for patients with a limited number of tumors and for whom vascular access is possible.

Irradiation Technique and Doses

Radiation techniques for liver metastases include whole liver radiation, stereotactic liver radiation, and selective internal radiation-therapy methods. Radiotherapy is often used to palliate liver-capsule pain and treat patients with chemotherapy-resistant disease. In addition, it can be used on patients with poor liver function, who have an expected survival of more than 3 months.

Whole Liver Irradiation

Normal liver has poor tolerance to EBRT if the entire liver is irradiated, and clinical liver failure can arise from low to moderate doses of whole-liver radiation (20 Gy to 30 Gy in 1.8- Gy to 2-Gy fractions). Higher doses have not been shown to be superior to lower doses. Care is taken to avoid exposure of the kidneys. Radiation has not had a significant role in the treatment of liver metastases in most institutions. It should be noted, however, that the risk for radiation-induced liver disease (RILD) is low if the whole liver dose is restricted to 30 Gy or less in fractions of 2 Gy or less.

Liver radiation for metastatic disease can be of palliative benefit, as found in an RTOG Phase II trial of 100 patients in whom palliation of pain was noted in 55%.[204] Survival for more than 6 months was significantly correlated with colorectal primary, good initial performance status, and lack of extrahepatic metastases. Median survival however even when these criteria are employed is only 4 months to 4.5 months.[205] Addition of chemotherapy provides little if any additional benefit.[206] Bydder used 5 Gy × 2 fractions and found improvement at 6 weeks in abdominal pain (63%), distention (30%), night sweats (63%), and nausea (44%). This abbreviated treatment provided results similar to those seen with more protracted courses and may be recommended for patients with poor performance status.[207]

Selective Internal Irradiation (SIRT)

Liver metastases can be treated with one of several embolization techniques, in which microscopic spheres (microspheres) are administered via the liver's arterial supply. Specific techniques include "bland embolization" in which the microspheres are not embedded with cytotoxic agents, transarterial chemotherapy embolization (TACE) in which the microspheres are embedded with chemotherapeutic agents, and SIRT in which the microspheres are embedded with radioactive Yttrium-90 (Y-90). It remains controversial as to which embolization technique is preferred for any given patient. Y-90–labeled microspheres have also been used in the treatment of hepatocellular carcinoma.[208]

Specifically, radioembolization is a highly conformal method of delivering radiation using the radioactive, beta emitter, isotope Y-90 embedded in a glass or resin microspheres. An interventional radiologist delivers these microspheres using the hepatic artery and the microsphere size allows it to become embedded in the tortuous vasculature of metastatic liver tumors. The high stopping power of the beta particle (maximum energy 2.28 MeV, average energy 0.94 MeV) allows for an average penetration range of about 2.5 mm in soft tissue. SIR-Spheres, a Y-90 labeled biocompatible resin microspheres (20 micrometers to 40 micrometers in diameter), is the only Y-90 radioembolization product approved in the United States for the treatment of unresectable liver metastases from primary colorectal cancer.

A study from Northwestern University (Chicago, IL) investigated 137 patients who underwent 227 administrations of Y-90–labeled microspheres for chemotherapy refractory liver metastases.[209] Fifty-nine percent of patients had >4 tumors. Most patients (>80%) had <25% of the liver involved. For all lesions in all patients, 87% experienced a biologic response. Toxicity was acceptable. Fifty-one patients had colorectal cancer; their median survival was about 15 months. Another study from Northwestern University demonstrated the safety and efficacy of Y-90–labeled microspheres in patients with liver metastases.[210]

In an early study from Australia of mostly patients with hepatic colorectal metastases, the combination of a single injection of Y-90–labeled microspheres plus regional hepatic artery chemotherapy was substantially more effective in increasing tumor responses and progression-free survival than the same regimen of hepatic artery chemotherapy alone. Clinical tumor response, carcinoembryonic antigen (CEA) level, and survival were all significantly improved with the addition of Y-90–labeled microspheres.[211] In another study by the same group, adding Y-90–labeled microspheres to systemic therapy yielded improved response rates and acceptable toxicity.[212] A Phase III trial published in 2010 comparing protracted intravenous fluorouracil infusion with or without Y-90 resin microsphere radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy showed that Y-90 microspheres plus fluorouracil is well tolerated and improves time to liver progression 2.1 versus 5.5 (p = 0.003).[213] A pooled analysis combined 19 studies that specifically investigated patients receiving Y-90–labeled microspheres for liver metastases from colorectal cancer. The reported median survival ranged from 10.8 months to 29.4 months.[208]

Liver metastases from neuroendocrine tumors also appear to be effectively treated with Y-90–labeled microspheres. In the study from Northwestern University, 19 patients had neuroendocrine carcinomas. Among these patients, the median survival was 26 months and the 2-year survival was 69%.[209] In a multiinstitutional report, 148 patients with liver metastases from neuroendocrine tumors underwent 185 administrations of Y-90 microspheres.[148] After treatment, 23% had stable disease, 61% partial response, 3% complete response, and 5% progressive disease. The 2-year survival was ~75% and the median survival was ~70 months. In another multiinstitutional study, 42 patients underwent Y-90 microspheres for liver

metastases from neuroendocrine tumors.[214] Greater than 90% achieved stable disease or a partial response. The median survival was on the order of 2 years. In an Australian study, 34 patients with liver metastases from neuroendocrine tumors were treated with Y-90 microspheres. Radiologic liver responses were observed in 50% of patients and included 6 (18%) complete responses and 11 (32%) partial responses; the mean overall survival was 29 months. Symptoms from the tumor were improved in 50%. The differences in survival between these studies demonstrate a heterogeneous patient population. Also, the survival without Y-90–labeled microspheres treatment cannot be determined in these patients, with a condition that is often slowly progressive. Only one of these studies addressed the potential of Y-90 microspheres treatment to alleviate symptoms from carcinoid tumors.

Evidence is accumulating supporting Y-90 use for hepatic metastatic tumor treatment in a wide variety of primary cancer histologies including breast, pancreatic, lung, renal, esophageal, ovarian, and intrahepatic cholangiocarcinoma.[215,216] Because of the expense and the limited data at this time, Y-90 is usually reserved for unresectable liver dominant metastatic hepatic disease with a projected life expectancy of at least 3 months. The prework-up of this procedure is relatively intensive and includes a pretreatment planning angiogram, microsphere angiography of the liver, and a 99m-Tc macroaggregated albumin scan that demonstrates lung shunting or flow to the gastrointestinal tract. A consensus statement addressing patient eligibility for Y-90–labeled microspheres states, "Patients considered for radioembolization therapy would include those with (1) unresectable hepatic primary or metastatic cancer, (2) liver-dominant tumor burden, and (3) a life expectancy of at least 3 months … Contraindications for radioembolization therapy may include (1) pretreatment 99m-Tc macro-aggregated albumin (MAA) scan demonstrating the potential of ≥30 Gy radiation exposure to the lung or flow to the gastrointestinal tract resulting in extrahepatic deposition of 99m-Tc MAA that cannot be corrected by catheter embolization techniques, (2) excessive tumor burden with limited hepatic reserve, (3) elevated total bilirubin level (≥2 mg/dL) in the absence of a reversible cause, and (4) compromised portal vein, unless selective or superselective radioembolization can be performed. Patients with prior radiotherapy involving the liver should be carefully reviewed on a case-by-case basis. It is unclear whether capecitabine chemotherapy treatments represent a contraindication to Y90 treatment.[217]

SBRT

Because the liver's regenerative powers make localized high-dose radiation achievable with minimal toxicity, SBRT has become popular for patients with a limited number of metastases and minimal extrahepatic tumors.[12,13,218,219] As with most SBRT approaches, respiratory arrest or gating is preferred, but four-dimensional CT has also achieved good results. Large and portal lesions can be treated safely, and most studies show local control rates of more than 70%.[218,219] No clear dose response has been measured, but all radiation doses and schedules have produced similar results.

Liver Tolerance

Although lethal RILD can occur when the median liver dose exceeds 37 Gy in standard fractionation, little or no toxicity is seen when more than 50% to 70% of the liver is maintained under 30 Gy.[220,221] Patients primarily report decreased appetite and gastritis; moreover, patients with cirrhosis may experience exacerbation of hepatitis, and those with subdiaphragmatic tumors can have asymptomatic right pleural effusions. After radiation, tumors often become hypointense on CT scans, and surrounding hepatic damage may correspond to the 37-Gy isodose line. These radiographic changes can be confused with tumor progression because tumors reach a maximum size at 6 weeks to 3 months after irradiation and recover at 6 months to 9 months. The contralateral lobe of the liver commonly hypertrophies to compensate for the lost liver mass; however, total liver volume usually maintains normal levels.

LUNG METASTASES

Disease can occur in the parenchyma and in mediastinal or hilar nodes. Metastases in the lung bases are more common than in upper regions.[11] Although peripheral lesions are often asymptomatic, central tumors can cause airway obstruction. Other signs and symptoms include cough, respiratory discomfort, shortness of breath, superior vena cava syndrome, and in severe cases hemoptysis or dysphagia. High-speed helical CT allows for high-precision detection of lung tumors smaller than 1 cm. Malignancy can be confirmed using PET/CT for glucose-avid tumor types, including colorectal, lung, and breast cancers.

Treatment

Standard treatment for pulmonary metastases is systemic chemotherapy. Tumor response to chemotherapy can be substantial, but it is usually short lived and oftentimes results in eventual recurrence. Minimally invasive surgical techniques paired with advanced imaging of the lung have made it possible to remove many small lesions. Although rarely employed for adult cancers, resection by open or minimally invasive techniques is commonly used for many childhood malignancies.[222,223] As with liver metastases, radiofrequency ablation and radiosurgical techniques are also employed.

SBRT

Use of pulmonary SBRT for metastasis to the lung has greatly increased with the advent of imaging technologies capable of identifying very small metastatic tumors. The more widespread availability of PET/CT has improved our ability to distinguish these small tumors from benign nodules. The incremental gain for patients, as with metastectomy, has been difficult to prove; still, as with surgical approaches, local control rates are consistently higher than 80% or 90%. New metastases in the lungs are also commonly low, and quality of life is improved with maintenance of pulmonary function. Additionally, most studies show increased long-term and disease-free survival, which indicates the potential for a cure.

The ability to give hypofractionated ablative doses of radiation relies on decreasing the size of the planned treatment volume to spare normal tissue from damaging penumbra. In the lung, the most severe limitation of a parsimonious PTV that covers the lesion is respiratory motion. Several methods for increased PTV accuracy include real-time imaging of the lesion during respiration, gating, and methods to decrease the severity of motion (breath hold, quiet breathing, real-time breathing feedback, and diaphragmatic immobilization). Radiation doses range from 30 Gy to 66 Gy given in 3 fractions to 10 fractions to 48 Gy to 60 Gy given in 10 fractions to 12 fractions.[224-227] Despite the wide variation in dose and fractionation, the results have been uniformly excellent with high control rates. Higher fraction sizes do not necessarily produce higher control rates for metastases, but grade-3 to grade-5 toxicity is most common with larger fraction sizes and central tumor locations.[225] In Rusthoven et al's[227] report on patients, with one to three metastases with a cumulative diameter under 7 cm, who were given 48 Gy to 60 Gy in 3 fractions: 63 lesions were treated in 38 patients with a local control rate of

96% at 2 years and 8% grade 3 and no grade 4 toxicity. Okunieff et al[224] report local failures in 8 of 125 lesions (local control rate of 94%) treated and followed for a minimum of 1 year. Tumors were up to 7.7 cm, and the dose was 50 Gy in 10 fractions. The progression-free survival progression-free survival (PFS) was 16% at 2 years. Grade-3 toxicity was seen in only 2% of patients; there was no grade-4 toxicity.

Most patients have already failed several courses of standard chemotherapy before being offered SBRT. Nevertheless, excellent tumor control with minimal toxicity and unexpectedly high rates of PFS suggest that SBRT improves morbidity and mortality.

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