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New Paradigms of Radiotherapy for Bone Metastasis

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Abstract

Proper care of patients with bone metastasis requires interdisciplinary treatments. Radiotherapy (RT) plays a central role in the management of painful bone metastasis. External beam RT can provide rapid successful palliation of painful bone metastasis in 50–80% of patients, is associated with very few adverse effects and leads to complete pain relief at the treated site in up to one-third of patients. Intensity-modulated RT (IMRT) or stereotactic body RT (SBRT) enables the delivery of higher doses to the target tumor while minimizing the dose to adjacent organs. Reirradiation using IMRT or SBRT is a valuable option for the management of bone metastases. A multidisciplinary team, especially one consisting of a spinal surgeon and rehabilitation physician, is particularly useful for treating patients with spinal bone metastases characterized by spinal instability. Rehabilitation intervention which increases the physical activity level and prevents deconditioning is important. Future developments in surgical procedures and RT will likely improve the management protocols for bone metastases and technology to reduce metal artifacts in radiation planning might improve the efficacy and safety of combination therapy.

Keywords: spinal metastases, intensity-modulated radiotherapy, rehabilitation, multidisciplinary team, stereotactic body radiotherapy

1. Introduction

Bone metastases are a common manifestation of malignancies that can cause severe and debilitating effects, including pain, spinal cord compression, hypercalcemia and pathologic

fractures. Proper care of patients with bone metastasis requires interdisciplinary treatments delivered by orthopedic surgeons, radiation oncologists, rehabilitation specialists, medical oncologists, pain medicine specialists, radiologists and palliative care professionals. Radiotherapy (RT) has played a central role for palliation of painful bone metastasis, leading to complete pain relief at the treated site in up to one-third of patients [1]. The role of RT and radiotherapeutic techniques using a multidisciplinary approach for the treatment of bone metastases have been discussed recently.

2. Indications and optimal doses for bone metastases RT

External beam RT (EBRT) continues to be the mainstay treatment for painful, uncomplicated, bone metastases. EBRT can provide rapid successful palliation of painful bone metastasis in 50–80% of patients, is associated with very few adverse effects and leads to complete pain relief at the treated site in up to one-third of patients. Although various fractionation schemes can provide good palliation rates, numerous prospective randomized trials have shown that 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction provide excellent pain control with minimal side effects (**Table 1**) [2–7]. Longer fractionated courses have the advantage of a lower incidence of repeat irradiation to the same site, whereas single fractions have proved more convenient for patients and caregivers. In addition, repeat irradiation with EBRT might be safe, effective and less commonly necessary in patients with a short life expectancy.

Author	Patients (n)	Dose and fractions	Overall pain relief (%)	Complete response (%)	Acute toxicity (%)	Late toxicity (%)	Repeat treatment rate (%)
BPTWP [2]	775	8 Gy in 1 Fx	78	57	30	2	23
		20 Gy in 5 Fx/30 Gy in 10 Fx	78	58	32	1	10
Foro [3]	160	8 Gy in 1 Fx	75	15	13	NA	28
		30 Gy in 10 Fx	86	13	18	NA	2
Hartsell [4]	898	8 Gy in 1 Fx/30 Gy in 10 Fx	66	15	10	4	18
Nielsen [5]	241	8 Gy in 1 Fx	62	15	35	5	21
		20 Gy in 4 Fx	71	15	35	5	12
Roos [6]	272	8 Gy in 1 Fx	53	26	5	5	29
		20 Gy in 5 Fx	61	27	11	4	24
Steenland [7]	1171	8 Gy in 1 Fx	72	37	Equivalent	4	25
		24 Gy in 6 Fx	69	33	Equivalent	2	7

BPTWP, Bone Pain Trial Working Party; NA, not assessed; Fx, fraction(s).

Table 1. Outcomes of single fraction or multifraction external beam radiotherapy for painful bone metastases.

For metastatic spinal cord compression (MSCC), EBRT is the standard of care. Although a total of 30 Gy in 10 fractions is the most frequently employed fractionation schedule, multiple fractionation schemes have been reported, which undoubtedly reflect the heterogeneity in patient populations and tumor histologies (Table 2) [8–11]. In a retrospective study, Rades et al. [11] suggested that dose escalation beyond 30 Gy in 10 fractions did not improve motor function and local control in patients with MSCC who had radioresistant tumors such as renal cell carcinomas, colorectal cancers and malignant melanomas. However, in patients with breast cancer, prostate cancer, myeloma or lymphoma and others who had a favorable prognosis, dose escalation beyond 30 Gy provided better local control and extended overall survival [10]. Therefore, the use of 30 Gy in 10 fractions could be regarded as the standard therapeutic dose for MSCC, although the available evidence is limited. In patients with a favorable survival prognosis, dose escalation beyond 30 Gy might improve local control and overall survival, but it might not improve functional outcome and dose escalation to 40 Gy in 20 fractions might be insufficient against radioresistant tumors.

Author	Study design	State of disease	Dose	Ambulatory rate before treatment (%)	Motor function improvement (%)	Local control	Overall survival
Maranzano [8]	RCT	Unfavorable prognosis	8 Gy in 1 Fx	64	12	NA	4 months (median)
			16 Gy in 2 Fx	67	21	NA	4 months (median)
Rades [9]	Prospective non-RCT	Various tumors	8 Gy in 1 Fx/20 Gy in 4 Fx	61	37	61% at 1 year	23% at 1 year
			30–40 Gy in 10–20 Fx	62	39	81% at 1 year	30% at 1 year
Rades [10]	Matched cohort	Favorable prognosis tumors	30 Gy in 10 Fx	85	40	71% at 2 years	53% at 2 years
			37.5 Gy in 15 Fx/40 Gy in 20 Fx	85	41	92% at 2 years	68% at 2 years
Rades [11]	Retrospective	Radioresistant tumors	30 Gy in 10 Fx	62	18	76% at 1 year	NA
			37.5 Gy in 15 Fx/40 Gy in 20 Fx	63	22	80% at 1 year	NA

RCT, randomized controlled trial; Fx, fraction(s); NA, not assessed.

Table 2. External beam radiotherapy outcomes for metastatic spinal cord compression.

3. Intensity-modulated RT or stereotactic body RT for bone metastases

Recently, intensity-modulated RT (IMRT) or stereotactic body RT (SBRT) has been applied for spinal bone metastases and the development of systemic treatments has improved

survival in patients with bone metastasis. However, in such cases, the standard regimens for bone metastases including 30 Gy in 10 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction were insufficient for long-term pain management. Therefore, to increase the duration of pain control, it might be necessary to consider more intense RT or treatment regimens.

IMRT delivers high doses to tumor targets while decreasing the dose to organs-at-risk and, therefore, presents a major dosimetric advantage over three-dimensional conformal RT. IMRT took radiation treatment planning and delivery to a higher level by combining technologies. It utilizes movement of the multileaf collimator (MLC) during the actual beam-on time to modulate, or alter, the radiation beam as it leaves the radiation treatment unit. Such beam modulation allows the application of concave dose distributions. The computer system calculates an IMRT plan incorporating several beams, or, alternatively, a moving arc arrangement with the movement of the MLC to create a plan that achieves the radiation-dosing goals (**Figure 1**). On the other hand, SBRT is emerging as an alternative RT technique to deliver dose-escalated radiation to tumor targets. Due to the application of several nonisocentric beams, SBRT delivers highly conformal large radiation dose fractions to target volumes with precision (<1 mm) and steep dose gradients. This allows for planning target volume reductions, thereby minimizing exposure to critical adjacent organs, which produces a toxicity profile comparable with that of conventionally fractionated RT, despite the use of higher doses per fraction (**Figure 2**).

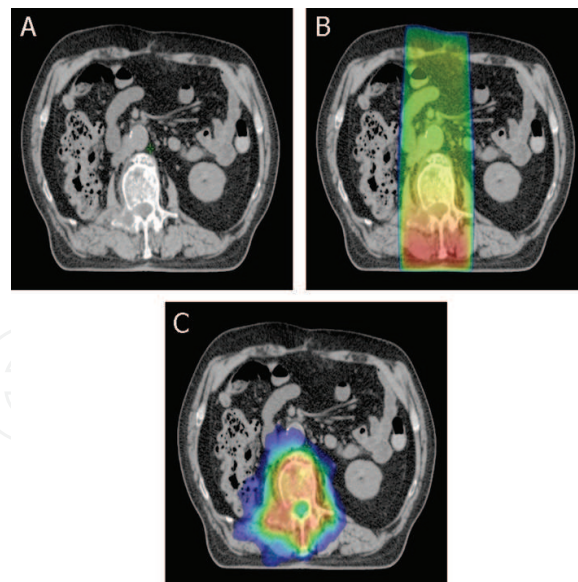


Figure 1. Comparison of radiation dose distributions between conventional radiotherapy and intensity-modulated radiotherapy (IMRT). (A) The osteolytic change in the lumbar vertebral body and infiltration into the spinal canal. (B) The dose distribution of conventional radiotherapy (two-directional anteroposterior-posteroanterior opposed irradiation at 30 Gy in 10 fractions). (C) The distribution of IMRT using volumetric modulated arc therapy (50 Gy in 10 fractions).

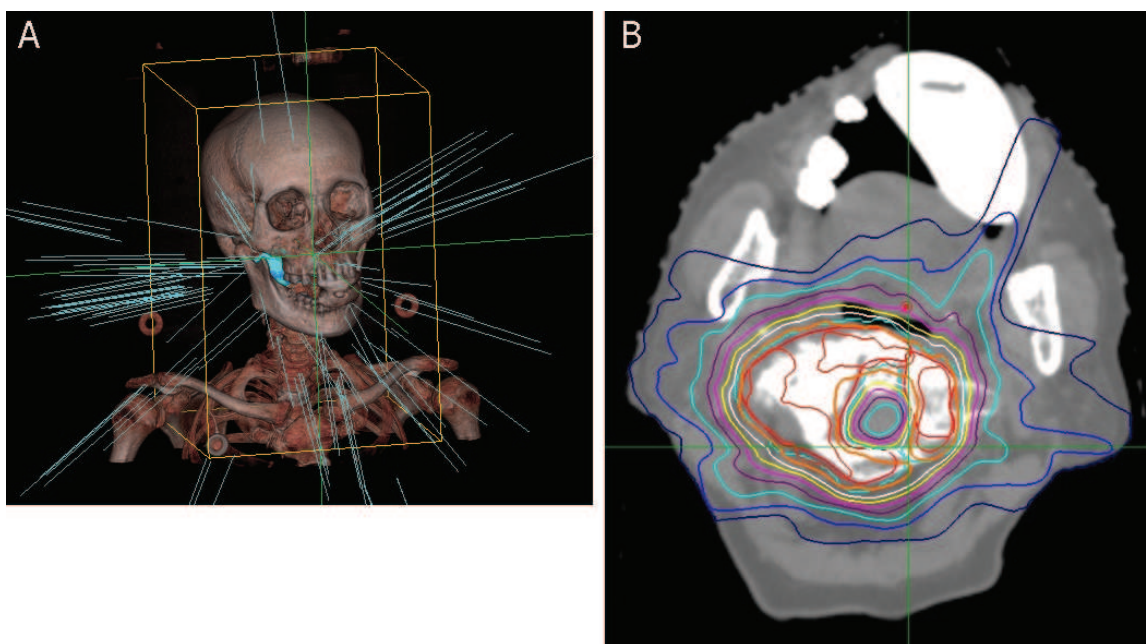


Figure 2. A 70-year-old male patient suffering from lung cancer with cervical vertebral bone metastasis. The schema and dose distribution of SBRT for bone metastasis using CyberKnife treatment system. (A) The blue line indicates the beam directions. (B) Representative dose distribution.

Three important factors should be considered for the decision to utilize IMRT or SBRT. First, IMRT or SBRT must be adapted for the treatment of oligometastasis in the bone. Long-term survival has been noted in patients diagnosed with isolated bone metastasis [12–15]. Therefore, successful control of oligometastasis of the bone due to the delivery of higher doses might contribute to improved treatment outcomes and quality of life (QOL). Second, IMRT or SBRT can be performed for reirradiation of the same site. It is technically difficult to reirradiate the same site using conventional RT. However, with IMRT or SBRT the dose to the spinal cord or adjacent organs can be reduced to within the tolerable range, facilitating reirradiation. Third, IMRT or SBRT can be applied for radioresistant bone metastases. Therefore, when indicating IMRT or SBRT for metastatic bone tumors, oncologists should consider the disease behavior and estimated life expectancy of the patient.

The treatment outcomes of previous studies that utilized IMRT or SBRT for bone metastases [16–19] are compared in **Table 3**. Each study performed IMRT or SBRT using various dose or fractionation protocols because standard regimens have not yet been proposed. The majority of studies demonstrated excellent local control without serious harmful phenomenon such as myelopathy. However, because most previous studies were retrospective and sufficient evidence has not yet been accumulated, any adaptation of IMRT or SBRT to deliver higher doses must be carefully discussed for individual patients. A multidisciplinary team comprising radiation oncologists, orthopedists, medical oncologists, radiologists, rehabilitation physicians

and palliative care medicine doctors would be ideal for discussing and deciding treatment options including the application of higher dose RT.

Authors	Machine/type	Dose	LCR	Adverse events
Murai [16]	Tomotherapy/IMRT	40 Gy in 8 fx/48 Gy in 16 fx	84% (1-year)	No radiation-induced myelopathy
Yamada [17]	Linear accelerator/IMRT	18–24 Gy in 1 fx	90%	No radiation-induced myelopathy
Guckenberger [18]	Linear accelerator/SBRT	Median 24 Gy in 3 fx	84% (2-year)	No radiation-induced myelopathy
Degen [19]	CyberKnife/SBRT	24 Gy in 1 fx	90%	No radiation-induced myelopathy

IMRT, intensity modulated radiotherapy; SBRT, stereotactic body radiotherapy; LCR, local control rate.

Table 3. Outcomes of IMRT or SBRT in bone metastasis.

4. Assessment of instability due to spinal metastasis: surgery, RT and the combination of both treatments

Oncologic care is improving and the survival rates of patients with various malignancies are increasing. Since the advent of recent technologic advancements in the detection methods used to locate new lesions and metastasis, orthopedic surgeons have been confronted with an increasing number of patients with spinal metastasis. Such patients can develop sudden paraplegia due to pathological fracture or tumor invasion into the spinal canal. Patients with symptomatic spinal metastasis present with severe pain and poor QOL [20].

If a multidisciplinary conference between radiation oncologist, spinal surgeons, physiotherapists and medical oncologists was developed, appropriate treatment strategies could be discussed and implemented. For example, a patient who develops sudden paraplegia sometimes needs urgent treatment including surgical decompression. Therefore, a simple classification method with easily assigned radiographic and patients factors could be helpful to facilitate communication and appropriate referral among the multidisciplinary oncology team, ensuring prompt and optimal treatment decisions.

Most cases of spinal metastasis occur in the vertebral body, intervertebral disc and anterior and/or posterior longitudinal ligament, whereas the involvement of anatomical structures related to spinal motion is rare. Batson's venous plexus and the avascular vein of the vertebral venous system play an important mechanistic role in the pathology of spinal metastasis. Namely, all cancers with a preference toward bone metastasis, such as bronchial, breast and prostate cancers are disseminated to the spine via these vessels. Consequently, the anterior spinal column is the most frequent site of spinal metastases, with ~80% of lesions appearing in the vertebral body [21].

Instability has been classified as segmental instability, which is mostly the result of trauma or degenerative changes, or component instability, which is caused by tumor invasion in the vertebral body. The type of instability present should be determined when considering the therapeutic management of spinal metastases. Therefore, specific criteria for stability assessments are required. In 2010, Fisher et al. [22] reported a novel classification system for spinal instability in neoplastic disease, which was established using the best evidence provided by systematic reviews and expert opinions. The spine instability neoplastic score (SINS) is a comprehensive classification system based on patient symptoms and radiographic criteria without consideration of neurologic status, histology, or general physical condition. The SINS considers spinal metastasis location, type, pain and lesion quality, spinal alignment, the extent of vertebral body collapse and posterolateral spinal element involvement. Furthermore, the predictive value of the SINS was validated by the analysis of the clinical and radiographic data of 30 patients. The SINS score is categorized into a three-tier system with 0–6 being stable, 7–12 being potentially unstable and 13–18 being unstable [23]. A surgical consultation is recommended for patients with a SINS score greater than 7.

Surgical treatment decisions are broadly based on spinal stability and patient-specific factors including patient health, prognosis and tumor histology [24]. The surgical approach is indicated for pathological fractures and sudden onset of neurological symptoms. The current indications for spinal surgery are radioresistant tumors, progressive neurologic deficits lasting no longer than 24 hours, bone fragments in the spinal canal and spinal instability due to pathologic fracture. In addition, life expectancy should be at least 3 months. Survival duration in patients with bone metastases is largely dependent upon controllability of the primary tumor. Several prognostic scoring systems have been reported in an attempt to indicate the appropriate surgical strategy [24–26]. Tokuhashi et al. [24] and Tomita et al. [25] recommended that patients expected to have a good prognosis should undergo wide excision including total en bloc spondylectomy, those expected to have an intermediate prognosis should undergo marginal or intralesional excision and spinal stabilization (**Figure 3**) and those expected to have a poor prognosis should be managed conservatively. However, it should be emphasized that local spinal pathology, rather than tumor histology, determines the degree of pain or severity of neurologic deficits. The ultimate surgical goals are to obtain good QOL and activity of daily living (ADL) scores by relieving pain and improving neurologic status (**Tables 4 and 5**).

Recently, a prospective analysis of the surgical outcome in 70 patients with symptomatic spinal metastasis was conducted [27]. Laminectomy and posterior stabilization following RT significantly improved the performance status and ADL in >95% of patients, with sustained improvement for at least 6 months in >80%. In a randomized, multicenter, nonblinded trial in 101 patients, Patchell et al. [28] revealed a major breakthrough for surgical treatment followed by RT. They compared the efficacy of surgery followed by RT with that of RT alone. Fifty patients were assigned to surgery followed by RT and 51 to RT alone. Significantly more patients were able to walk after surgery followed by RT (84%) compared with after RT alone (57%). Moreover, the duration of walking ability maintenance was significantly longer in the surgery followed by RT Arm (median, 122 days) compared with the RT alone Arm (median, 13 days).

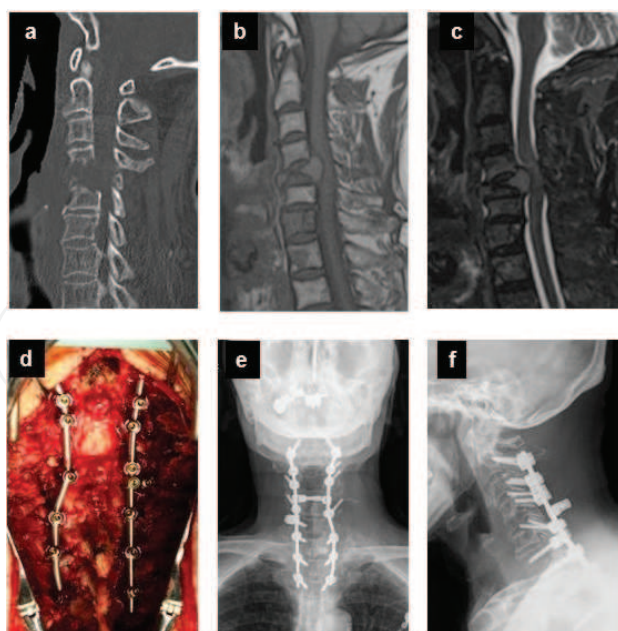


Figure 3. Laminectomy and posterior stabilization in a 76-year-old male with C5 metastasis of thyroid cancer. A patient presented with right deltoid muscle weakness and intractable pain in the right shoulder. The Tomita and Tokuhashi scores were 7 and 9 points, respectively. He underwent combination spinal surgery with a C5 laminectomy and C2 to T2 posterior stabilization, and postoperative conventional radiation therapy (30 Gy in 10 fractions). (a) Preoperative computed tomography. (b) and (c): Preoperative magnetic resonance imaging with T1-weighted and T2-weighted images, respectively. (d): Intraoperative image. (e) and (f): Postoperative radiographs.

	Treatment	Baseline	1 month	3 months	6 months
Median PS	Surgery	4	2	1	1
	Nonsurgery	3	4	4	4
Mean BI	Surgery	43.8 ± 28.0	74.2 ± 26.7	74.9 ± 31.8	82.5 ± 28.1
	Nonsurgery	48.5 ± 31.9	37.9 ± 34.1	35.5 ± 31.0	31.7 ± 10.4

Surgery patients ($n = 46$), nonsurgery patients ($n = 24$). PS, Eastern Cooperative Oncology Group Performance Status; BI, Barthel Index.

Table 4. Surgical outcome of performance score and activities of daily life in patients with spinal metastases.

The complication rate after surgery can be as high as 20–30% and this must be weighed against the intended benefits. Postsurgical complication and mortality rates were evaluated in 26,233 patients included in the National Inpatient Sample of United States [29]. The in-hospital mortality rate was 5.6% and the complication rate was 21.9%. Pulmonary (6.7%) and postoperative (5.9%) hemorrhage or hematoma were the most commonly reported complications. Complication rates were higher in older patients and those with comorbidities including hypertension, chronic lung disease and diabetes mellitus; having a

single comorbidity increased the risk of in-hospital death by ~4 fold. In a retrospective series of 123 patients treated for spinal metastases, the rate of major wound complications (dehiscence or wound infection) was 32% in the group that underwent RT before surgery, whereas it was 12% in the group of patients first treated using surgery. Therefore, in patients with symptomatic MSCC, postoperative RT appeared to be more beneficial than preoperative RT [30].

	Total	Surgery	Nonsurgery
	No. (%) (n = 70)	No. (%) (n = 46)	No. (%) (n = 24)
PS			
Improved	49 (70.0)	45 (97.8)	4 (16.7)
Unchanged	13 (18.6)	1 (2.2)	12 (50.0)
Deteriorated	8 (11.4)	0 (0.0)	8 (33.3)
Redeteriorated	9 (12.9)	9 (20.0)	0 (0.0)
ADL			
Improved	45 (64.3)	44 (95.7)	1 (4.2)
Unchanged	14 (20.0)	2 (4.3)	12 (50.0)
Deteriorated	11 (15.7)	0 (0.0)	11 (45.8)
Redeteriorated	9 (12.9)	9 (20.5)	0 (0.0)

PS, Eastern Cooperative Oncology Group Performance Status; ADL, activities of daily living.

Table 5. Outcomes of endpoints in patients undergoing surgical treatment and nonsurgical treatment.

In patients with spinal bone metastasis, the goals of spinal surgery are to restore spinal stabilization, preserve neurologic function and provide pain relief. For appropriately indicated patients, spinal surgery can provide significant improvements in both QOL and ADL, possibly leading to the administration of adjuvant systemic therapies.

5. Rehabilitation for bone metastasis after surgery or RT

Because of the advances in diagnostic and therapeutic technologies, the overall survival of cancer patients has been prolonged, although the cancer survivors treated with RT has increasing. Patients during/after RT often suffer from the RT-related toxicities including radiation sickness, fatigue, nausea, vomiting, mucous membrane disorder, etc. These symptoms markedly reduce the physical activity level of patients and lead to deconditioning,

such as muscular weakness, flexibility deterioration, cardiorespiratory dysfunction and psychological symptoms. Therefore, the rehabilitation intervention which increases the physical activity level and prevents deconditioning is important. Mock et al. reported that the walking exercise program during RT improved the physical functions, fatigue, emotional distress and difficulty sleeping in breast cancer patients during RT [31]. And Segal et al. showed that the resistance/aerobic training improved the QOL, aerobic fitness and strength in prostate cancer patients during RT [32]. Also in the guidelines from American College of Sports Medicine (ACSM) [33], the rehabilitation intervention recommended to improve physical function, aerobic fitness, QOL and fatigue in cancer patients during/after RT.

Furthermore, the number of elderly cancer patients treated with RT has been recently increasing. The elderly patients who have sarcopenia and frailty easily suffer from RT-related toxicities and deconditioning, then, decrease the completion rate of treatment [34], so the rehabilitation should be positively applied to cancer patients during/after RT, especially for elderly patients.

Moreover, the incidence of cancer survivors with bone metastasis has increased. Troublesome bone metastasis develops in 10–20% of patients with cancer. The majority of these patients have an increased risk for skeletal-related events (SREs) including pathologic fractures, spinal cord compression, the need for surgery, the need for RT and hypercalcemia [35]. SREs have been associated with significant morbidity, limited function and a decreased QOL [36–38]. In particular, pathologic fractures and spinal cord compression restrict ADL. Therefore, multidisciplinary team management of SREs (so-called bone management) is paramount in these patients. In these patients, rehabilitation over the course of treatment for the prevention of SREs and improvement of ADL and QOL is a key aspect of “bone management”.

5.1. Purpose of rehabilitation for patients with bone metastasis

The essential points of the rehabilitative interventions for patients with bone metastasis are as follows [39]. (1) Rehabilitation aims to prevent patients from becoming bed-bound and helps them to maintain as much independence as possible with regard to ADL. (2) Rehabilitation commonly focuses on training patients to use their residual functions or to develop compensatory techniques by training in the use of assistive equipment or orthoses and educating both patients and their family members to help them adjust to the altered way of life. (3) Rehabilitation has inherent risks such as pathologic fractures and spinal cord compression. Improvements in physical function and physical activity levels due to rehabilitation might lead to an increased risk of pathologic fracture during ADL. However, bed rest, as an alternative, has various complications including muscle contractures, weakness and atrophy, orthostatic hypotension, pressure sores, pneumonia, confusion and disorientation (so-called disuse syndrome). Therefore, rehabilitation with the management of SREs risk would be more beneficial compared with bed rest.

5.2. Rehabilitative intervention paradigms

For patients with bone metastasis, rehabilitation mostly provides the adequate settlement of bed rest angles, training for the use of orthoses, instructions for adequate movements for ADL and exercises to maintain and increase physical function and ADL through discussion at bone metastasis board.

5.2.1. Settlement of bed rest levels: spinal bone metastasis

In cases of pathologic fracture or fragility in the vertebral body (high risk of paralysis), the head end of the Gatch bed should be raised by 30 degrees and patients wear a rigid spinal brace. Patients are moved using the logroll technique without flexion or rotation of the spine. In cases with a low risk of pathologic fracture (bone cortex remains), patients should wear a rigid spinal brace, but there is no restriction on the bed rest angle.

5.2.2. Settlement of bed rest levels: pelvic/lower extremity bone metastasis

In the case of pathologic fracture or fragility in weight-bearing bones or joints, patients are advised to avoid weight-bearing on the affected bone or joint. In patients with remaining bone cortex and an absence of pain, there are no restrictions in ADL.

5.2.2.1. Introduction of orthoses

In patients with bone metastasis, orthoses are applied to decrease bone pain, prevent or treat pathologic fractures and paralysis and to improve physical function. In patients with cervical metastasis, in stable cases, a soft cervical collar is applied to restrict flexion and extend the cervical vertebrae. In unstable cases, a Philadelphia collar and halo vest is applied to inhibit flexion, extension, rotation and lateral bending of the cervical vertebrae. In patients with thoracolumbar metastasis, spinal orthoses are applied to facilitate local rest by restricting the flexion, extension, rotation and lateral bending of the spinal column, which helps to reduce bone pain and inflammation, thereby reducing adverse psychological effects.

In the case of conservative treatment, a functional brace is applied to the humeral diaphyseal fracture and a patellar tendon-bearing orthosis is applied to the weight-bearing bone or joint below the lower leg. It takes a long time to increase bone strength, even after RT and long-term nonweight bearing is necessary. Therefore, surgery should be considered for the bone metastasis in the weight-bearing bones of the lower extremities.

5.2.2.2. Instructions for adequate movements

In the rehabilitation setting, to decrease the risk of the pathologic fractures and pain, patients are instructed on how to move when conducting ADL. The examples are shown in **Table 6**.

Examples	
Daily life behaviors	<ul style="list-style-type: none"> ·For patients with spinal bone metastasis, excess flexion, and rotation of the trunk should be avoided in rolling over and getting up from bed. ·For patients with bone metastasis of the weight-bearing bones in the lower extremities and pelvis, the transfer of motion with non-weight bearing should be instructed. ·In getting up from the bed, patients should use the automatic bed Gatch up function.
Assistive device	<ul style="list-style-type: none"> ·A cane, crutch, or walker should be used to decrease pain and weight-bearing. ·A wheelchair should be used to decrease the physical burden in moving long distances. ·Self-help devices, such as a Sox aid, should be used to avoid the pain caused by trunk flexion.
Living environment adjustment	<ul style="list-style-type: none"> ·Install handrails to decrease pain with ambulation. ·Install handrails and higher toilet seats in the restroom to decrease pain and assist with standing up from a seated position.

Table 6. Examples of instructions of movements for activities of daily living.

5.2.2.3. Bone metastasis board

Under the concept of “bone management,” the multidisciplinary team approach is necessary to achieve the early detection and treatment of bone metastasis and the clinical practice of multidisciplinary therapy. In the treatment of bone metastasis, surgery, radiation therapy, rehabilitation and pain control should be considered, so the multidisciplinary team should discuss and decide the treatment plan in bone metastasis board. The necessity of rehabilitation and orthosis, settlement of bed rest level and risk management are also discussed in bone metastasis board, so the rehabilitation intervention can be safely provided to the bone metastatic patients.

5.3. Efficacy of rehabilitation

Previous studies have reported that rehabilitation during multidisciplinary therapy improved pain, physical function, ADL, QOL and prognosis in patients with bone metastasis (Table 7). Ruff et al. [40] showed that patients with spinal epidural metastasis who underwent rehabilitation had less pain, consumed less pain medication, were less depressed and had a greater satisfaction with life, compared with those who did not undergo rehabilitation. Other studies have reported that the rehabilitative intervention in patients with bone metastases improved functional independence measure scores, prognosis, physical function (muscle strength, submaximal aerobic exercise capacity and ambulation), physical activity level and QOL [41–44]. The rehabilitation with risk management by the multidisciplinary team could be effective in preventing SREs and improving pain, ADL, QOL and prognosis in patients with bone metastases. However, reports on the efficacy of rehabilitation in patients with bone metastasis are limited and were usually conducted in small populations. Therefore, further studies in larger populations are needed to validate the efficacy of rehabilitation.

Author	Subjects	Study design	Intervention	Primary outcome	Major results
Ruff [40]	42, spinal epidural metastasis	Controlled retrospective study	Training in transfers, bowel and bladder care, incentive spirometry, nutrition, and skin care	Pain, depression, life satisfaction	Intervention group had less pain, consumed less pain medication, were less depressed, and had greater life satisfaction.
Tang [41]	63, metastatic spinal cord compression	Retrospective descriptive study	Neuro-oncology rehabilitation, tailored to the needs of the patient	Functional independence measure scores, Tokuhashi score	Functional independence measure score improved. Longer survival in patients with high Tokuhashi scores.
Cormie [42]	20, bone metastatic prostate cancer	Randomized controlled study	Aerobic exercise and resistance exercise	Fatigue, physical function, body composition	Physical function, physical activity level, and lean mass improved.
Jane [43]	72, bone metastasis	Randomized controlled study	Massage: 3-month training program	Pain intensity, sleep quality, symptom distress scale	Beneficial effects on pain, mood, muscle relaxation, and sleep quality.
Rief [44]	60, bone metastasis	Randomized controlled study	Isometric resistance training of the muscles along the entire vertebral column	Pain, concurrent medication, oral morphine equivalent dose	Pain relief over a 6-months period and reduced oral morphine equivalent dose, as well as concomitant pain medication.

Table 7. Details of previous reports concerning rehabilitation for bone metastasis patients.

6. Reirradiation for bone metastases

RT is one of the most useful modalities for pain relief in patients with bone metastases. Although the American Society for Therapeutic Radiology and Oncology guidelines recommend 8 Gy in a single fraction as the standard method for palliative RT in uncomplicated painful bone metastases, reirradiation is required in 20–40% of cases [45, 46]. The reirradiation rates are 2.5-fold higher after single fraction RT compared with after multifraction RT [1]. Single fraction RT is commonly used for reirradiation. According to the prospective randomized trial of reirradiation undertaken by the National Cancer Institute of Canada Clinical Trial Group, single fraction RT of 8 Gy seemed to be noninferior and less toxic than multifraction RT of 20 Gy [47]. The pain relief response rate following reirradiation is 60–70%, with complete and partial responses of about 20 and 50%, respectively [46, 48], which are similar to the response rates seen with an initial effective RT. Although initial responders are more likely to respond to reirradiation than initial nonresponders, about half of the nonresponders can be expected to respond to retreatment [48].

Reirradiation is also effective to maintain walking abilities of patients with MSCC. However, the median duration of response is relatively short (about 4–5 months) [49, 50]. The degree of motor function after reirradiation is associated with the walking ability before RT. More than

80% of ambulant patients before RT will be expected to maintain the walking ability, whereas less than 20% of not ambulant patients will recover the function [49, 50]. SBRT is well suited for reirradiation of the spine due to its superiority of dose distribution compared with conventional techniques. SBRT has a major potential to provide superior local control without increasing toxicity (**Table 8**) [51–54]. A care must be taken when SBRT is applied to patients with MSSC, because the existence of tumor too close to the spinal cord is a risk factor for local recurrence due to underdose [51]. Relatively little is known regarding the long-term toxicities of reirradiation. Because reirradiation has the potential to exceed normal tissue tolerance, it might be appropriate to sum the biologically effective doses (BEDs) from the initial and repeat treatment regimens to estimate the safety of treatment. The BED is calculated according to the linear-quadratic model [$BED = D \times (1 + d/\alpha/\beta)$, D: total dose, d: fractional dose] with generally using α/β value of 2 (Gy_2) for the late effects. For example, the BED for 30 Gy in 10 fractions is 75 Gy_2 and 8 Gy in single fraction is 40 Gy_2 . Regarding the spinal cord, higher cumulative RT doses ($BED > 135.5 Gy_2$), higher doses for each RT course ($BED > 98 Gy_2$) and a short interval between the courses (<6 months) could be associated with a higher probability of developing radiation-induced myelopathy [55]. These dose constraints for the spinal cord seem to be reproducible in SBRT [56].

Author (year)	Patients/lesions (n)	Previous EBRT dose/Fx	Median dose/Fx (range)	Local control	Overall survival	Neural toxicity
Garg [52]	59/63	NA	30 Gy in 5 fx, 27 Gy in 3 fx	76% at 1 year	76% at 1 year	2 of G3 Radiculopathy
Mahadevan [53]	60/81	30 Gy in 10 fx (median)	24 Gy in 3 fx, 25–30 Gy in 5 fx	93% at last follow-up	11 month (median)	None
Hashmi [54]	215/247	30 Gy in 10 fx (median)	8–22 Gy in 1 fx, 14–50 Gy in 3(2–20) fx	93% at 6 months	64% at 6 months	None

SBRT, Stereotactic body radiotherapy; EBRT, external beam radiotherapy; Fx, fraction; NA, not available; G3, grade3

Table 8. Outcomes of reirradiation by spinal SBRT.

7. Beyond metal implant artifacts

Metallic surgical implants are commonly used in patients who undergo RT for bone metastasis. In computed tomography, metallic hardware can dramatically attenuate the X-ray beam and severe beam hardening effect and lead to faulty or inconsistent projection data [57, 58]. Consequently, so-called metallic artifacts or bright and dark streak artifacts can dramatically degrade the image quality. **Figure 4** illustrates a typical case of a patient who underwent spine-stabilization before adjacent RT. Strong artifacts induced by the titanium-based pedicle screws make it difficult to distinguish target lesions from surrounding normal tissues.

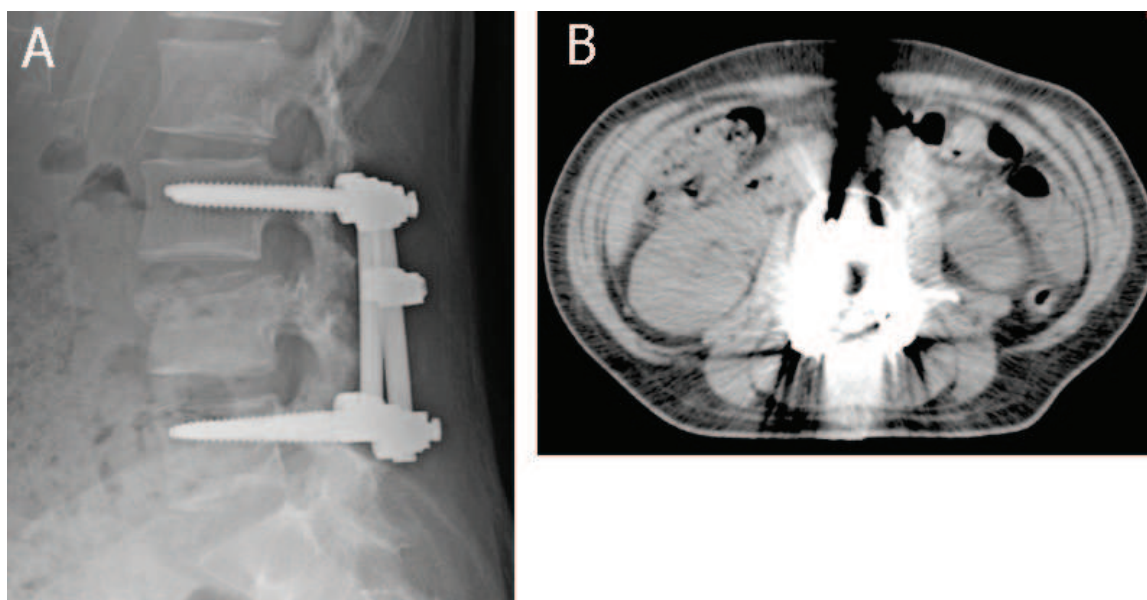


Figure 4. Artifacts of metallic surgical implants. (A) 2D radiography image shows a patient with implanted titanium pedicle screws. (B) Computed tomography image of a patient with titanium pedicle screws. Streak artifacts are present around the metallic implants.

For modern-era RT protocols, target delineation and dose calculation are performed on CT images using treatment-planning systems. Therefore, metallic artifacts, that are commonly located directly adjacent to the target volume and organs-at-risk and that degrade the delineation accuracy and dose calculation might lead to poor local control and a high risk of complications. Several studies have investigated the metallic-implant-related dosimetric impact using Monte Carlo simulations. Spadea et al. [59] reported that low-Z materials such as titanium might not cause relevant dose discrepancies, while high-Z materials including gold and platinum might lead to underestimation of the delivered dose during photon beam irradiation. Verburg et al. [60] investigated the effect of titanium implants on dosimetric errors in photon therapy treatment planning. They revealed dose discrepancies of up to 10% with range differences of up to 10 mm in artifact-contaminated areas. **Figure 5** illustrates examples of dose differences caused by titanium-based artifacts introduced by Verburg [58]. Factors including the beam-implant interaction, radiation beam type and the physical characteristics of the metals differ and eventually lead to dose uncertainties. For bone metastasis, especially in cases of infield recurrence of metastatic spinal lesions, the high dosimetric accuracy for organs-at-risk becomes clinically significant because of the limited spinal cord radiation tolerance. Recently, several promising approaches to reduce metallic artifacts have been proposed, such as metal artifact reduction (MAR) algorithms [61–63] and monoenergetic extrapolations from dual-energy computed tomography (DECT) [64, 65]. **Figure 6** briefly illustrated reduction of metal artifacts using a frequency split MAR method introduced by Meyer et al. Antiartifact approaches have proven useful for improving target delineation and dose calculation in RT, but to date, they have not been widely implicated for routine clinical use.

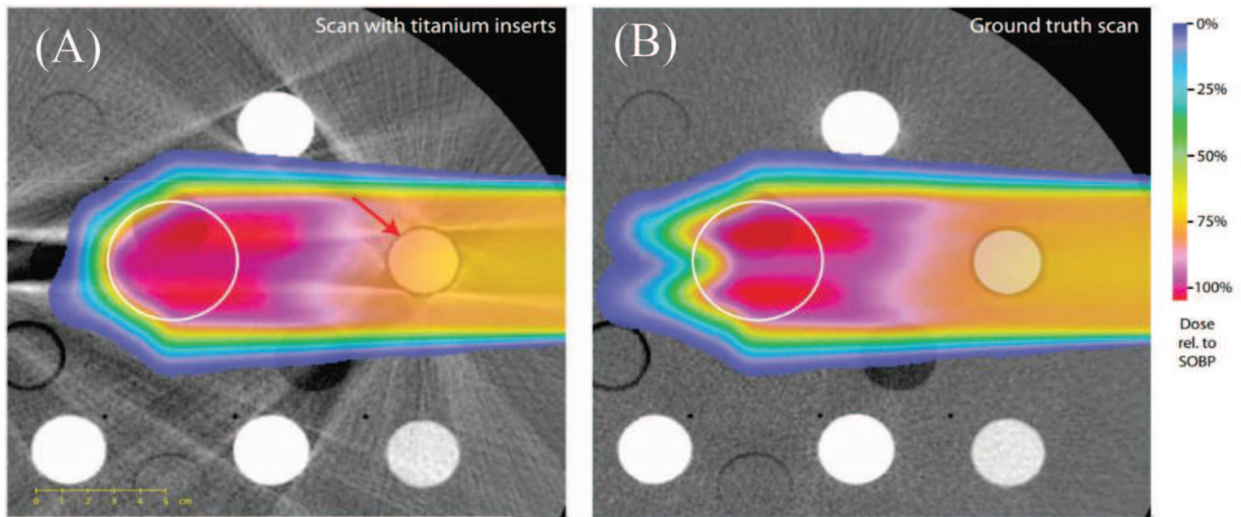


Figure 5. Differences in dose calculation of photon beams passing through the metal artifact region. (A) Dose calculation on the artifact-affected computed tomography image. The arrow indicates the titanium insert. (B) Dose calculation on the ground truth computed tomography image without the artifact.

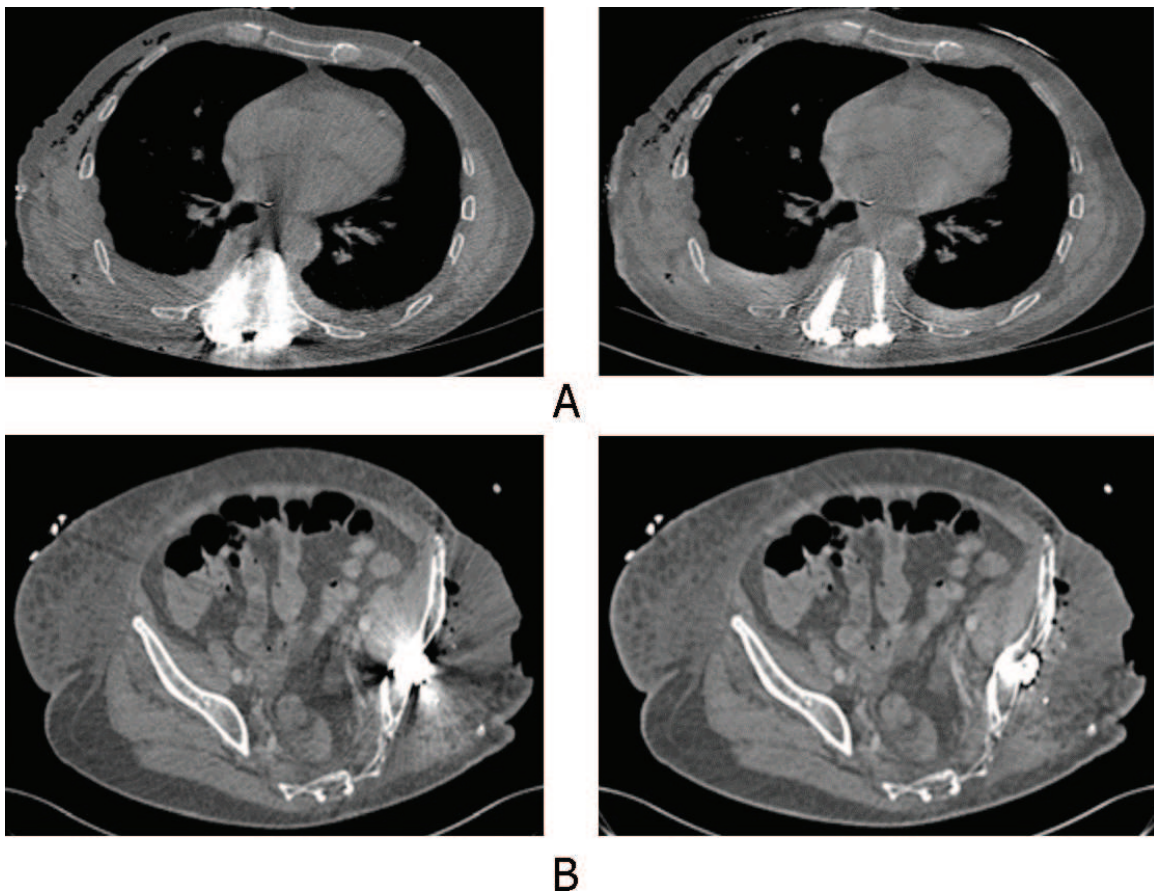


Figure 6. Reduction of metal artifacts using a frequency split MAR method. (A) Patient with implanted pedicle screws. (B) Patient with implanted unilateral hip endoprosthesis, Left: original computed tomography image; right: MAR corrected computed tomography image.

In conclusion, in cases of bone metastases, the impact of dose uncertainties due to metallic implants is critical in modern RT, especially in patients undergoing reirradiation. Promising antiartifact approaches might be useful options to achieve the anticipated magnitude of clinical benefit.

8. Conclusion

RT plays a central role in the management of painful bone metastasis. Compared with conventional RT, IMRT, or SBRT enables the delivery of higher doses to the target tumor while minimizing the dose to adjacent organs. Not only pain relief but also the restoration of spinal stability and preservation of neurologic function are associated with RT in patients with spinal bone metastases. A multidisciplinary team, especially one consisting of a spinal surgeon and rehabilitation physician, is particularly helpful for treating patients with spinal bone metastases characterized by spinal instability. Reirradiation using IMRT or SBRT is a valuable option for the management of bone metastasis. Future developments in surgical procedures and RT will likely improve the management protocols for bone metastases and technology to reduce metal artifacts in radiation planning might improve the efficacy and safety of combination therapy.

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