Conventional Radiotherapy and Stereotactic Radiosurgery in the Management of Metastatic Spine Disease

Hao-ran Zhang, MD[1], Ji-kai Li, MD[2], Xiong-gang Yang, MD[2],
Rui-qi Qiao, MD[2], and Yong-Cheng Hu, MD, PhD[1] (iD)

Abstract

Spinal metastases are a common manifestation of malignant tumors that can cause severe pain, spinal cord compression, pathological fractures, and hypercalcemia, and these clinical manifestations will ultimately reduce the health-related quality of life and even shorten life expectancy in patient with cancer. Effective management of spinal bone metastases requires multidisciplinary collaboration, including radiologists, surgeons, radiation oncologists, medical oncologists, and pain specialists. In the past few decades, conventional radiotherapy has been the most common form of radiotherapy, which can achieve favorable local control and pain relief; however, it lacks precise methods of delivering radiation and thus cannot provide sufficient tumoricidal dose. The advent of stereotactic radiosurgery has changed this situation by using highly focused radiation beams guided by 3-dimensional imaging to deliver a high biologic equivalent dose to the target region, and the spinal cord can be identified and excluded from the target volume to reduce the risk of radiation-induced myelopathy. Separation surgery can provide a 2- to 3-mm safe separation of tumor and spinal cord to avoid radiation-induced damage to the spinal cord. Targets for separation surgery include decompression of metastatic epidural spinal cord compression and spinal stabilization without partial or en bloc tumor resection. Combined with conventional radiotherapy, stereotactic radiosurgery can provide better local tumor control and pain relief. Several scoring systems have been developed to estimate the life expectancy of patients with spinal metastases treated with radiotherapy. Thorough understanding of radiotherapy-related knowledge including the dose-fractionation schedule, separation surgery, efficacy and safety, scoring systems, and feasibility of combination with other treatment methods is critical to providing optimal patient care.

Introduction

The spine is a common site of metastatic lesions. These usually involve the vertebral body, posterior arch, and pedicles, resulting in varying degrees of drug-resistant pain, pathological fractures, and neurological deficits that negatively affect patients' health-related quality of life. Following improvements in and the availability of various treatment methods, the life expectancy of patients with spinal metastases is gradually increasing, and the incidence of spinal metastases is also increasing. Spinal metastases occur in approximately 30% to 40% of patients with cancer.[1,2]

[1] Department of Bone Tumor, Tianjin Hospital, Tianjin, China
[2] Graduate School, Tianjin Medical University, Tianjin, China

Corresponding Author:
Yong-Cheng Hu, Department of Bone Tumor, Tianjin Hospital, 406 Jiefang Southern Road, Tianjin, China.
Email: huyongcheng62@126.com

Usually, the treatment of spinal metastases is aimed at relieving severe pain, restoring neurological function, and stabilizing the motion segments of spine in an effort to improve patients' quality of life and life expectancy. Appropriate care for patients with spinal metastases requires interdisciplinary collaboration between radiologists, surgeons, radiation oncologists, medical oncologists, and pain specialists. Conventionally, surgery and radiotherapy are the 2 mainstays of treatments for spinal metastases. Surgery ensures stabilization of the spine and decompression of neural elements, while radiotherapy achieves the local tumor control.

Conventional radiotherapy (CRT) is the most common form of radiotherapy and is widely used either alone or in combination with other treatment modalities.[3,4] In most cases, it requires the use of anterior and posterior beams or the use of a posterior beam alone without high conformality. Usually, the treatment volume includes 1 or 2 vertebral bodies above and below the target vertebral body. However, the effectiveness of CRT for local control is limited by spinal cord tolerance, which often leads to suboptimal palliation and a high risk of retreatment.[5,6] Recently, advances in imaging- and computer-aided technology have allowed for the consideration of novel radiotherapeutic strategies to maximize local control rates and minimize radiation-related complications.

The terms stereotactic radiosurgery (SRS) and stereotactic body radiotherapy are often used interchangeably in the treatment of spinal metastases. This technique was originally used to treat functional disorders of the brain and has been applied to the extracranial sites in the past few decades.[7]

Unlike CRT, the basic requirements for effective SRS include a small and well-defined target, high conformality of radiotherapy dose, and precise dose delivery system. Stereotactic radiosurgery uses highly focused radiation beams guided by 3-dimensional imaging to deliver a high biologic equivalent dose (BED) to the target region. The spinal cord should be able to be identified and excluded from the target volume to minimize the risk of radiation-induced myelopathy. The advantages of SRS include (1) avoidance of excessive radiation of dose-limiting structures, (2) short treatment time (especially if the patient's life expectancy is short), (3) effective treatment of previously irradiated areas, (4) effective treatment of radioresistant tumors, (5) long duration of pain relief, and (6) noninvasive treatment.

This review discusses the dose-fractionation schedules, separation surgery, efficacy and safety, scoring systems, as well as feasibility of combination with surgery for CRT and SRS. Thorough understanding of careful patient selection, pretreatment planning, and post-treatment complications is critical to the proper clinical application of radiation therapy.

Dose-Fractionation Schedules

Schedule for CRT

The clinician's choice of dose-fractionation schedule depends on a variety of factors, including the primary site of the malignancy, the location of the metastatic tumor, the history of previous radiotherapy, the risk of pathological fractures, and the life expectancy of patient with cancer.

The most common dose-fractionation schedule is 30 Gy in 10 fractions; however, a single-fraction radiotherapy with a dose of 8 Gy is considered the gold standard for pain relief for the noncomplicated bone metastases.[8] Wu et al[9] believed that a single 8-Gy treatment was a standard dose-fractionation schedule for symptomatic and uncomplicated bone metastases in patients in whom pain relief is the primary therapeutic goal. This recommendation applies to adult patients with single or multiple radiographically confirmed bone metastases without prior irradiation, pathological fractures, or spinal cord compression.

Several reports have shown that a short-course schedule of even single fraction is sufficient for the need of pain relief of most patients.[10-13] Wu et al[10] compared the pain relief effects associated with various dose-fractionation schedules of CRT in patients with painful bone metastases and observed the single-fraction (8-Gy), and multifraction radiotherapy did not differ significantly in complete and overall pain relief effects. This finding was also reported by Falkmer et al[11] and Maranzano et al.[12,13]

In addition to providing good pain relief effects, radiotherapy should provide acceptable local control of tumor and favorable patients' life expectancy. A multicenter randomized controlled trial comparing the clinical efficacy and toxicity of short-course CRT (8 Gy × 2) and split-course CRT (5 Gy × 3; 3 Gy × 5) in the treatment of metastatic spinal cord compression indicated that no significant differences were found between the 2 groups in response, duration of response, median survival, or radiation-induced toxicity.[13] The authors concluded that short-course schedules serve as an ideal radiotherapy regimen for clinical decision-making in patients with metastatic spinal cord compression with regard to patient convenience and treatment time. Another study, reported by Maranzano et al[12] in 2009, randomized 327 patients with metastatic spinal cord compression to 8 Gy × 2 group or to 8 Gy × 1 group. Similarly, there were no significant differences between the 2 groups in terms of response, duration of response, and median overall survival. These results seem to show a conclusion: A long-course and high-dose radiotherapy regimen cannot maintain a better local control and survival time and may increase the patient's economic burden owing to prolonged treatment.

However, Wu et al[10] found that the likelihood of retreatment was 2.5-fold higher in patients receiving the single-fraction treatment than in those receiving multifraction treatment, and the risk of subsequent pathologic fractures was significantly increased in patients receiving a single-fraction treatment. To compare local tumor control from short-course regimen (1 × 8 Gy/5 × 4 Gy) and long-course regimen (10 × 3 Gy/15 × 2.5 Gy/20 × 2 Gy), Rades et al[14] performed a prospective study. The local control at 1 year was 61% and 81% in the short-course group and long-course group, respectively ($P = .005$). Multivariate analysis also confirmed that improved local

control was associated with long-course regimen ($P = .018$). There was no obvious difference in 1-year survival rate between the 2 groups ($P = .28$). Rades and colleagues suggested that patients with a relatively favorable life expectancy should receive a long-course regimen to achieve more complete local tumor control.

Although no definitive high-quality study has been produced to confirm the most appropriate dose-fractionation schedule, inferences can be drawn from existing researches. Long-course and high-dose regimens appear to offer no benefit with regard to neurological recovery or overall survival compared to short-course and low-dose regimen, but long-course radiotherapy improves local control rates, which serves as an advantage in group of patients with longer life expectancy. Short-course regimens are more cost-effective and less time-consuming. Therefore, they can be considered for patients with extensive visceral metastases, for those with a life expectancy of less than 6 months, and for those with poor general condition. Long-course and high-dose regimens can be considered for patients with a life expectancy of more than 6 months and for those with less visceral metastases.

Schedule for SRS

The optimal dose-fractionation schedule for SRS is unclear. Most authors stand for a dose of 10 to 24 Gy in 1 to 5 fractions to achieve favorable symptomatic relief and local tumor control, although another important finding was that higher radiation doses can achieve better local tumor control.[15,16]

In a study of 21 patients with spinal cord compression from tumor treated with surgical decompression and instrumentation followed by high-dose single-fraction radiosurgery (dose range 18-24 Gy, median 24 Gy), Moulding *et al*[15] noted that the overall local tumor control rate was 81%, and the local control rates in the low-dose and high-dose groups were 40% (2/5) and 93.8% (15/16), respectively. Competitive risk analysis demonstrated that the patients who underwent higher doses of radiosurgery had significantly higher local tumor control rates. In a study of 93 patients with spinal metastases treated with intensity-modulated radiotherapy (dose range 18-24 Gy, median 24 Gy) between 2003 and 2006, Yamada *et al*[16] demonstrated that the overall actuarial local tumor control rate was 90% (7 patients had local failure), and the radiation dose was an independent predictor of local control rate (24 Gy vs <24 Gy, $P = .03$; >23 Gy vs <23 Gy, $P = .04$).

Separation Surgery

Currently, the greatest limitation in the application of SRS in the management of spinal metastases is the inability to provide adequate tumoricidal doses in the presence of significant spinal cord compression. Despite the high degree of accuracy and conformality of the current delivery systems, radiation-induced injury to the spinal cord cannot be completely prevented in cases of severe metastatic spinal cord compression.

Separation surgery can provide a 2- to 3-mm safe separation of tumor and spinal cord to avoid radiation-induced damage to the spinal cord. Targets for separation surgery include decompression of metastatic epidural spinal cord compression and spinal stabilization without partial or en bloc tumor resection.

Moulding *et al*[15] investigated 21 patients with high-grade, epidural, neoplastic spinal cord compression, who underwent surgical decompression and instrumentation, followed by single-fraction high-dose SRS treatments. After radiosurgery, 17 (81%) of the 21 patients showed successful local tumor control until the death or recent follow-up, with a 1-year local progression risk of 9.5%. They concluded that adjuvant SRS after decompression for the metastatic epidural spinal cord compression is an effective tool for controlling local disease and retaining neural function. This finding was also reported by Laufer *et al*.[17] They studied 186 patients with metastatic epidural spinal cord compression treated with surgical decompression, instrumentation, and postoperative SRS. The primary end point was cumulative incidence of local progression at 1 year. The results of this study indicated that the overall cumulative incidence of local progression at 1 year was 16.4% and that patients receiving high-dose hypofractionated SRS showed the lowest cumulative incidence of local progression (4.1%).

Based on these data, it is reasonable to conclude that separation surgery is a safe and effective treatment option for patients with high-grade metastatic epidural spinal cord compression. The combination of surgery with SRS will shift the surgical goal from maximal resection of the tumor to separation of the tumor from the spinal cord to facilitate subsequent high-dose radiosurgery treatment.

Response to CRT/SRS

Conventional radiotherapy is an effective palliative treatment method for spinal metastases, especially in the domains of pain relief and maintenance of neurological function. In most cases, patients with cancer are well tolerated, and severe complications are rarely mentioned in the literature.[12,14,18-20]

In a prospective trial of 209 consecutive patients with metastatic spinal cord compression treated with CRT (30 Gy) without surgery, Maranzano *et al*[19] found that the median survival time was 6 months and the 1-year survival rate was 28%. With regard to symptomatic relief, 54% and 17% of patients achieved complete or partial relief of back pain, and approximately 20% of patients experienced increased pain; 76% of patients achieved full recovery or maintenance of walking ability, while 44% of patients had improved sphincter dysfunction. Survival time was longer for patients able to walk before and/or after radiotherapy, those with favorable histologies, and females. Meanwhile, there was a consistency between the survival time and the duration of response in patient with cancer.

In another prospective randomized, phase III clinical trial designed by Maranzano *et al*,[13] 276 patients with metastatic spinal cord compression were randomly assigned to a short-

course regimen (8 Gy × 2) or to a split-course regimen (5 Gy × 3; 3 Gy × 5), with a median follow-up of 33 months. With regard to symptomatic relief, pain relief was observed in 157 (56.9%) patients, of whom 92 (33.3%) patients had complete relief and 65 (23.6%) patients had partial relief; 90% of walking patients maintained this function, 35% of patients who were previously unable to walk regained walking ability, and 17 paraplegic patients showed no improvement, Of the 29 patients with sphincter dysfunction, 4 (14%) patients regained urethral control, only 4 (2%) patients with good sphincter function worsened and required indwelling catheters, while others maintained the primary sphincter function. With regard to survival time, the median survival time was 4 months in both groups and the median duration of response was 3.5 months. The 1-year survival rates for short-course regimens and split-course regimens were 10.1% and 18.1%, respectively. The walking ability before and after treatment and the histology significantly affected the overall survival.

Conventional radiotherapy is a widely accepted therapeutic modality for spinal metastases; therefore, clinicians have gained vast clinical experience in its application in clinical practice. However, theoretically, the use of SRS as a treatment method for spinal metastases still has many advantages, such as higher proportion of local tumor control and more complete pain relief. Many studies have also revealed the efficacy of this newer modality of radiotherapy for spinal metastases.[15,16,21-23] In a meta-analysis of SRS for spinal metastases published by Kaloostian et al[18] in 2014, the overall local control rate was 92% (range 82%-100%), the percentage of pain improvement was 83% (range 36%-97%), and the percentage of pain increase was 4% (range 2%-7%).

In a prospective interventional case-series study of consecutive 102 patients with 134 malignant spinal tumors treated with single-fraction CyberKnife SRS between August 2005 and October 2007, Wowra et al[21] noted that the median survival time after radiosurgery and diagnosis of primary tumor were 1.4 and 18.4 years, respectively, and the local tumor control rate at 15 months after treatment was 98%. Multivariate analysis showed that the Karnofsky performance status (KPS) score was the independent predictive factor for survival time after radiosurgery. For patients with tumor-related pain, the visual analog scale (VAS) scores after radiosurgery (median 1) were significantly lower than those at baseline (median 7), and analysis of variance showed that there was a significant correlation between the VAS score at baseline and the pain relief after radiosurgery.

Another prospective nonrandomized cohort study further demonstrated the value of SRS in the management of spinal metastases.[22] This study included 500 lesions of histologically proven spinal metastases treated with CyberKnife SRS, with a median follow-up of 21 months. The incidence of long-term pain relief was 86% in all cases, the overall long-term radiographic local tumor control rate was 88%, and 85% of the patients with progressive neurological deficits before radiosurgery achieved neurological improvement.

Conventional Radiotherapy Versus Stereotactic Radiosurgery

Both CRT and SRS are effective treatment methods for spinal metastases, both of which are well tolerated and provide effective local tumor control and symptomatic relief. Stereotactic radiosurgery seems to offer a higher local control rate and could be applied to patients with radioresistant histologies, despite there is little high-quality evidence to support this.[5,24]

A nonblinded, randomized trial was conducted by Sprave and colleagues to compare the difference in pain relief between SRS (24 Gy in single fraction) and CRT (30 Gy in 10 fractions) for painful spinal metastases.[24] The results showed no significant difference in VAS scores between the 2 groups at 3 months ($P = .13$), but during this time, the VAS scores in the SRS group decreased faster significantly ($P = .01$). At 6 months, the VAS scores in the SRS group were significantly lower than those in the CRT group ($P = .002$). There was no difference in the consumption of opioids at 3 months ($P = .761$) or at 6 months ($P = .174$). Based on the Common Terminology Criteria for Adverse Events classification, acute or late adverse events ≥grade 3 did not occur in either group.

Sohn and colleagues performed a multicenter, matched-pair study to analyze the difference in pain relief and progression-free survival between SRS and CRT for spinal metastases from renal cell carcinoma.[5] The overall median survival after treatment in the SRS group and CRT group was 15 and 7 months, respectively, while there was no significant difference in overall survival between the 2 groups ($P = .08$). Compared with the baseline status, the VAS scores of the SRS group (2.8 vs 7.5, $P = .0001$) and the CRT group (3.1 vs 5.6, $P = .007$) were significantly lower, whereas the VAS scores of the SRS group had a larger reduction ($P = .04$). The progression-free survival of the SRS group was significantly higher than that of the CRT group ($P = .01$). Probably because of the small number of patients in each group, there was no significant difference in radiation-related toxicity between the 2 groups, with 38.5% of patients in SRS group and 53.9% of patients in CRT group were observed to develop toxic reactions.

Surprisingly, no differences were found in another matched-pair study.[25] This study included 36 patients with breast cancer with spinal metastases, 18 patients received SRS and 18 patients received CRT, and the 2 groups were comparable with regard to all matched factors and general pretreatment parameters. Overall, there was no statistically significant difference in walking ability between the 2 groups within 24 months after treatments, and there were similar trends in KPS scores and pain relief rates. Although the survival time of patients treated with SRS was slightly longer, the Kaplan-Meier analysis did not show significance ($P = .27$). With regard to radiation-related toxicity, the percentage of patients with any grade of acute toxicity in the CRT group was 56% (10/18) and in the SRS group was 39% (7/18), the χ^2 test showed the difference was not statistically significant ($P > .2$). Based on these results, SRS did not appear to offer advantages over CRT; however, it should be noted that most patients in the SRS group (17/18) had

a history of CRT for these lesions before they underwent radiosurgery, which can certainly lead to bias. Female patients who had received CRT may be in the late stages of the disease process, and the general conditions and life expectancy of these patients may be not satisfactory, which would certainly weaken the statistically visible benefits.

Complications of CRT/SRS

Radiation-induced complications can be classified into acute, subacute, and late according to the occurrence time. Acute complications are toxic reactions that occur in tissues adjacent to sites receiving radiotherapy and include nausea, emesis, and radiation-induced esophagitis. Subacute complications include radiation myelopathy, vertebral compression fracture, and bone marrow toxicity. Late complications include secondary malignant tumors.

Compared with reversible acute complications, the more feared complications are usually subacute complications, such as radiation myelopathy that may take years to appear. However, usually, the expected survival of patients with spinal metastases is shorter than the time at which these subacute complications are expected to occur. Radiation myelopathy is very rare, and there are few cases reported in the literature, whether in the CRT treatments or SRS treatments. A study focusing on the late toxicity of SRS for the treatment of spinal metastases showed that the actuarial 5- and 10-year rates of grade ≥ 2 late toxicity were 17% and 17%, respectively. And maximum point $BED_3 > 110$ Gy to spinal cord or cauda equina was associated with grade ≥ 2 late neuropathy.[26]

No radiation-induced spinal cord injury was found in the study of 500 cases of metastases to the spine treated with SRS, with a median follow-up of 21 months.[22] A retrospective study including 1075 patients with benign or malignant spinal tumors treated with CyberKnife SRS between 1996 and 2005 suggested that only 6 patients (3 tumors were metastatic and 3 tumors were benign) developed radiation myelopathy with a mean of 6.3 months (range 2-9 months) following radiosurgery.[27]

Radiation myelopathy occurred over a range of dose parameters, which prevented the precise identification of dosimetric factors that lead to this complication.[20] Although accurate determination of spinal cord dose tolerance is challenging, Emami and colleagues believed that the 5-year risk of radiation myelopathy was 5% or less when the spinal cord dose is 50 Gy to <5 cm of spinal cord in a standard fraction.[28]

In order to investigate the risk of radiation myelopathy and the tolerated dose of spinal cord, several studies had been conducted. Sahgal et al[29] compared 5 patients with radiation myelopathy with 19 patients without radiation myelopathy after SRS and found that 10 Gy in a single fraction (BED of 30 Gy 2/2) and a BED of 30 to 35 Gy 2/2 in up to 5 fractions to a maximum point within the thecal sac remained a low risk of radiation myelopathy. In order to analyze the partial volume tolerance of the spinal cord to single-fraction SRS, Ryu et al[30] reviewed 177 patients with spinal metastases treated with SRS

with 8 to 18 Gy in single fraction to determine the partial volume tolerance of the spinal cord to single-fraction SRS. The results of this study indicated that although the maximum tolerance of spinal cord to single-fraction radiosurgery was still unclear, the partial volume tolerance of spinal cord was at least 10 Gy to 10% of the volume.

Whether using CRT or SRS, vertebral compression fractures are often reported as potential adverse events after treatments. Although most fractures are asymptomatic and do not require surgical interventions, vertebral compression fractures may be associated with increased pain and neurological dysfunction. Therefore, it is important to identify high-risk population and take preventive measures in a timely manner. Several studies have analyzed the frequency and risk factors for vertebral compression fractures following SRS or CRT.[31-33]

A study aimed to analyze the predictors of vertebral compression fractures after CRT specific to colorectal cancer showed that the incidence of vertebral compression fractures was 9.3%, and sex, osteolytic lesions, and pretreatment fractures were associated with vertebral compression fractures following CRT.[33] Boehling et al[32] retrospectively analyzed data obtained from 93 patients with spinal metastases treated with SRS. The results showed that 25 (20%) patients had new or ongoing fractures and the median time from SRS to progression was 3 months. In multivariate analysis, the age >55 years, previous fractures, and pretreatment pain were determined as independent risk factors for vertebral compression fracture, and the obesity was a protective factor. Knowledge of these risk factors is useful to surgeons for appropriate patient selection to determine those who require prophylactic spinal stabilization or augmentation surgeries. A study by Wardak and colleagues[34] indicated that prophylactic vertebroplasty within 1 month after single-fraction SRS improved pain relief and prevented vertebral compression fractures compared with CRT alone.

Scoring Systems for CRT/SRS

Several scoring systems have been developed to estimate the life expectancy of patients with spinal metastases treated with radiotherapy.[35,36] Rades and colleagues retrospectively analyzed 11 potential prognostic factors for survival after radiotherapy based on the data of 1852 patients with metastatic spinal cord compression treated with CRT between January 1992 and October 2005.[35] In multivariate analysis, 6 independent prognostic factors were identified, including primary tumor type (breast cancer vs prostate cancer vs myeloma/lymphoma vs lung cancer vs other tumors), interval between diagnosis and metastatic spinal cord compression (<15 months vs >15 months), the presence of other bone metastases (no vs yes), visceral metastases (no vs yes), ambulatory status before treatment (nonambulatory vs ambulatory), and interval until onset of motor dysfunction before treatment (<14 days vs >14 days) were independent prognostic factors for survival after radiotherapy. A separate score was calculated for each of the independent prognostic factors, and the total score was categorized

into 5 groups according to the 6-month survival rate. The survival rates at 1 year for the 5 groups were 0%, 6%, 23%, 70%, and 89%, respectively, and the difference was statistically significant ($P < .001$).

From the perspective of helping doctors to assess the survival time of patients with cancer and guiding the choice of dose-fractionation schedule, the following were the authors' observations: The patients in groups A and B could receive short-course regimens because of the short life expectancy and unavailability of long-course regimens for prolonging survival; the patients in groups D and E should receive long-course regimens because of the longer life expectancy; and a short-course regimen was considered appropriate for the "gray zone" (group C).

In a study of 174 patients treated with SRS for spinal metastases, Chao and colleagues[36] performed Kaplan-Meier analysis to screen out potentially important variables associated with overall survival, followed by recursive partitioning analysis to create a regression tree. The results showed that the age, time from primary diagnosis (TPD), and KPS score were the most important prognostic factors. The authors created the following prognostic groups based on overall survival: Group 1 comprised patients with TPD of >30 months and KPS of >70; group 2 comprised patients with TPD of >30 months and KPS of ≤70 or with TPD of <30 months and age <70 years; and group 3 comprised patients with TPD of <30 months and age ≥70 years. The median overall survival of the 3 prognostic groups was 21.1, 8.7, and 2.4 months, respectively ($P < .0001$).

With regard to the target population best suited to receive SRS, Chao *et al* determined that SRS would be most beneficial to patients in group 1 because of their long life expectancy, whereas CRT would be best suited for patients in group 3. Both SRS and CRT were deemed acceptable for patients in group 2, and SRS was particularly suitable for patients with better general health conditions or for those with radioresistant histopathological findings or those with a history of radiotherapy.

Combination of Surgery and Radiation Therapy

If spinal tumors are not resected or partially resected during open or minimally invasive surgeries, radiotherapy can be used to treat the residual tumors, thus further improving local tumor control and overall survival. Gu and colleagues[37] found that immediate postoperative radiotherapy helped to suppress early inflammatory reactions and reduce the number of infiltrating macrophages and neutrophils. The interval between surgery and radiotherapy is preferably 2 to 3 weeks to allow adequate soft-tissue healing. Notably, radiotherapy can be further delayed to 4 to 6 weeks after surgery in patients who undergo bone grafting.[38]

Postoperative radiotherapy has been shown to be beneficial for both open surgery and kypho/vertebroplasty. Townsend *et al*[39] found that patients with postoperative radiotherapy had more complete pain relief and less risk of reoperation at the same site. In a retrospective study, Rock *et al*[40] performed SRS treatments in 18 postoperative patients with residual spinal

tumors, 92% of those with initial neurological deficits had stable or improved neurological function, and only 1 patient was observed to have toxicity associated with radiotherapy.

With regard to minimally invasive surgery, a prospective study involving 26 patients with pathological compression fractures treated with kyphoplasty followed by spinal radiosurgery showed that 92% of the 26 patients had pain relief and no acute radiotoxicity or progression of neurological deficit was observed.[41] This study demonstrated that the combination of kyphoplasty and SRS can immediately restore spinal stability and effectively maintain local tumor control while avoiding radiation-induced complications.

Preoperative radiotherapy is usually not recommended owing to the risk of severe wound complications and poor walking activity. In a retrospective study of 85 patients with symptomatic metastatic spinal cord compression, Ghogawala *et al*[42] demonstrated that the incidence of wound complications was 32% in patients who underwent radiotherapy before surgical decompression, which was significantly higher than that of patients who underwent *de novo* surgery ($P < .05$). Moreover, the percentage of patients who maintained an ambulatory status and were continent 1 month after treatment was lower in the radiotherapy group, followed by the surgery group than that in the *de novo* surgery group (50% vs 75%).

Conclusions and Perspectives

Effective management of spinal metastases requires multidisciplinary collaboration, with radiotherapy being the cornerstone of treatment. Conventional radiotherapy is safe and effective and provides good symptomatic relief with local tumor control, particularly for radiosensitive tumors, such as lymphomas, myelomas, and seminomas. Stereotactic radiosurgery is also widely accepted owing to its safety and efficacy in the treatment of spinal metastases, with prolonged symptomatic relief and local tumor control, even in patients with radioresistant histological findings and/or prior irradiation. Although CRT remains the most common form of radiation therapy, based on evidence provided by previous studies, it is reasonable to recommend SRS, rather than CRT, for the treatment of oligometastases and/or radioresistant metastatic lesions in the absence of relative contraindications.

ORCID iD

Yong-Cheng Hu ⓘ https://orcid.org/0000-0002-9846-6735

References

1. Wong DA, Fornasier VL, MacNab I. Spinal metastases: the obvious, the occult, and the impostors. *Spine*. 1990;15(1):1-4.
2. Gómez JAO. The incidence of vertebral body metastases. *International Orthopaedics*. 1995;19(5):309.
3. Nater A, Sahgal A, Fehlings M. Management – spinal metastases. *Handb Clin Neurol*. 2018;149:239-255.
4. Choi D, Bilsky M, Fehlings M, et al. Spine oncology-metastatic spine tumors. *Neurosurgery*. 2017;80(suppl 3):S131-S137.
5. Sohn S, Chung CK, Sohn MJ, et al. Stereotactic radiosurgery compared with external radiation therapy as a primary treatment in spine metastasis from renal cell carcinoma: a multicenter, matched-pair study. *J Neuro Oncol*. 2014;119(1):121-128.
6. Zeng KL, Tseng CL, Soliman H, et al. Stereotactic body radiotherapy (SBRT) for oligometastatic spine metastases: an overview. *Front Oncol*. 2019;9:337.
7. Bhatt AD, Schuler JC, Boakye M, Woo SY. Current and emerging concepts in non-invasive and minimally invasive management of spine metastasis. *Cancer Treat Rev*. 2013;39(2):142-152.
8. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Instit*. 2005;97(11):798-804.
9. Wu JS, Wong RK, Lloyd NS, Johnston M, Bezjak A, Whelan T; Supportive Care Guidelines Group of Cancer Care Ontario. Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases – an evidence-based practice guideline. *BMC Cancer*. 2004;4:71.
10. Wu JS, Wong R, Johnston M, Bezjak A, Whelan T. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys*. 2003;55(3):594-605.
11. Falkmer U, Jarhult J, Wersall P, Cavallin-Stahl E. A systematic overview of radiation therapy effects in skeletal metastases. *Acta Oncol*. 2003;42(5-6):620-633.
12. Maranzano E, Trippa F, Casale M, et al. 8 Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. *Radiother Oncol*. 2009;93(2):174-179.
13. Maranzano E, Bellavita R, Rossi R, et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. *J Clin Oncol*. 2005;23(15):3358-3365.
14. Rades D, Lange M, Veninga T, et al. Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys*. 2011;79(2):524-530.
15. Moulding HD, Elder JB, Lis E, et al. Local disease control after decompressive surgery and adjuvant high-dose single-fraction radiosurgery for spine metastases. *J Neurosurg Spine*. 2010;13(1):87-93.
16. Yamada Y, Bilsky MH, Lovelock DM, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *Int J Radiat Oncol Biol Phys*. 2008;71(2):484-490.
17. Laufer I, Iorgulescu JB, Chapman T, et al. Local disease control for spinal metastases following "separation surgery" and adjuvant hypo fractionated or high-dose single-fraction stereotactic radiosurgery: outcome analysis in 186 patients. *J Neurosurg Spine*. 2013;18(3):207-214.
18. Kaloostian PE, Yurter A, Zadnik PL, et al. Current paradigms for metastatic spinal disease: an evidence-based review. *Ann Surg Oncol*. 2014;21(1):248-262.
19. Maranzano E, Latini P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial. *Int J Radiat Oncol Biol Phys*. 1995;32(4):959-967.
20. Gerszten PC, Mendel E, Yamada Y. Radiotherapy and radiosurgery for metastatic spine disease: what are the options, indications, and outcomes? *Spine*. 2009;34(suppl 22):S78-S92.
21. Wowra B, Zausinger S, Drexler C, et al. CyberKnife radiosurgery for malignant spinal tumors: characterization of well-suited patients. *Spine*. 2008;33(26):2929-2934.
22. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. *Spine*. 2007;32(2):193-199.
23. Faul CM, Flickinger JC. The use of radiation in the management of spinal metastases. *J Neuro-Oncol*. 1995;23(2):149-161.
24. Sprave T, Verma V, Forster R, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. *Radiother Oncol*. 2018;128(2):274-282.
25. Gagnon GJ, Henderson FC, Gehan EA, et al. Cyberknife radiosurgery for breast cancer spine metastases: a matched-pair analysis. *Cancer*. 2007;110(8):1796-1802.
26. Ling DC, Flickinger JC, Burton SA, et al. Long-term outcomes after stereotactic radiosurgery for spine metastases: radiation dose-response for late toxicity. *Int J Radiat Oncol Biol Phys*. 2018;101(3):602-609.
27. Gibbs IC, Patil C, Gerszten PC, John RA Jr, Steven AB. Delayed radiation-induced myelopathy after spinal radiosurgery. *Neurosurgery*. 2009;64(suppl 2):A67-A72.
28. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. 1991;21(1):109-122.
29. Sahgal A, Ma L, Gibbs I, et al. Spinal cord tolerance for stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010;77(2):548-553.
30. Ryu S, Jin JY, Jin R, et al. Partial volume tolerance of the spinal cord and complications of single-dose radiosurgery. *Cancer*. 2007;109(3):628-636.
31. Mantel F, Sweeney RA, Klement RJ, et al. Risk factors for vertebral compression fracture after spine stereotactic body radiation therapy: long-term results of a prospective phase 2 study. *Radiother Oncol*. 2019;141:62-66.

32. Boehling NS, Grosshans DR, Allen PK, et al. Vertebral compression fracture risk after stereotactic body radiotherapy for spinal metastases. *J Neurosurg Spine*. 2012;16(4):379-386.

33. Lee J, Rhee WJ, Chang JS, Sei Kyung C, Woong SK. Evaluation of predictive factors of vertebral compression fracture after conventional palliative radiotherapy for spinal metastasis from colorectal cancer. *J Neurosurg Spine*. 2018;28(3):333-340.

34. Wardak Z, Bland R, Ahn C, et al. A phase 2 clinical trial of SABR followed by immediate vertebroplasty for spine metastases. *Int J Radiat Oncol Biol Phys*. 2019;104(1):83-89.

35. Rades D, Dunst J, Schild SE. The first score predicting overall survival in patients with metastatic spinal cord compression. *Cancer*. 2008;112(1):157-161.

36. Chao ST, Koyfman SA, Woody N, et al. Recursive partitioning analysis index is predictive for overall survival in patients undergoing spine stereotactic body radiation therapy for spinal metastases. *Int J Radiat Oncol Biol Phys*. 2012;82(5):1738-1743.

37. Gu Q, Wang D, Cui C, Gao Y, Xia G, Cui X. Effects of radiation on wound healing. *J Environ Pathol Toxicol Oncol*. 1998;17(2): 117-123.

38. Itshayek E, Yamada J, Bilsky M, et al. Timing of surgery and radiotherapy in the management of metastatic spine disease: a systematic review. *Int J Oncol*. 2010;36(3): 533-544.

39. Townsend PW, Rosenthal HG, Smalley SR, Cozad SC, Hassanein RE. Impact of postoperative radiation therapy and other perioperative factors on outcome after orthopedic stabilization of impending or pathologic fractures due to metastatic disease. *J Clin Oncol*. 1994;12(11):2345-2350.

40. Rock JP, Ryu S, Shukairy MS, et al. Postoperative radiosurgery for malignant spinal tumors. *Neurosurgery*. 2006;58(5): 891-898.

41. Gerszten PC, Germanwala A, Burton SA, Welch WC, Ozhasoglu C, Vogel WJ. Combination kyphoplasty and spinal radiosurgery: a new treatment paradigm for pathological fractures. *J Neurosurg Spine*. 2005;3(4):296-301.

42. Ghogawala Z, Mansfield FL, Borges LF. Spinal radiation before surgical decompression adversely affects outcomes of surgery for symptomatic metastatic spinal cord compression. *Spine*. 2001; 26(7):818-824.