Risk-adapted stereotactic body radiotherapy for patients with cervical spinal metastases

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Abstract

Owing to the complex anatomical structure and biomechanics, the current standard palliative treatments for cervical spinal metastases are associated with a high risk of recurrence and complications. Stereotactic body radiotherapy (SBRT) can provide radical dose to tumors while protecting normal organs to the maximum extent. However, the efficacy and safety of SBRT for cervical spinal metastases is not well characterized. Data from 71 patients with cervical spine metastases who were treated with SBRT using CyberKnife between 2006 and 2021 were obtained from our prospectively maintained database. Primary endpoint was pain response at 12 weeks following SBRT completion; secondary endpoints included local control (LC), overall survival (OS), and adverse events. Standard-risk patients were planned to receive 30 Gy (range 21–36) with median fractions of 3 (range 1–3) and high-risk patients 35 Gy (range 24–50) with median fractions of 5 (range 4–5) according to the spinal cord and esophagus dose constraints. The median follow-up time was 17.07 months (range 3.1–118.9). After 12 weeks of SBRT completion, 54 (98.2%) of 55 patients with baseline pain achieved pain response and 46 (83.6%) achieved complete pain response. LC rates were 93.1% and 90% at 1 year and 2 year, respectively. The 1-year and 2-year OS rates were 66.2% and 37.4%, respectively. Eight patients experienced grades 1–4 adverse events (six vertebral compression fracture [VCF], five of them had VCF before SBRT; and two hemiparesis). No grade 5 adverse events were observed.
Therefore, risk-adapted SBRT for cervical spine metastases achieved high pain control and LC rates with acceptable adverse events.

**KEYWORDS**
cervical spinal metastases, local control, pain response, risk-adapted SBRT, toxicity

# 1 INTRODUCTION

Spine is a common site of bone metastasis of malignant tumors, accounting for 40% of all cancer patients with metastatic disease, and cervical spine metastases account for 4–18% of spine metastases.1 The cervical spine has unique anatomical and functional characteristics; it is highly mobile and bears less weight than other vertebrae. Therefore, cervical spine metastases often cause severe pain, neurological deficit, spine instability, and fracture, which can seriously affect the quality of life of patients.2

Surgery can provide temporary pain relief, partially restore neurological function and spinal stability, and improve the quality of life of patients with spinal metastases; however, due to the highly complex anatomical structure and biomechanics of the cervical spine, surgery for cervical spine metastasis is challenging and associated with a high risk of serious complications.3,4 Conventional external beam radiotherapy (EBRT) has long been used in the palliative treatment of spinal metastases. However, patients treated with EBRT have shown a modest pain response and local control (LC) rates, ~10–20% complete response rate for pain and 40–80% for 1-year LC.5-7 In addition, the cervical spine cord’s sensitivity to irradiation generally precludes high radiation doses to the spine or re-irradiation using EBRT.8

Now that patients with spine metastases appear to live longer, treatment intent has shifted from the goal of short-term symptom palliation to one of long-term, durable tumor control. This change has led to the early interest in stereotactic body radiotherapy (SBRT) for spine metastases as a means for biological dose escalation. In recent years, SBRT has been used to provide a radical dose to a tumor, while protecting normal organs to the maximum extent.9 Many studies have indicated the safety and effectiveness of SBRT in the treatment of spinal metastases.2,10-12 However, there is no clear consensus on the clinically accepted doses used in spinal SBRT, with wide variability in the dose schedules ranging from 16 to 45 Gy administered in 1–5 fractions; moreover, the use of a large, single-fraction dose was shown to be associated with a high rate (20–39%) of vertebra body fracture.13 Importantly, patients with spinal cervical metastases were duly excluded due to the complex anatomy of the neck, more stringent dose limitation of the organs at risk, and limited coverage of the target volume.14 Therefore, the efficacy and safety of SBRT in the treatment of cervical spine metastases is unclear. The main objective of this study was to evaluate the clinical efficacy and safety of risk-adapted SBRT for cervical spinal metastases and to identify potential predictors of pain response and LC.

# 2 PATIENTS AND METHODS

## 2.1 Patients

This was a retrospective review of patients with cervical spinal metastases treated with risk-adapted SBRT between 1 January 2006 and 31 December 2021. Patients were identified from our prospectively maintained SBRT database. All patients were examined in a multidisciplinary setting by surgeon, medical oncologist, radiologist, and radiation oncologists at the time of treatment. The study was in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the independent ethics committees at our hospital (No. Ek2017106).

The inclusion criteria were as follows: (1) any age; (2) Karnofsky performance scale (KPS) score ≥ 50; (3) histologically proven diagnosis of solid cancer; (4) cervical spine metastases diagnosed by positron emission tomography/computed tomography (PET-CT) images, single-photon emission computed tomography (SPECT), and/or magnetic resonance imaging (MRI); (5) patient written informed consent for the treatment and database; (6) patients with spinal instability prior to spine SBRT were consulted with spine surgeons. Exclusion criteria were as follows: (1) patient with involvement of more than three consecutive vertebral segments; (2) contraindication to receiving SBRT; and (3) uncontrolled comorbid condition (neurological symptoms/deficits, metabolic, or psychiatric).

## 2.2 SBRT

Briefly, the patients were immobilized using a vacuum mattress before CT simulation. Then a set of treatment-planning CT scans of the neck was performed with a slice thickness of 1.25 mm. The images need to have had enough margins above and below the tumor according to pre-treatment-planning MRI and/or PET/CT images. CT images were transferred to the doctor’s workstation and fused with MRI, and/or PET-CT images in the CyberKnife system (CK; Accuray Inc.). The gross tumor volume (GTV) was defined as the tumor seen on imaging and delineated based on the CT, MRI, and/or PET-CT fused images. The planning target volume (PTV) was defined as a 3-mm expansion of the GTV in the x, y, and z-axis directions. To protect the spinal cord or esophagus, the edge of PTV was adjusted appropriately if it overlapped encountered the spinal cord or esophagus. All patients were treated with CyberKnife, an image-guided robotic radiosurgical system, and the Xsight spine- or skull-tracking system (Accuray Inc.) was used for real-time correction to ensure
accuracy of treatment. Dose-fractionation schedules were established at the discretion of the treating physician, using a formulaic risk-adapted approach to minimize spinal cord and esophagus toxicity while maximizing cancer killing, and were used mainly based on location, volume, and primary tumor, and so forth. It is worth noting that we divided eligible patients into standard-risk lesions and high-risk lesions because the SBRT planning and quality assurance were specifically required to meet the UK SABR Consortium Guidelines, the HyTEC, and other suggested criteria such as the Timmerman tables.15–18 Standard-risk patients were planned to receive 30 Gy (range 21–36) with median fractions of 3 (range 1–3) and high-risk patients 35 Gy (range 24–50) with median fractions of 5 (range 4–5). The representative examples of risk-adapted SBRT treatment plans for the cervical spinal metastases with/without spinal cord involvement are shown in Figure 1.

2.3 | Follow-up

The patients were observed at 1–2 months after completion of SBRT, then every 3 months for the first year, and every 6 months thereafter until 6 March 2022. Imaging especially MRI scan, symptoms, adverse events, and compliances of all patients were monitored for the follow-up period using our prospectively maintained databases. Patients were considered to have failed locally according to recommendations of the SPIne response assessment in the Neuro-Oncology (SPINO) group, which consisted of one or more of the following: a gross unequivocal increase in volume or linear dimension; new or progressive tumor in the epidural space, or neurological deterioration attributable to pre-existing epidural disease with equivocal increased epidural disease dimensions specific to the target volume site.19 In addition, MRI and/or PET-CT scanning was used to assist with differentiating radiation-related changes with local recurrence.

2.4 | Evaluation

The primary endpoint was pain response at 12 weeks following SBRT completion at the treated site; the secondary endpoints included LC, overall survival (OS), and adverse events. Pain scores at the treated spine were scored on a scale of 0 to 10 using the Brief Pain Inventory (BPI) to record the maximum pain scores at baseline (before SBRT) and thereafter at 1, 2, 3, 4, 8, and 12 weeks after SBRT completion. Pain was divided into four grades: no pain (0), mild pain (1–4), moderate pain (5, 6), and severe pain (7–10). Pain response and LC were evaluated by a medical oncologist, radiation oncologist, and neuroradiologist according to the SPINO group recommendations.19 Pain response was defined as the sum of complete pain response and pain response. The International Consensus on Palliative Radiotherapy Endpoints (ICPRE)20 defines a complete response for pain as a worst pain score of 0 on the BPI with no associated increase in daily oral morphine equivalent (OME) consumption. In accordance with the ICPRE definitions, a response for pain is defined as a reduction in the worst pain score of two points or more compared with baseline and no increase in daily OME consumption, or no increase in the worst pain score and a reduction in daily OME consumption of at least 25%. Pain progression was defined as an increase in the worst pain score from baseline by two or more points without reduced daily OME consumption, or as no

![Figure 1](image-url) Representative examples of risk-adapted SBRT treatment plans for the cervical spinal metastases. (Upper row) spinal cord involvement and (lower row) spinal cord uninvolvedment.
change in the worst pain score and an increase in daily OME consumption of at least 25%. Pain flare was defined as an increase of ≥2 points pain with the BPI, during treatment or at the end of treatment. The degree of epidural disease was assessed according to the epidural spinal cord compression (ESCC) grading system established by Bilsky, which classifies the degree of ESCC into six levels: 0, 1a, 1b, 1c, 2, and 3. In addition, all patients were divided into two groups according to the degree of compression of the spinal cord: the spinal cord uninvolved group (ESCC grades 0–1c), and the spinal cord involved group (ESCC grades 2–3). Adverse events were assessed using the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE version 5.0).

2.5 Statistical analysis

Descriptive statistics were used to summarize categorical and continuous variables. The curves of pain response, LC, and OS were plotted using the Kaplan–Meier method, and univariate analysis was performed by log-rank test to compare levels of patient characteristics and other potential predictive factors. In the multivariate analysis, a Cox proportional hazards model was applied to variables considered as significant in the univariate analysis. The differences between the spinal cord uninvolved group and the spinal cord involved group with respect to patient characteristics, treatment parameters, and treatment outcomes were assessed using Fisher’s exact probability method. Pain scores between groups were compared using t-test for independent samples. Differences between pain scores at baseline and each post-treatment time-point were assessed using paired t-test. Two-sided p-values <0.05 were considered indicative of statistical significance. SPSS 26.0 software was used for statistical analyses.

3 RESULTS

3.1 Patient, tumor, and treatment characteristics

Clinical information on 7368 patients treated with SBRT between 1 January 2006 to 31 December 2021 from our prospective maintained SBRT database was reviewed. Of these, 285 patients had spinal metastasis and were initially evaluated by a multidisciplinary tumor board. Finally, 71 patients with cervical spinal metastases were included in this analysis. There were no significant differences in baseline demographic and clinical characteristics between spinal cord involved group and spinal cord uninvolved group except for ESCC grade, BPI pain score before SBRT, American Spinal Injury Association (ASIA) Impairment Scales (AIS) neurological grades, pain medication usage before SBRT, and systemic treatment after SBRT (all p <0.05). The demographic, clinical characteristics and treatment characteristics of patients are summarized in Table 1.

The median follow-up time after cervical spine metastases SBRT was 17.07 months (range 3.1–118.9 months). The main primary tumors included 34 (47.9%) cases of lung cancer, eight (11.3%) cases of liver cancer, six (8.5%) cases of thyroid cancer. In total, 48 (67.6%) patients had radioresistant tumors including liver cancer, thyroid cancer, rectal cancer, kidney cancer, sarcoma, and so forth. Median time from diagnosis to SBRT was 21 days (range 1–715). In total, 51 (71.8%) patients received osteoclast inhibitors, and 60 (84.5%) patients underwent systemic therapy after SBRT completion. The median target volume was 15.0 cc (range 1.7–108.5). Standard-risk patients were planned to receive 30 Gy (range 21–36) with median fractions of 3 (range 1–3) and high-risk patients 35 Gy (range 24–50) with median fractions of 5 (range 4–5) according to the spinal cord and esophagus dose constraints. The spinal cord involved group were all in high-risk lesions. This corresponded to a median biologic effective dose (BED) of 60 Gy (range 35.7–100) for standard-risk and high-risk patients. There were significant differences in the mean ± standard deviation (SD) of the maximum doses to 0.1, 0.5, 1.0, and 5.0 cc as well as the maximum point maximum dose within the spinal cord in the spinal cord involved group (32.4 ± 2.0, 28.6 ± 2.8, 25.3 ± 4.1, and 9.4 ± 6.1 Gy, respectively) and the uninvolved group (24.1 ± 7.4, 20.2 ± 6.7, 17.5 ± 5.1, and 6.9 ± 7.3 Gy, respectively) (all p <0.05 except for D_{Scc}).

Only one (1.4%) patient underwent epidural spinal cord decompression and received internal fixation surgery prior to SBRT. In total, 64 (90.1%) patients had unilateral or bilateral posterolateral involvement and 28 (39.4%) had bilateral posterolateral spinal involvement. Of the 71 patients, 42 (59.2%) had epidural disease at baseline, and 6 (8.5%) had metastatic lesions presenting with spinal cord involvement. There were significant differences in pain scores, spinal alignment, and vertebra body collapse between spinal cord involved group and uninvolved group before SBRT (all p <0.05). The baseline spine instability neoplastic score (SINS) characteristics of patients are summarized in Table 2.

3.2 Pain responses

Pain scores were obtained for 55 (77.5%) of 71 patients at each time-point before and after SBRT because 16 patients (22.5%) had no pain at baseline without oral analgesics. After 12 weeks of SBRT completion, 54 (98.2%) of 55 patients who had pain at baseline achieved pain response and 46 (83.6%) of 55 patients achieved complete pain response, including two (4.3%) patients in the spinal cord involved group and 44 (95.7%) patients in the spinal cord uninvolved group. We noted significant reductions in the pain scores from baseline to 1–12 weeks after SBRT completion. The mean ± SD of the maximum pain scores on BPI at baseline, 1-, 2-, 3-, 4-, 8-, and 12-week after SBRT completion are shown in Figure 2A. The pain scores at each post-treatment time-point were significantly lower than that at baseline (all p <0.05). We observed a rapid decline in pain scores from baseline to the third week, with the greatest decline in the first week and a flat pain score curve from the third week to the 12th week. Figure 2B
| Characteristics                  | No.      | Spinal cord involvement | p-values |
|----------------------------------|----------|-------------------------|----------|
|                                 |          | Yes (n = 6)             | No (n = 65) |          |
| **Age (years)**                  |          |                        |           |          |
| <59                              | 35 (49.3%) | 2 (33.3%)               | 33 (50.8%) | 0.67     |
| ≥59                              | 36 (50.7%) | 4 (66.7%)               | 32 (49.2%) |           |
| **Gender**                       |          |                        |           |          |
| Male                             | 42 (59.2%) | 4 (66.7%)               | 38 (58.5%) | 1.00     |
| Female                           | 29 (40.8%) | 2 (33.3%)               | 27 (41.5%) |           |
| **KPS**                          |          |                        |           |          |
| <80                              | 11 (15.5%) | 2 (33.3%)               | 9 (13.8%)  | 0.23     |
| ≥80                              | 60 (84.5%) | 4 (66.7%)               | 56 (86.2%) |           |
| **Primary tumor**                |          |                        |           |          |
| Lung                             | 34 (47.9%) | 4 (66.7%)               | 30 (46.2%) | 1.00     |
| Liver                            | 8 (11.3%)  | 1 (16.7%)               | 7 (10.8%)  |           |
| Thyroid                          | 6 (8.5%)   | 1 (16.7%)               | 5 (7.7%)   |           |
| Breast                           | 5 (7.0%)   | 0                       | 5 (7.7%)   |           |
| Esophagus                        | 4 (5.6%)   | 0                       | 4 (6.2%)   |           |
| Rectum                           | 3 (4.2%)   | 0                       | 3 (4.6%)   |           |
| Kidney                           | 3 (4.2%)   | 0                       | 3 (4.6%)   |           |
| Sarcoma                          | 2 (2.8%)   | 0                       | 2 (3.1%)   |           |
| Ovarian                          | 2 (2.8%)   | 0                       | 2 (3.1%)   |           |
| Others                          | 4 (5.6%)   | 0                       | 4 (6.2%)   |           |
| **Histology**                    |          |                        |           |          |
| Radioresistant                   | 48 (67.6%) | 4 (66.7%)               | 44 (67.7%) | 1.00     |
| Radiosensitive                   | 23 (32.4%) | 2 (33.3%)               | 21 (32.3%) |           |
| **Spinal vertebrae**             |          |                        |           |          |
| C1                               | 13 (18.3%) | 0                       | 13 (20.0%) | 0.23     |
| C2                               | 11 (15.5%) | 0                       | 11 (16.9%) |           |
| C3                               | 8 (11.3%)  | 1 (16.7%)               | 7 (10.8%)  |           |
| C4                               | 10 (14.1%) | 0                       | 10 (15.4%) |           |
| C5                               | 11 (15.5%) | 2 (33.3%)               | 9 (13.8%)  |           |
| C6                               | 12 (16.9%) | 0                       | 12 (18.5%) |           |
| C7                               | 19 (26.8%) | 3 (50.0%)               | 16 (24.6%) |           |
| **ESCC grade (Bilsky score)**    |          |                        |           |          |
| 0                                | 29 (40.8%) | 0                       | 29 (44.6%) | 0.001    |
| 1a                               | 20 (28.2%) | 0                       | 20 (30.8%) |           |
| 1b                               | 11 (15.5%) | 0                       | 11 (16.9%) |           |
| 1c                               | 5 (7.0%)   | 0                       | 5 (7.7%)   |           |
| 2                                | 6 (8.5%)   | 6 (100%)                | 0          |           |
| 3                                | 0         | 0                       | 0          |           |
| **BPI pain score before SBRT**   |          |                        |           |          |
| 0                                | 16 (22.5%) | 0                       | 16 (24.6%) | 0.001    |
| 1–4                              | 21 (29.6%) | 0                       | 21 (32.3%) |           |
| 5–6                              | 20 (28.2%) | 1 (16.7%)               | 19 (29.2%) |           |
| 7–10                             | 14 (19.7%) | 5 (83.3%)               | 9 (13.8%)  |           |

(Continues)
| Characteristics                              | No.         | Spinal cord involvement | p-values |
|---------------------------------------------|-------------|-------------------------|----------|
|                                             |             | Yes (n = 6)  | No (n = 65) |          |
| Oligometastatic disease                     |             |             |             |          |
| Yes                                         | 11 (15.5%)  | 2 (33.3%)  | 9 (13.8%)   | 0.23     |
| No                                          | 60 (84.5%)  | 4 (66.7%)  | 56 (86.2%)  |          |
| Visceral metastases                         |             |             |             |          |
| Yes                                         | 36 (50.7%)  | 3 (50.0%)  | 33 (50.8%)  | 1.00     |
| No                                          | 35 (49.3%)  | 3 (50.0%)  | 32 (49.2%)  |          |
| Neurological grades (ASIA)                  |             |             |             |          |
| Grade A-D                                   | 22 (31.0%)  | 6 (100%)   | 16 (24.6%)  | 0.001    |
| Grade E                                     | 49 (69.0%)  | 0           | 49 (75.4%)  |          |
| Local treatment before SBRT                 |             |             |             |          |
| Yes                                         | 5 (7.0%)    | 0           | 5 (7.7%)    | 1.00     |
| No                                          | 66 (93.0%)  | 6 (100%)   | 60 (92.3%)  |          |
| Pain medication usage before SBRT           |             |             |             |          |
| Yes                                         | 41 (57.7%)  | 6 (100%)   | 35 (53.8%)  | 0.04     |
| No                                          | 30 (42.3%)  | 0           | 30 (46.2%)  |          |
| Osteoclast inhibitors usage                 |             |             |             |          |
| Yes                                         | 51 (71.8%)  | 4 (66.7%)  | 47 (72.3%)  | 1.00     |
| No                                          | 20 (28.2%)  | 2 (33.3%)  | 18 (27.7%)  |          |
| Time from diagnosis to SBRT (days)          |             |             |             |          |
| <21                                         | 35 (49.3%)  | 4 (66.7%)  | 31 (47.7%)  | 0.43     |
| ≥21                                         | 36 (50.7%)  | 2 (33.3%)  | 34 (52.3%)  |          |
| Target volume (cc)                          |             |             |             |          |
| <15                                         | 36 (50.7%)  | 1 (16.7%)  | 35 (53.8%)  | 0.11     |
| ≥15                                         | 35 (49.3%)  | 5 (83.3%)  | 30 (46.2%)  |          |
| Total dose/fractions                        |             |             |             |          |
| 30 Gy/3 f                                   | 19 (26.8%)  | 0           | 19 (29.2%)  | 0.17     |
| 33 Gy/3 f                                   | 4 (5.6%)    | 0           | 4 (6.2%)    |          |
| 35 Gy/5 f                                   | 23 (32.4%)  | 3 (50.0%)  | 20 (30.8%)  |          |
| 40 Gy/5 f                                   | 7 (9.9%)    | 2 (33.3%)  | 5 (7.7%)    |          |
| Othersb                                     | 18 (25.4%)  | 1 (16.7%)  | 17 (26.2%)  |          |
| Prescription isodose line                  |             |             |             |          |
| <73%                                        | 34 (47.9%)  | 2 (33.3%)  | 32 (49.2%)  | 0.68     |
| ≥73%                                        | 37 (52.1%)  | 4 (66.7%)  | 33 (50.8%)  |          |
| Systemic treatment after SBRT               |             |             |             |          |
| Yes                                         | 60 (84.5%)  | 3 (50.0%)  | 57 (87.7%)  | 0.04     |
| No                                          | 11 (15.5%)  | 3 (50.0%)  | 8 (12.3%)   |          |
| Follow-up (months)                          |             |             |             |          |
| <17.07                                      | 35 (49.3%)  | 4 (66.7%)  | 31 (47.7%)  | 0.43     |
| ≥17.07                                      | 36 (50.7%)  | 2 (33.3%)  | 34 (52.3%)  |          |

Abbreviations: ASIA, American spinal injury association impairment scale; BPI, the brief pain inventory; C1-7, the first-seven cervical vertebra; ESCC, epidural spinal cord compression; Gy, gray; KPS, Karnofsky performance status; SBRT, stereotactic body radiotherapy.

bOthers including gastric cancer (one patient), nasopharyngeal cancer (one patient), ureteral cancer (one patient), and non-Hodgkin's lymphoma (one patient).

bOthers dose of SBRT was 30 (range 21–50) Gy at 3 (range 1–5)/fraction.

Bold-faced denotes p-value < 0.05.
WANG et al. showed the proportion of all 71 patients with no pain, mild pain, moderate pain, and severe pain from baseline to 12 weeks after SBRT completion, according to the pain-at-its-worst ratings on BPI. The percentage of patients with moderate-to-severe pain decreased significantly between baseline and 12 weeks after SBRT completion, from 34 (61.8%) to 1 (1.8%) patients.
Importantly, there was a significant difference between cord involved group and uninvolved group with respect to pain response at 4–12 weeks after SBRT completion (all \( p < 0.05 \), Table 3). The difference in daily OME consumption from baseline was also significantly different between spinal cord involved group and uninvolved group (\( p < 0.05 \), Table 3). In addition, we did observe one case of pain flare at 8 weeks after SBRT completion. Some factors were selected as potential predictors of pain response in patients with pain at baseline as assessed by univariate and multivariate analyses. However, no independent predictor of pain response was identified on univariate and multivariate analyses.

### 3.3 Local control, overall survival, and pattern of progression

At the last follow-up, LC rates at 1 year and 2 years were 93.1% and 90%, respectively. There was a significant difference between the spinal cord involved group and uninvolved group with respect to LC (\( p = 0.001 \); Figure S1). On univariate analysis, KPS score (\( p = 0.025 \)), ESCC grade (\( p = 0.001 \)), and systematic treatment after SBRT (\( p = 0.004 \)) were significant prognostic factors for LC (Table S1). However, on multivariate analyses, only ESCC grade was the independent predictor of LC (\( p = 0.001 \)). The median OS was 17.3 months (range 3.1–118.9). The 1-year and 2-year OS rates were 66.2% and 37.4%, respectively. At the time of analysis, 54 (91.5%) of 59 patients had died without local progression, and the death was attributed to progression of systemic disease. Local progression was identified in three (4.6%) of 65 patients and two (33.3%) of six patients in the spinal cord uninvolved group and spinal cord involved group, respectively (\( p = 0.001 \)).

### 3.4 Adverse events

In this study, adverse events were as anticipated, but no grade 5 adverse events were recorded during the study period. In total, eight patients (9.9%) experienced adverse events; three patients in the spinal cord uninvolved group (two vertebral compression fracture [VCF], one of them had VCF before SBRT and one had hemiparesis), and five patients in the spinal cord involved group (four of them had VCF before SBRT and one had hemiparesis). Among them, three patients who experienced grade 3 VCF were in the spinal cord involved group, and one patient who experienced grade 4 hemiparesis was in the spinal cord uninvolved group, respectively. There was a significant difference between the spinal cord involved group and the spinal cord uninvolved group with respect to adverse events (\( p = 0.0001 \)). The adverse events of patients are summarized in Table S2.

The grade 4 radiation-induced myelopathy details of a representative patient are as follows: a patient with breast cancer was diagnosed with C4 cervical spine metastasis (involving vertebral body, left pedicle, left lamina, and left transverse process) with a grade 1b epidural lesion at 33 months postoperatively (standard-risk lesions). She was treated with a prescribed dose of 30 Gy in three fractions, encompassing the target volume of 5.6 cc. The maximum point dose for spinal cord was 26.5 Gy, and the doses to the spinal cord volume of 0.1, 0.5, 1.0, and 5.0 cc were 19.0, 13.5, 10.2, and 3.6 Gy, respectively. After 4 months of SBRT completion, the C4 metastasis was significantly decreased, but after 8 months of SBRT completion, the patient who developed anesthesia and dyskinesia, ultimately developed progressive hemiparesis in the left upper and lower extremities, and then underwent surgery at 17 months after SBRT completion for cervical instability (Figure 3).

### 4 DISCUSSION

To the best of our knowledge, no studies have reported the outcomes of risk-adapted SBRT for cervical spinal metastasis. In this largest sample study, SBRT achieved high rates of pain response and complete pain response at 12 weeks. There was rapid improvement in pain scores along with a significant reduction in daily OME consumption from baseline. We also observed high rates of LC (93.1% and 90% at 1 year and 2 years, respectively). Only eight patients developed adverse events after risk-adapted SBRT, and there was no grade 5 adverse events. Larger prospective clinical trials are required to further evaluate the optimal dose-fractionation schedules for cervical spinal metastases.

Currently, there is no standardized strategy for the surgical treatment of spinal metastases, and the debate has focused on the preferred treatment for patients with ESCC grades 1c–3. In clinical practice, some cancer centers consider ESCC grade as one of the indications for surgery, and patients with mild ESCC grades 1a–1c are also offered surgical treatment. However, some studies have suggested that radiosurgery can be the initial therapy for severe ESCC. In recent years, NOMS has been shown to be an effective tool for the multidisciplinary management of spinal metastases by combining conventional EBRT, SBRT, and minimally invasive or open surgery, taking into account the four aspects of neurologic, oncologic, mechanical, and systemic assessment. Our results are consistent with the treatment recommendations of the NOMS Framework for spinal metastases. Patients with ESCC grades 0–2 can achieve high rates of complete pain response and LC after risk-adapted SBRT, with durable clinical efficacy and acceptable adverse events. Importantly, risk-adapted SBRT appears to be a viable treatment for cervical spinal metastases and patients with ESCC grade 2 may avoid surgical treatment.

The standard of care for patients with spinal metastases was a low total dose of radiation delivered in >5 fractions of EBRT, however, complete response rates for pain were low, typically ranging from 10% to 20%. Importantly, radiation dose escalation within EBRT has not improved the response rates for pain. Over the past decade, the field of radiation oncology has undergone a technical transformation, allowing for SBRT to routinely deliver high dose per fraction radiation precisely within the body in only a few treatment
WANG et al. reported a multicenter, randomized, phase 2/3 trial that included 229 patients treated with SBRT versus EBRT for painful spine metastases. The prescription was 24 Gy/2 fractions in SBRT group and 20 Gy/10 fractions in EBRT group. At 3 months after treatment, SBRT was superior to EBRT not only in improving the complete response rate for pain, but also in

| Characteristics                  | No. (n = 55) | Spinal cord involvement | p-values |
|----------------------------------|--------------|-------------------------|----------|
|                                  |              | Yes (n = 6)             | No (n = 49) |         |
| 2-week assessment                |              |                        |           |
| Complete response                | 15 (27.3%)   | 0                       | 15 (30.6%) | 0.17    |
| Partial response                 | 40 (72.7%)   | 6 (100%)                | 34 (69.4%) |         |
| Stable pain                      | 0            | 0                       | 0         |         |
| Progressive pain                 | 0            | 0                       | 0         |         |
| Indeterminant                    | 0            | 0                       | 0         |         |
| Daily OME consumption, mg (mean) | 22.82 (28.3) | 77.33 (31.97)           | 16.63 (20.67) | 0.001   |
| Mean change in SINS from baseline| −0.87 (1.03) | −0.33 (0.75)            | −0.94 (1.94) | 0.45    |
| 4-week assessment                |              |                        |           |
| Complete response                | 32 (58.2%)   | 0                       | 32 (65.3%) | 0.003   |
| Partial response                 | 23 (41.8%)   | 6 (100%)                | 17 (34.7%) |         |
| Stable pain                      | 0            | 0                       | 0         |         |
| Progressive pain                 | 0            | 0                       | 0         |         |
| Indeterminant                    | 0            | 0                       | 0         |         |
| Mean daily OME consumption, mg   | 9.27 (16.02) | 31.67 (19.51)           | 6.53 (13.14) | 0.001   |
| Mean change in SINS from baseline| −1.60 (1.09) | −1.33 (0.94)            | −1.63 (1.10) | 0.53    |
| 8-week assessment                |              |                        |           |
| Complete response                | 41 (74.5%)   | 2 (33.3%)               | 39 (79.6%) | 0.011   |
| Partial response                 | 13 (23.6%)   | 3 (50.0%)               | 10 (20.4%) |         |
| Stable pain                      | 0            | 0                       | 0         |         |
| Progressive pain                 | 1 (1.8%)     | 1 (16.7%)               | 0         |         |
| Indeterminant                    | 0            | 0                       | 0         |         |
| Mean daily OME consumption, mg   | 5.64 (16.27) | 23.33 (35.90)           | 3.47 (9.80) | 0.003   |
| Mean change in SINS from baseline| −1.91 (1.05) | −2.17 (1.07)            | −1.88 (1.04) | 0.52    |
| 12-week assessment               |              |                        |           |
| Complete response                | 46 (83.6%)   | 2 (33.3%)               | 44 (89.8%) | 0.002   |
| Partial response                 | 8 (14.5%)    | 3 (50.0%)               | 5 (10.2%)  |         |
| Stable pain                      | 0            | 0                       | 0         |         |
| Progressive pain                 | 1 (1.8%)     | 1 (16.7%)               | 0         |         |
| Indeterminant                    | 0            | 0                       | 0         |         |
| Mean daily OME consumption, mg   | 5.00 (17.96) | 25.00 (43.87)           | 2.55 (8.46) | 0.002   |
| Mean change in SINS from baseline| −2.13 (0.99) | −2.17 (1.07)            | −2.12 (0.98) | 0.91    |

Note: Pain responses at 2-, 4-, 8-, and 12-week after SBRT relative to baseline assessments were based on International Consensus on Palliative Radiotherapy Endpoints. OME: oral morphine equivalent.
Abbreviation: SINS, the spine instability neoplastic score.
Bold-faced denotes p-value < 0.05.

fractions. For example, Sahgal and colleagues reported a multicenter, randomized, phase 2/3 trial that included 229 patients treated with SBRT versus EBRT for painful spine metastases. The prescription was 24 Gy/2 fractions in SBRT group and 20 Gy/10 fractions in EBRT group. At 3 months after treatment, SBRT was superior to EBRT not only in improving the complete response rate for pain, but also in...
showing a faster decrease within the period. Therefore, it is noted that the use of SBRT is appropriate in the definitive setting for symptom control for selected patients with spinal metastases.

In recent years, the application of SBRT in spinal metastases has been frequently reported, but there is a wide variation in the dose-fractionation schemes. In the phase 2/3 NRG Oncology/RTOG 0631 trial, which compared SBRT at a dose of 8 Gy in one fraction with 16 or 18 Gy in one fraction, no improvement in response rates for pain was observed. However, a high rate (20–39%) of vertebra compression fracture has been associated with large, single-fraction doses. More recently, in some studies, LC rate appeared to be greater after multiple-fraction SBRT compared with single-fraction SBRT. However, not only optimal dose-fractionation schemes, but also safety and efficacy for cervical spinal metastases are not clear. In part, because patients with cervical spinal metastases were duly excluded due to the complex anatomy of the neck, more stringent dose limitation of the organs at risk, and the limited coverage of the target volume are needed. Surprisingly, our results showed that patients with cervical spinal metastases had higher rates of complete pain response and LC rate with an acceptable rate of adverse events after risk-adapted SBRT compared with those mentioned above.

In this study, risk-adapted SBRT was found to achieve excellent LC with 2-year LC rates of 90% on long-term follow-up. These results were supported by a report from the MD Anderson Cancer Center, which reported an overall LC rate of 91% at median follow-up of 6.7 years of 261 sites treated with risk-adapted SBRT. Importantly, our results were superior to other studies, and the possible reasons were as follows. First, it is worth noting that the higher pain control and LC rates may partly be explained by primary tumor types, but the proportion of radioresistant tumors was higher than that in other studies (67.6% versus 31.81%–60%, respectively). Second, higher rates may also be explained by the baseline epidural lesions. The proportion of patients with baseline high-grade epidural disease (ESCC grade 2–3) was much smaller than in other studies (8.5% versus 26.7–44.0%, respectively). Finally, the prescribed dose-fractionation schemes may also be a determinant of the efficacy of SBRT for spinal metastases, and the median prescription dose/fraction in our study was higher than that of other studies (33 Gy/4 fractions versus 24 Gy/2 fractions).

Our results are consistent with a published study in which local progression was identified in five (7.0%) of 71 patients. Among them, three (4.6%) of 65 patients and two (33.3%) of six patients were in the spinal cord uninvolved group and the spinal cord involved group, respectively. These results suggested that the prescription dose for patients with epidural lesions is often compromised due to the limited radiation tolerance of the spinal cord, especially in patients with spinal cord involvement, resulting in a suboptimal dose to the cervical spine metastasis. Tseng and colleagues investigated a cohort of patients with de novo spinal metastases treated with 24 Gy in two fractions; they found that presence of epidural disease was a predictor of local progression, and the higher the grade of epidural disease, the higher was the incidence of local progression. Similarly, a study...
by Al-Omair and coworkers demonstrated that postoperative epidural disease grade was a significant predictor of LC. In this setting, one proposed strategy involved surgical removal of epidural tumors to increase the spacing between the tumor and the spinal cord. This approach can improve the minimum radiation dose to the spinal cord and therefore decrease the rate of local failure.

Our results were consistent with the results of the above studies. The complete pain response rates at 12 weeks were 33.3% in the spinal cord involved group and 89.8% in the spinal cord uninvolved group; the 1-year LC rates were 66.7% and 95.8%, and the 2-year LC rates were 66.7% and 92.5%, respectively. Complete pain response and LC were significantly different between these two groups (all \( p < 0.05 \)). However, the results reported by Anand and colleagues were different to our results; they investigated 52 patients with 76 spinal metastases who were treated with 24 Gy in a median of three fractions for the involved vertebra and 21 Gy in three fractions for the uninvolved elements. In this study, 90% of patients with malignant epidural compression (MEC) and 93.75% of patients with non-MEC achieved completed the pain response. There were no significant differences between groups with or without MEC with respect to pain control, LC, or OS. These findings suggested that the presence of spinal cord involvement may be related to the efficacy, and that risk-adapted SBRT could be a safe and effective treatment for patients with cervical spinal cord involvement.

In addition to these favorable outcomes, we found a very low incidence of late toxicities among our patients. With long-term follow-up, radiation myelopathy and VCF are the most serious late radiation-induced toxic effects after spinal SBRT and, although rare, can cause both paralysis and death. Two of our patients developed radiation-induced myelopathy, but no grade 5 was recorded during the study period. This was consistent with the HyTEC and other suggested cord constraints such as the Timmerman tables. However, four patients (66.7%) and two patients (3.6%) experienced VCF in the spinal cord involved group and the spinal cord uninvolved group, respectively. SBRT-induced VCF was a more frequent and yet serious late effect, but only 5% of patients had symptoms. Reports showed that crude risk ranged from 11% to 39%, which was higher than that seen with EBRT. However, it needs to be considered that almost one-quarter of the patients had VCF before SBRT, and other factors for VCF were lytic lesions and higher dose per fraction. Importantly, ~32% of patients who developed SBRT-induced VCF required a salvage spinal reconstruction procedure. Similarly, five patients (83.3%) with VCF had VCF before SBRT, and four of these patients required stabilization surgery after SBRT in this study.

Some limitations of this study should be acknowledged: First, we reported our experience using risk-adapted SBRT for the treatment of spinal metastases in a heterogeneous cohort of patients. The cohort was heterogeneous both in terms of primary tumor and treatment strategies received. This heterogeneity reflects the evolving practice pattern over time, and previously published reports have included similarly heterogeneous cohorts; this has hampered finding an optimal dose and fractionation schemes. Second, many patients included in this study had extensive metastases with a short survival period, which prevented long-term observation of efficacy and adverse events. Third, the small sample size, the single-center scope of the study, and relatively short follow-up time may potentially bias the statistical inferences. Larger studies are required to provide more definitive evidence.

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DISCLOSURE
The author declares no conflict of interest.

INFORMED CONSENT
All included patient must be able to understand and given written informed consent and report adverse events.

ETHICS STATEMENT
Approval of the research protocol by an Institutional Reviewer Board: This study was in accordance with the ethical guidelines of the Declaration of Helsinki and the approval of the research protocol by an Institutional Reviewer Board at our hospital (No. Ek2017106).

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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