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Evaluation of treatment results of stereotactic body radiotherapy for spinal metastases: A single center experience

Uğur Yılmaz, Gökhan Yaprak, Naciye Işık
Kartal Dr. Lütfi Kirdar City Hospital, Department of Radiation Oncology, İstanbul, Turkey

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ABSTRACT

Aim: To assess oncological outcomes and adverse events of patients receiving single or multi-fraction stereotactic body radiotherapy (SBRT) for spine metastases.

Material and Method: Patients with any pathologically proven solid tumor histology who had SBRT to the spine for recurrent or metastatic disease between the years 2010 and 2021 at our department were identified from institutional database. Patient, tumor and treatment characteristics, and follow-up medical records were retrospectively reviewed. Local control (LC) and overall survival (OS) rates were calculated, and adverse events were evaluated.

Results: A total of 47 patients were treated to 50 spine metastases. Median age was 53 years for all patients. Histologies included breast cancer (45%), non-small cell lung cancer (NSCLC; 21%), prostate cancer (15%) and other types (19%). Median follow-up was 16 months for all patients. Of 47 patients, six (13%) developed local failure and 15 (32%) died without local failure. One and two-year actuarial LC rates were 90.1% and 83.6%, respectively. One and two-year OS rates were 75.1% and 62.7%, respectively. Twenty-two (47%) patients had pain before SBRT. Fifteen (68%) of them had complete or partial pain response at 3 months after SBRT. Vertebral compression fracture, which was grade 1 in severity according to the Common Terminology Criteria for Adverse Events (CTCAE [v.4.03]), was observed in only one (2%) patient and it occurred 46 months after SBRT. No cases of treatment-related radiation myelopathy or any≥grade 3 RT induced acute or late toxicities occurred.

Conclusion: This study supports that SBRT to the spine results in high LC without any significant toxicity. The results of ongoing phase 3 trials will highlight whether this high LC benefit reflects to survival in oligometastatic disease.

Keywords: Stereotactic body radiotherapy, Spine, Metastasis

INTRODUCTION

Palliative radiotherapy (RT) is effective in achieving pain relief, preventing the morbidity of bone metastases and therefore, it has been used as one of the standarts of care in bone metastases (1,2). 8 Gy in a single fraction provides equivalent pain and narcotic relief at 3 months compared to 30 Gy in 10 fractions for patients with painful bone metastases from breast or prostate cancers however, the 8-Gy arm have a higher rate of re-treatment but have less acute toxicity than the 30-Gy arm (3).

Stereotactic body radiotherapy (SBRT), which is an innovative modality based on high precision planning and delivery, has the ability to dose escalate the tumor volume while sparing the adjacent organs-at-risk compared to conventional external beam RT (4, 5). Pain relief was similar between SBRT and conventional RT arms in NRG Oncology/RTOG 0631 phase 3 trial (6). However, Sahgal et al. (7) demonstrated that SBRT was associated with significantly higher complete response rates for pain compared to conventional external beam RT at 3 months and 6 months after treatment. Thus, there has been a paradigm shift in the management of spine metastases towards SBRT due to improving pain relief.

We, herein, reviewed and analyzed the data of our patients who received SBRT to the spine.

MATERIAL AND METHOD

The study was carried out with the permission of the Kartal Dr. Lütfi Kırdar City Hospital, Clinical Researches Ethics Committee (Date: 30.03.2022, Decision No: 2022/514/222/15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Corresponding Author: Uğur Yılmaz, druguryilmaz@gmail.com
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Patients

Patients with any pathologically proven solid tumor histology who had SBRT to the spine for recurrent or metastatic disease between the years 2010 and 2021 at our department were identified from institutional database. Prior therapy including previous RT was not an exclusion criterion. Patient, tumor and treatment characteristics, and follow-up medical records were retrospectively reviewed.

Spinal Instability Neoplastic Score (SINS) of spine disease was assessed according to the system devised by the Spine Oncology Study Group (8). It evaluates and scores 6 variables: location of lesion, characterization of pain, type of bony lesion, radiographic spinal alignment, degree of vertebral body destruction, and involvement of posterolateral spinal elements. The SINS ranges from 0 to 18, with higher values indicating greater instability; a SINS score of 0–6 denotes stability, 7–12 denotes potentially unstability, and 13–18 denotes unstability.

Stereotactic Body Radiotherapy and Follow-up Evaluation

Axial T1-weighted post-gadolinium and axial T2-weighted non-contrast enhanced magnetic resonance imaging (MRI), including the target vertebral segment and at least one vertebral body above and below, those were acquired with a slice thickness of 1 mm were ordered before SBRT planning. Patients underwent immobilization with vac-loc bags and planning computed tomography (CT) scan was obtained in the treatment position. Pre-SBRT MRI was fused to planning CT scan for delineation of the gross tumor volume (GTV), clinical target volume (CTV), spinal cord and thecal sac. GTV, CTV, and organs at risk were deliniated. The planning target volume (PTV) was defined as CTV plus a 1 mm margin. Radiation dose and fractionation were determined for each patient on the basis of PTV volume, prior RT dose, and spinal cord and thecal sac tolerances. Treatment plans consisted of one, two, three, or five fractions for median doses of 17, 16, 21, and 22 Gy, respectively. Biological effective dose (BED) was calculated using the linear quadratic formula utilizing an α/β ratio of 10 for tumor. Two of two patients treated with two fractions, one of 29 patients treated with three fractions, and six of nine patients treated with five fractions had previously received RT.

Spinal cord D0.1cc and thecal sac Dmax were restricted to 10 and 12.4 Gy in one fraction, 18 and 20.3 Gy in three fractions, and 23 and 25.3 Gy in five fractions for de novo treatments, respectively (9, 10). Thecal sac and spinal cord dose constraints were individualized in the retreatment setting, and prior radiation spine dose and time interval since the prior RT were taken into account. Dose planning was carried out with the Multiplan Software (Accuray Inc., Sunyvale, CA, USA). CyberKnife treatment was performed in an outpatient setting. Treatment was delivered utilizing Xsight spine image tracking.

Follow-up care consisted of clinical examination and positron emission tomography - computed tomography (PET/CT), spine MRI with contrast, or spine CT according to the physician preference every three months unless clinically indicated at an earlier time point.

Outcomes

All times to event were measured from the date of SBRT. Event was defined for local control (LC) as a progressively enhancing lesion or soft tissue mass at the treated vertebral level that was depicted by MRI, CT or PET/CT scans, or pathology that demonstrated malignancy. Patients without an event were censored at the last contact date and patients were also censored when they died. OS was defined as the time from SBRT to death from any cause.

Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE [v.4.03]) (11).

Statistical Analysis

Rates of LC and OS were estimated using the Kaplan–Meier method. The log rank method was used for statistical comparisons of groups. Mann-whitney U test was used to compare the differences between two independent groups.

P values<0.05 were considered statistically significant. The data processing and statistical analysis were performed with statistical software package IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Patient and Tumor Characteristics

A total of 47 patients were treated to 50 spine metastases. Baseline patient characteristics are showed in **Table 1.** Median age was 53 years for all patient cohort whereas 58 and 51 years for men and women, respectively. Of 47 patients, 39 (83%) patients had metastasis at one spinal segment, five (11%) patients had metastases at two consecutive spinal segments, and three (6%) patients had metastases at two non-consecutive spinal segments. Histologies included breast cancer (45%), non-small cell lung cancer (NSCLC; 21%), prostate cancer (15%) and other types (19%). Thirty-nine (81%) patients did not have RT history to target vertebrae whereas nine (19%) patients, presented with relapse of spine metastasis, had previously received 30 Gy palliative RT.

Table 1. Patients' characteristics

Patient characteristics	n (%)
Age, years	
Median (range)	53 (32-80)
Gender	
Male	21 (44.7)
Female	26 (55.3)
ECOG performance status	
0	19 (40.4)
1	26 (55.3)
2	2 (4.3)
No. of patients with primary tumors	
Breast	21 (44.7)
NSCLC	10 (21.3)
Prostate	7 (14.9)
Others	9 (19.1)
Previous RT to target vertebrae	
Yes	9 (18)
No	41 (82)
CT appearance of spine lesion	
Lytic	19 (38)
Sclerotic	20 (40)
Mixed (Lytic/Sclerotic)	11 (22)
SINS score	
0-6	28 (56)
7-12	19 (38)
13-18	3 (6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, Non-small cell lung cancer; RT, Radiotherapy; CT, Computed Tomography; SINS, Spinal Instability Neoplastic Score

Treatment characteristics are demonstrated in **Table 2.** SBRT was delivered in a median of three fractions (range one-five) with a median total dose of 21 Gy (range 13-28).

Table 2. Treatment characteristics

Treatment characteristics	n (%)
Site of target vertebrae	
Cervical	4 (8)
Thoracic	26 (52)
Lumbar	17 (34)
Sacral	3 (6)
Total SBRT dose	
Median (range)	21 Gy (13-28)
Number of SBRT fractions	
1	10 (20)
2	2 (4)
3	29 (58)
5	9 (18)
Volume of PTV	
Median (range), mm^3	33748 (4799-164310)
BED10 of the prescription dose	
Median (range), Gy	35.7 (28-65.1)

Abbreviations: SBRT, Stereotactic Body Radiotherapy; PTV, Planning target volume; BED, Biologically equivalent dose

Local Control, Overall Survival and Toxicity Outcomes

Median follow-up was 16 months for all patients and 23 months for alive patients. Of 47 patients, six (13%) developed local failure and 15 (32%) died without local failure during follow-up. Of six patients with local failure; four had breast cancer primary, two had other primaries. There was no local failure in patients with prostate cancer or NSCLC. The median BED10 of the prescription dose or the median PTV volume were not statistically different between the tumors with local failure and those without local failure (p=0.240 and p=0.302).

One and two-year actuarial LC rates were 90.1% and 83.6%, respectively (see **Figure a**). LC rates at one-year were as follows; 95.7% for patients with SINS 0-6 vs 82.5% for those with SINS 7-18 (p=0.253), 95.8% for patients with sclerotic or mix metastases vs 80.4% for those with lytic metastases (p=0.136), and 100% for patients with previous RT to target vertebrae vs 88.1% for those without previous RT to target vertebrae (p=0.769). One and two-year OS rates were 75.1% and 62.7%, respectively (see **Figure b**).

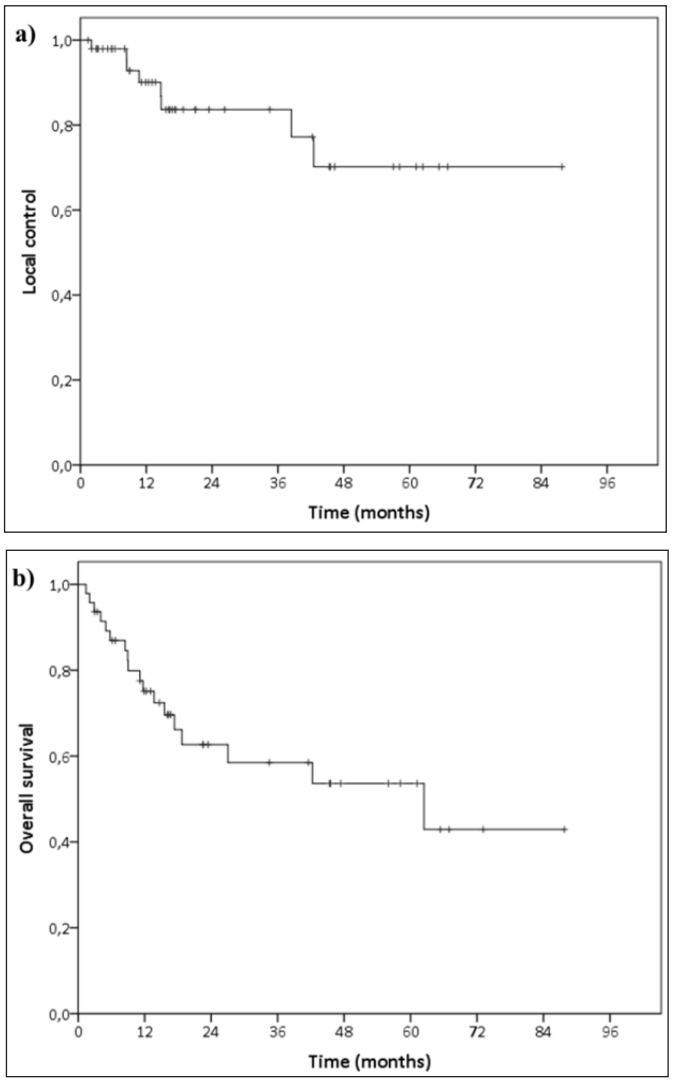

Figure 1. Operational duration according to the groups

Twenty-two (47%) patients had pain before SBRT. Fifteen (68%) of 22 patients had complete or partial pain response at 3 months after SBRT.

SBRT was altogether tolerated well. Vertebral compression fracture, which was grade 1 in severity according to the CTCAE (v.4.03), was observed in only one (2%) patient and it occurred 46 months after SBRT with the prescription dose of 17 Gy in one fraction. No cases of treatment-related radiation myelopathy or any≥grade 3 RT induced acute or late toxicities occurred.

DISCUSSION

There exists controversies in clinical trials about whether SBRT leads to improved pain control over conventional palliative RT (6,7,12). In the phase 2 trial conducted by Sprave et al. (12), 24 Gy single-fraction SBRT provided quicker and improved pain response compared to conformal RT with 30 Gy in 10 fractions. On the contrary, pain control at 3 months was not improved due to the lower pain control rate than expected in the SRS arm in NRG Oncology/RTOG 0631 phase 3 trial (6). In that trial, SBRT consisted of a total dose of 16 to 18 Gy delivered in one fraction, thus one may think that RT dose could be relatively low for producing greater pain relief. Nonetheless, Sahgal et al. (7) showed in their phase 2/3 trial that SBRT significantly improved the complete response rate for pain compared with conventional external beam RT. Patients received a total dose of 24 Gy in two consecutive daily fractions in SBRT arm in their trial which represents a high biologically equivalent SBRT dose than that used in NRG Oncology/RTOG 0631 trial. Of 22 patients who presented with pain prior to SBRT, 14 (64%) had complete or partial pain response at 3 months after SBRT in our study. This rate seems relatively higher than the pain response rate which was 53% at 3 months after SBRT in the randomized phase 3 trial conducted by Shagal et al (7). Pre-SBRT and post-SBRT pain evaluation was not done according to any pain scale in our patient population. Thus, this could be a limitation of our study. However, that type of pain response evaluation is beyond the scope of this study.

Apart from pain control, SBRT could be applied for improving survival for patients with limited burden of metastatic disease (13, 14). Although there exists several limitations (i.e. including multiple histologies and assigning the large majority of patients with prostate cancer to the SBRT arm), long term results of SABR-COMET phase 2 trial (15) demonstrated that SBRT was associated with a significant improvement in progression-free survival and OS in a group of patients with an oligometastatic disease (mostly with 1–3 metastatic lesions). Several phase-3 trials are accruing patients and are evaluating the impact of SBRT on survival in patients with oligometastases (16-18). Twenty-five of 47 (53%) patients did not have pain in our patient population but they had limited burden of disease and thereby being treated with SBRT.

Vertebral compression fracture is one of the common toxicities of spine SBRT (19-21). In the trial conducted by Sahgal et al. (19), the median time to vertebral fracture was 2.46 months (range, 0.03 to 43.01 months), and 65% developed in the first 4 months following SBRT. The two-year cumulative incidence of vertebral fracture was 13% and they observed that≥20 Gy in single-fraction posed a significant risk for fracture compared to lower SBRT dose. In the study conducted by Mehta et al. (20), patients treated with two to five fractions SBRT with a median total dose of 24 Gy (in a median of three fractions) and vertebral body fracture occurred in 5.3% of those without surgery or vertebroplasty prior to SBRT. Only one (2%) patient, who were treated with 17 Gy in single fraction, experienced vertebral fracture with grade 1 in severity in our study. It developed 46 months after SBRT. Up to us, the lower rate of vertebral fracture in our patient population is due to smaller sample size and our SBRT dose and fractionation schemes such as that 79% of patients were treated in multi-fraction with limited biologically equivalent dose.

SBRT for spine metastases was safely performed without causing any increase in adverse effects as compared to conventional EBRT in randomized controlled trials (6, 7). SBRT applied safely to our patient population, and no radiation myelopathy and any≥grade 3 toxicity was observed. This could be due to the our general clinical approach in which a threshold of less than 5% risk of serious adverse effects is chosen for organs at risk dose recommendations (9,10).

Several SBRT dose fractionation schedules were assessed compared to conventional RT as mentioned above. However, there are no dose finding randomized trials to evaluate the superiority of ideal dose fractionation in SBRT. One-year LC rate was 90% in our study population. This rate is consistent with the literature (22). However, heterogeneous dose-fractionation protocols were applied due to the organs at risk doses and prior RT history to the target vertebrae in our study. Thus, it is difficult to draw a conclusion for the effectiveness of a specific dose-fractionation protocol. This could be limitation of our study. In additon, small sample size and retrospective design are the other limitations of our study. Small sample size and high LC rate might have induced not to determine any significant factor assosicated with improved or decreased LC.

CONCLUSION

SBRT to the spine results in improved pain response and high LC without any significant toxicity. The results of ongoing phase 3 trials mentioned above will highlight whether this high LC benefit reflects to survival in oligometastatic disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Kartal Dr. Lütfi Kırdar City Hospital, Clinical Researches Ethics Committee (Date: 30.03.2022, Decision No: 2022/514/222/15).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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