Stereotactic radiosurgery for metastasis to the craniovertebral junction preserves spine stability and offers symptomatic relief

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OBJECTIVE Metastatic disease to the craniovertebral junction (CVJ) is rare but presents unique management challenges. To date, studies on using stereotactic radiosurgery (SRS) for CVJ metastases have been limited to case reports and small case series. The aim of this analysis was to evaluate the utility of SRS in the management of these secondary lesions.

METHODS Clinical and radiological information from the charts of 25 patients with metastatic disease of the CVJ who were treated with SRS between 2005 and 2013 at the Stanford CyberKnife Center were retrospectively reviewed.

RESULTS Seven male and 18 female patients with a median age of 58 years (range 34–94 years) were identified. The most common primary tumors were breast cancer ($n = 5$) and non–small cell lung cancer ($n = 5$), and the most frequent symptom was neck pain ($n = 17$). The average tumor volume treated was 15.9 cm^3 (range 0.16 – 54.1 cm^3), with a mean marginal radiation dose of 20.3 Gy (range 15 – 25.5 Gy). The median follow-up was 18 months (range 1–81 months), though 1 patient was lost to follow-up.

SRS provided radiographic tumor stability in over 80% of patients, offered pain alleviation in nearly two-thirds of patients, and produced no serious complications. Moreover, SRS preserved spinal stability in all but 1 patient, in whom pre-SRS stability was established. There was no evidence of radiation toxicity in the patient population. Median survival was 28 months (range 2–81 months), with survival of 13.3% at 5 years.

CONCLUSIONS In the absence of unstable pathological fracture and spinal cord compression, metastatic tumors of the CVJ can be safely and effectively treated with SRS. This treatment option offers palliative pain relief and can halt tumor progression with only a low risk of complications or spinal instability.

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KEY WORDS craniovertebral junction; metastasis; stereotactic radiosurgery; CyberKnife; oncology

METASTASIS to the craniovertebral junction (CVJ) is defined as the anatomical involvement of the occipital condyles and/or atlantoaxial spine. This occurrence is rare, accounting for 0.5% of all metastatic lesions to the spine.¹⁷ The primary tumors that most often seed the CVJ include breast carcinoma (35%), non–small cell lung carcinoma (13%), and prostate cancer (10%).^{2,4}

The mean age at presentation of upper cervical spine metastases is 60 years old.¹³ Patients with metastatic disease to this region often experience severe neck pain, which often requires operative or radiosurgical interventions in addition to medical management (Fig. 1).

Management is palliative and should strive to preserve spinal stability, optimize pain control, maintain neurolog-

ABBREVIATIONS CVJ = craniovertebral junction; NOMS = neurological, oncological, mechanical, and systemic; SINS = spinal instability neoplastic score; SRS = stereotactic radiosurgery.

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FIG. 1. Preoperative T1-weighted postcontrast sagittal (A) and axial (B) images. The lesion is indicated by the *white arrow*. The 0.64-cm³ C2-level lesion in this patient was treated with 20 Gy in 2 fractions, and 96.3% coverage was achieved.

ical function, and achieve local tumor control.¹³ Open surgical management is indicated in patients with spine instability or patients who cannot receive radiation therapy due to previous radiation treatment fields overlapping the CVJ^{6,19}; however, open surgical management may be associated with substantial morbidity.^{7,10,18}

Stereotactic radiosurgery (SRS) has been demonstrated to improve local tumor control and lower complication rates in patients with spine metastatic disease relative to external beam radiotherapy and surgical resection (Fig. 2).^{5,20} Though evidence specific to the CVJ is limited, small case series have yielded promising results.^{9,16,21} SRS at the CVJ is not without challenges, given the proximity of adjacent neurocritical structures including the brainstem, upper cervical spinal, and lower cranial nerves. We present the largest patient series, to our knowledge, of SRS for CVJ metastasis and demonstrate the role of this treatment modality in preserving spinal stability and alleviating pain.

Methods

Cohort Creation

Between 2005 and 2013, 25 patients with metastatic disease to the CVJ underwent SRS at the Stanford CyberKnife Center. Criteria for study inclusion were osseous metastatic lesions that involved the CVJ, which was defined as lower third of the clivus, occipital condyles, and C1–2 vertebrae. No patients who met these criteria were excluded. A retrospective review of these patients was undertaken by obtaining clinical and radiological information from an institutional review board–approved database. Data collected included patient demographics, date of diagnosis of spinal metastasis and its location, previous treatments (including chemo-, immuno-, and/or radiotherapy), preintervention pain (by subjective report), postintervention pain (by subjective report), preintervention spinal instability neoplastic score (SINS),³ total SRS dose (Gy) and fractions administered to the CVJ, postintervention radiographic occurrence of deformity or compression fracture, and need for further surgery at the spinal SRS index level.

FIG. 2. Postoperative T1-weighted postcontrast sagittal (A) and axial (B) images. The remaining lesion is indicated by the *white arrow*.

Image-Guided Radiosurgery Treatment

Image-guided radiosurgery in the form of the CyberKnife was used throughout this study. All patients underwent immobilization in a noninvasive head restraint, such as the molded Aquaplast mask (WFR/Aquaplast) during cranial treatments or a custom alpha cradle mold (Smithers Medical Products) during spinal treatments.

Thin-slice contrast-enhanced CT scans (1.25 mm) and MRI (2.0 mm) scans were obtained, loaded onto the treatment planning computer, and fused. Tumor tracking was provided by the Xsight spine tracking system (Accuray). Dose constraints for single and hypofractionated regimens were determined based on the guidelines defined by the American Association of Physicists in Medicine Task Group 101. For single fractions to the cord and esophagus, the constraints were 10 Gy and 11.9 Gy, respectively. For 3 fractions to the cord and esophagus, the constraints were 18 Gy and 17.7 Gy, respectively. For 5 fractions to the cord and esophagus, the constraints were 23 Gy and 19.5 Gy, respectively.¹

Follow-Up

Median follow-up was 18 months (range 1–81 months), though 1 patient was lost to follow-up. Patients underwent clinical follow-up at 3 months and 6 months posttreatment and then every 6 months for the first 2 years, though this was not possible for all patients due to death among the patients with metastatic disease. Images with a minimum of 3.5-mm slice thickness were obtained, and tumor size was calculated by measuring along the 3 axes to provide a volumetric figure. Any net decrease along 1 or more of the axes by 3 mm was recorded as tumor reduction. Likewise, a net increase of 3 mm in any of the dimensions was considered to indicate tumor growth. Follow-up images were also assessed for evidence of radiation necrosis.

Results

Cohort Characteristics

Our retrospective review yielded 7 male and 18 female patients with a median age of 58 years (range 34–94 years). The most common primary lesions were breast cancer (n = 5) and non–small cell lung cancer (n = 5). The

TABLE 1. Clinical overview of patients with metastases to the CVJ

Case No.	Age at SRS (yrs)	Sex	Primary Tumor	Symptoms at Presentation	Follow-Up* (mos)	Tumor Location†
1	56	F	Mediastinal teratoma	Constipation, incontinence	54	D
2	43	F	Parotid acinic cell carcinoma	Neck pain, CN palsy	42	V
3	58	F	NSCLC	Neck pain	38	D
4	59	F	NSCLC	Neck pain, weight loss	16	V
5	51	M	Melanoma	Neck pain	28	D
6	49	F	Breast cancer	NR	2	B
7	69	M	Prostate cancer	Neck pain	2	V
8	69	F	NSCLC	Neck pain	18	V
9	74	M	Lung adenocarcinoma	Neck pain	16	V
10	94	F	Merkel cell carcinoma	Neck pain	39	V
11	65	M	Prostate cancer	Neck pain	48	V
12	69	F	Lingula adenocarcinoma	NR	44	B
13	58	F	Breast cancer	Neck pain, CN palsy	81	V
14	58	F	NSCLC	Neck pain	8	V
15	52	F	Ovarian cancer	NR	75	V
16	52	F	Breast cancer	CN palsy	36	V
17	81	F	Breast cancer	Neck pain	18	B
18	70	M	Renal cell carcinoma	NR	16	D
19	52	F	Colorectal cancer	Neck pain	5	B
20	57	F	Colorectal cancer	Neck pain, hand tremor	0	V
21	62	F	Liposarcoma	Neck pain, CN palsy	36	B
22	72	M	Prostate cancer	Neck pain	3	B
23	52	M	Breast cancer	NR	NR	V
24	34	F	NSCLC	L-5 radiculopathy	7	V
25	38	F	Gastric carcinoma	Neck pain	1	B

B = both ventral and posterior elements; CN = cranial nerve; D = dorsal elements (spinous process and laminae); NR = not reported; NSCLC = non-small cell lung cancer; V = ventral elements (vertebral body and pedicles).

* Follow-up is the duration of time from initial CyberKnife SRS treatment to the last clinical and/or radiographic follow-up.

† Tumor location relative to the spinal cord.

most frequent symptom was neck pain ($n = 17$), followed by cranial nerve palsy ($n = 4$). Other presenting symptoms included constipation, urinary incontinence, weight loss, hand tremor, and lumbar radiculopathy (Table 1).

All but 1 patient had some form of prior treatment for the primary tumor. However, no patient received radiation therapy or resection for the CVJ metastasis prior to SRS.

Radiosurgical Treatment

Among the 25 lesions, 1 lesion received 5 fractions, 7 lesions received 3 fractions, 5 lesions received 2 fractions, and 12 lesions received a single fraction. The number of fractions delivered was determined by discussion between the neurosurgeon and radiation oncologist and based on the patient and lesion characteristics, chiefly tumor size and anatomical location. Critical structures were contoured to limit the radiation dose to these structures.

Treatment plans were personalized for each patient based on tumor size, location, isodose coverage, and tissue doses. The average tumor volume treated was 15.9 cm^3 (range $0.16\text{--}54.1 \text{ cm}^3$), with a mean marginal radiation

dose of 20.3 Gy (range $15\text{--}25.5 \text{ Gy}$) and a mean maximum intratumoral dose of 26.4 Gy (range $20.3\text{--}35.7 \text{ Gy}$). The mean number of isocenters was 141.7, the mean conformity index was 1.46, and the mean percentage of coverage was 94.4% (Table 2). In this cohort, we did not note any toxicity related to SRS.

Preoperative Spine Stability

Preintervention SINS was calculated for all 25 treated lesions. The mean SINS was 7.3 (range 3–12). Nine lesions were classified as stable (SINS 0–6), and 15 lesions were classified as indeterminate (SINS 7–12). No lesions were classified as unstable. Because our cohort includes patients selected for spinal SRS, it is comprehensible that no analyzed lesions qualified as frankly unstable per the SINS criteria, as such lesions are more appropriate for surgical intervention.

Postoperative Outcome

In our series, only 2 patients required post-SRS sur-

TABLE 2. CyberKnife radiosurgery dosimetry for the treatment of CVJ metastases

Case No.	Lesion Volume (ml)	Fractions	Rx Dose (Gy)	Maximum Dose (Gy)	Biological Equivalent Dose (Gy ₁₀)	Level of SRS	No. of Isocenters	Conformality Index	Coverage (%)
1	0.64	2	20	26.7	40	C1–2	106	1.49	96.3
2	6.47	2	20	25.0	40	C1	117	1.60	96
3	41.54	3	24	28.9	43.2	C1–3	138	1.38	90.2
4	30.92	3	24	29.3	43.2	C1–2	142	1.44	91.1
5	0.77	1	24	30.0	81.6	C1	103	1.67	95.7
6	10.10	3	21	25.9	35.7	C1	130	1.47	98.4
7	54.07	2	20	26.7	40	C1–2	223	1.37	94.7
8	12.11	1	18	22.8	50.4	C1	166	1.75	94.2
9	21.81	1	18	22.5	50.4	C1–2	189	1.76	95.5
10	19.98	3	24	30.0	43.2	C1	196	1.70	99.7
11	11.25	1	16	21.9	41.6	C1	142	1.29	98.3
12	5.08	1	19	23.2	55.1	C1	100	1.21	94.9
13	21.98	1	15	20.3	37.5	C1	NR	1.41	94.7
14	1.66	2	20	24.7	40	C1–2	184	1.51	98.4
15	1.49	5	25	35.7	37.5	C1	147	1.35	91.5
16	9.66	1	16	22.9	41.6	C2	119	1.11	90.8
17	17.06	1	16	21.1	41.6	C2	128	NR	92.1
18	0.16	1	18	21.7	50.4	C2–3	163	1.64	83.3
19	10.80	1	20	25.3	60	C2	139	1.53	91.6
20	7.35	1	18	23.7	50.4	C2	103	1.39	95.7
21	28.10	3	24	32.0	43.2	C1–2	123	1.37	NR
22	35.15	3	24	34.3	43.2	C2	140	1.28	94.4
23	15.63	2	20	27.4	40	C1	109	1.43	97.4
24	3.78	1	18	24.3	50.4	C2	145	1.46	95.9
25	29.00	3	25.5	34.5	47.18	C2–3	148	1.41	94.6

Rx = radiation.

gery to stabilize the cervical spine. The first patient had documented pre-SRS spinal instability, but this patient was deemed a poor candidate for surgery due to chronic obstructive pulmonary disease exacerbations. Following SRS, the patient required laminectomy with tumor resection and posterior cervical arthrodesis from the occiput to the C-6 level. The second patient developed a pathological fracture with collapse of the C-2 vertebral body following initial SRS, underwent spinal fusion from the occiput to the C-6 level, and eventually received a second SRS which resulted in tumor regression and further symptomatic relief.

Of the patients who reported neck pain ($n = 17$), marked decrease or full resolution was observed in 8 patients, no change was reported in 5 patients, and changes in pain were not reported in 4 patients. Cranial nerve palsy improved in 3 of the 4 patients who presented with this symptom. Following SRS, lesion size was radiographically determined at the most recent follow-up in 19 patients and found to be decreased in 4 patients, unchanged in 12 patients, and increased in 3 patients. There was no evidence of radiation toxicity in our patient population. Median survival was 28 months (range 2–81 months), and the

overall Kaplan-Meier survival at 3 years following SRS was 46.7% (Table 3; Fig. 3).

Discussion

Patients with metastatic disease to the CVJ had a median survival of nearly 3 years in our study (Table 4). This underscores the importance of optimizing the quality of life of these patients. In our study of 25 patients with metastases to the CVJ, SRS provided radiographic tumor stability in over 80% of patients, offered pain alleviation in over 60% of patients, and produced no serious complications. Moreover, we found that SRS preserved spinal stability in all but 1 patient, in whom pre-SRS stability was established.

A number of predictors of survival following spinal metastatic disease have been indicated in previous studies, including pain at presentation¹¹ and local progression after SRS.¹⁴ In our analysis, these indicators showed no significant influence on survival or symptomatic resolution. Moreover, we found no significant association between preoperative spinal instability (as determined by SINS) and patient outcome following initial patient selection for

TABLE 3. Postoperative outcomes for patients undergoing SRS for CVJ metastasis

Case No.	Survival (mos)	CN Palsy Improvement	Pain Improvement	Pathological Fracture	Spine Surgery	Change in Lesion Size
1	54	NA	NA	No	No	Decreased
2	42	Yes	Yes	No	No	Decreased
3	38	NA	No	No	Yes	Unchanged
4	16	NA	Yes	No	No	Unchanged
5	28	NA	No	No	No	Unchanged
6	2	NA	NA	No	No	Unchanged
7	2	NA	NR	No	No	NR
8	18	NA	Yes	No	No	Unchanged
9	16	NA	Yes	No	No	Unchanged
10	NR	NA	Yes	No	No	Increased
11	48	NA	NR	No	No	NR
12	44	NA	NA	No	No	Unchanged
13	81	No	Yes	No	No	Unchanged
14	NR	NA	No	No	No	Increased
15	75	NA	NA	No	No	NR
16	NR	Yes	NA	No	No	Unchanged
17	NR	NA	Yes	No	No	Unchanged
18	NR	NA	NA	No	No	Decreased
19	5	NA	Yes	No	No	Increased
20	NR	NA	NR	No	No	NR
21	NR	Yes	No	Yes	Yes	Decreased
22	NR	NA	No	No	No	Unchanged
23	NR	NA	NA	NR	No	NR
24	7	NA	NA	No	No	Unchanged
25	NR	NA	NR	No	NR	NR

NA = not applicable.

SRS. The neurological, oncological, mechanical, and systemic (NOMS) framework suggests that the histology of the primary tumor can influence the radiation susceptibility of the tumors to external-beam radiation therapy, but posits that responses to SRS are largely independent of primary tumor histology.¹² Thus, our findings agree with the NOMS framework, in that we found no notable difference in outcomes between the lesions of different histological origins.

Metastatic disease of the CVJ poses a therapeutic challenge given the mechanical and neuroanatomical complexity of the region; open surgery and SRS are possible management options that could help avoid or alleviate issues of pain or structural instability. Surgical resection is a valuable option to address unstable fractures and symptomatic brainstem or spinal cord compression.² However, the efficacy of open surgery can vary with tumor pathology, anatomical location, and surgical approach.^{7,8,15} Fusion of the CVJ reduces the occipitocervical range of motion and can increase the risk of dural laceration, dysphagia, vertebral artery injury, and neurological injury.¹⁰

SRS can be considered a viable alternative to open surgery for metastatic disease to the stable CVJ. Recently, Tuchman et al. presented a series of 9 patients with 10

CVJ tumors.²¹ The most frequent diagnosis was hepatocellular carcinoma (n = 4), and the median lesion volume was 9.66 cm³. The most common presenting symptom was headache or neck pain (n = 6). The median dose for patients receiving Gamma Knife radiosurgery (n = 2) was 17 Gy, and the median survival was 4 months (range 1–51 months) for patients receiving 20.5 Gy (n = 7). Five of the 6 patients who presented with pain had improvement in their symptoms after treatment, and CVJ instability requiring surgical stabilization was not noted either before or after SRS in any patient.²¹ Our results are consistent with the findings of Tuchman et al. and strengthen the case for administering SRS to patients with metastatic disease to the CVJ.

Our study is not without limitations. Given the wide geographic distribution of patients referred to Stanford Hospital and Clinics, comprehensive follow-up was not available for all patients. However, follow-up was available for the majority of patients in all reported outcomes. Furthermore, neck pain was not measured through the use of a visual analog scale. Our study derived information regarding pain alleviation from the subjective patient reports in the medical charts, in which neck pain was either expressed as a categorical variable (e.g., yes, no, or same)

FIG. 3. Kaplan-Meier survival curve following SRS for CVJ metastatic lesion.

or as an integer (1–10) using the comparative pain scale. Although these limitations are important to note, we believe our findings, when contextualized with previous reports and case series, demonstrate the value of SRS in the management of metastatic lesions to the CVJ.

TABLE 4. Characteristics of patients with CVJ metastases treated with SRS

Characteristic	Value
No. of patients	25
No. of females, n (%)	18 (72.0)
Median age, yrs (range)	58 (34–94)
Median survival, mos (range)	28 (2–81)
Mean tumor volume, cm ³ (range)	15.9 (0.2–54.1)
Mean marginal dose, Gy (range)	20.3 (15–25.5)
No. of patients with tumor reduction, n (%)	4 (21.0)
No. of patients with stable tumor, n (%)	12 (63.2)
No. of patients with pain reduction, n (%)	8 (61.5)
No. of patients with post-SRS spine surgery, n (%)	2 (8.0)

Conclusions

To our knowledge, this is the largest sample of patients with metastatic disease of the CVJ treated with SRS. In the absence of unstable pathologic fracture and spinal cord compression, metastatic tumors of the CVJ can be safely and effectively treated with SRS. This treatment option offers palliative pain relief and halts tumor progression with only a low risk of complications or spinal instability.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: Azad, Esparza. Analysis and interpretation of data: Azad, Esparza. Drafting the article: all authors. Critically revising the article: Chang, Azad, Chaudhary. Statistical analysis: Azad. Administrative/technical/material support: Chang, Chaudhary. Study supervision: Chang, Chaudhary.

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