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CyberKnife Radiosurgery for Malignant Spinal Tumors

Characterization of Well-Suited Patients

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Study Design. A prospective interventional case-series study.

Objective. To provide clinical results of CyberKnife fiducial-free spinal radiosurgery. The study focused on patients with no more than 2 malignant spinal tumors.

Summary of Background Data. Progress in frameless radiosurgical technology has enabled the application of radiosurgery to the spine. The CyberKnife System has been used extensively for spine radiosurgery. Until recently, the system required metallic fiducial implants for precise target tracking. Fiducial-free spinal radiosurgery with the CyberKnife has recently become possible, but until now clinical results obtained with this method had been limited.

Methods. From August 2005 until October 2007, a consecutive series of 102 patients with a total of 134 malignant spinal tumors were selected for single-fraction, fiducial-free CyberKnife radiosurgery (CKRS). The study was limited to patients with a maximum of 2 tumors. Malignant primaries included breast cancer in 23 (22.6%) patients, renal cancer in 20 (19.6%) patients, gastro-intestinal cancers in 12 (11.8%) patients, prostate cancer each in 12 (11.8%) patients, lung cancer in 9 (8.9%) patients, sarcomas in 7 (6.9%) patients. A variety of other malignant tumors were found in 19 (18.6%) patients. Patients with spinal cord compression or evidence of myelopathy were excluded. The sequential neurologic status was recorded. Tumor-associated spinal pain was prospectively scored according to the visual analogue scale (VAS).

Results. Of 102 individuals, 22 (21.6%) died due to progression of their systemic disease. Mean survival after CKRS was 1.4 years (CI: 1.2–1.6). Karnofsky performance score was the only independent predictor of survival after radiosurgery on log-rank test ($P < 0.0001$), and on Cox regression analysis (hazard ratio, 0.864, $P < 0.0001$, CI: 0.809–0.922). Median survival after initial tumor diagnosis was 18.4 years (CI: 15.1–23.4). Two (2%) patients suffered complications after radiosurgery; a tumor hemorrhage occurred in one, and another developed spinal instability. These and 2 other patients were stabilized by kyphoplasty. Neurotoxicity or myelopathy was not observed. Local tumor control 15 months after CKRS was 98% (95% CI: 89–99%). Tumor-associated pain was observed in 52 (51%) patients. In these patients the median pretreatment pain score of VAS = 7 (95% CI: 6–7) was significantly reduced to VAS = 1 (95% CI: 4–6) ($P < 0.001$) within 1 week after CKRS. Analysis of variance identified the initial pain score as the only significant variable to predict pain reduction after CKRS ($P < 0.03$). Pain recurrence in correlation with tumor recurrence was observed for 3 (6%) patients.

Conclusion. Spinal radiosurgery with the CyberKnife technology is a noninvasive, safe, and effective treatment method for patients with 1 or 2 small spinal malignant tumors. The best benefit of the treatment can be expected in patients with good to excellent clinical condition and patients with severe tumor associated pain.

Key words: CyberKnife, stereotactic, robotic surgery, fiducial-free tracking, spine metastasis, spine tumors. **Spine 2008;33:2929–2934**

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Radiosurgery is well established as an effective therapeutic method for brain metastasis.[1] The CyberKnife technology (Accuray Inc., Sunnyvale, CA) expands the application of radiosurgery to the spinal column.[2] In contrast to the immobile brain, spontaneous movements of spinal structures have to be compensated during spinal radiosurgery. Until recently, spinal radiosurgery using CyberKnife required the implantation of fiducials (*e.g.*, metallic seeds or screws) to assure accurate tumor tracking. In a preceding publication we described the principle of fiducial-free spinal CyberKnife radiosurgery (CKRS) using the Xsight software (Accuray Inc.).[3] A high accuracy indicated by a total targeting error of 0.52 ± 0.22 mm was found. The study also showed that fiducial-free tracking spinal radiosurgery was feasible for cervical, thoracic, lumbar, and sacral regions of the spine. There was no need for any immobilization devices. For treatment, the patients were placed just in a supine position with a cushion under the legs. All patients were treated in an outpatient setting. In this study, we will present clinical results obtained with fiducial-free spinal radiosurgery in selected patients with spinal malignant tumors with emphasis on tumor control, patient survival, and in patients with tumor associated pain relief.

Materials and Methods

A consecutive series of 102 patients with 1 or 2 malignant spinal tumors underwent spinal CKRS from August 2005 to October 2007. All treatments were performed in an outpatient setting. All patients had a Karnofsky performance score (KPS)[4] of 70 or above (KPS was not available for the date of the primary diagnosis) and histologically confirmed diagnosis. For metastatic lesions at least the histology of the primary site was

Table 1. Characteristics of Patients (n = 102, lesions = 134) and Treatment Parameters

Patients	
Age (yr, median, range)	58.6 (18.4–82.6)
Sex (female/male)	36/66
Previous external beam irradiation (n, %)	33 (32.4%)
Previous surgery at treated spine lesion (n, %)	17 (16.7%)
Spinal tumor associated pain (n, %)	52 (51%)
Pain score (VAS*) before CKRS† (median, range)	7 (2–10)
Pain score (VAS) after CKRS (median, range)	1 (0–10)
Spine levels treated	
Cervical (n, %)	18 (17.7%)
Thoracic (n, %)	40 (39.2%)
Lumbar (n, %)	25 (24.5%)
Sacral/pelvis (n, %)	19 (18.6%)
Two lesions treated (n, %)	31 (30.4%)
Tumor and dose parameters	
Tumor volume (cm^3)	16.4 (0.4–64.3)
Peripheral dose (D_{min}; Gy)	19.4 (15.0–24.0)
Maximum dose (D_{max}; Gy)	28.6 (20.0–38.6)
Peripheral isodose (%)	70 (50–85)

*VAS indicates visual analogue scale; †CKRS, CyberKnife radiosurgery.

substantiated. Tumor status and KPS were used to pre-estimate life expectancy. Only patients with a preestimated life expectancy of 3 months or more were selected. Spinal instability was assumed if a significant lytic destruction of a vertebra was accompanied by a pain syndrome that was aggravated by movements and diminished by recumbency.[5] Evidence of spinal instability, as well as lesions with compression of the spinal cord and concomitant neurologic deficits precluded CKRS. There were 36 (35.3%) women, median age of all patients was 58.6 years (range: 18–83). Table 1 summarizes the characteristics of the treatment group and Table 2 shows the distribution of tumor histologies.

Treatment Procedure

The treatment procedure has been published in detail recently.[2,6–8] The CyberKnife and the skeletal structure tracking software (Xsight), were used for spinal radiosurgery in all patients. Previous studies have shown the feasibility and submillimeter accuracy of this method (fiducial-free frameless real-time image guided CKRS).[3,6] Planning and delivery of treatment were performed as outpatient procedures. The planning computed tomography (CT) was acquired with the patient in supine position without any support. CT image slice thickness was 1.2 mm and the stack of images included a minimum margin of 5 cm above and below the target lesions. In most cases axial magnetic resonance imaging (MRI) scans of the lesion were fused with the planning CT for better soft tissue discrimination (T1w + gadolinium contrast). Furthermore, in some patients, positron emission tomography scans were applied to support target definition. The dose distribution was calculated using the Multiplan software (Accuray Inc.). All treatments were performed in a single fraction. The procedure time was between 1 and 3 hours. For treatment delivery the patients were placed on the CyberKnife treatment couch reproducing their individual position during pretreatment CT scanning. If required, patients were given analgesics or mild sedation. The interval between the first interview of the patients and the radiosurgical procedure did not exceed 10 days.

Table 2. Lesion Histopathologies (n = 102)

	No.	%
Breast cancer	23	22.6%
Renal cancer	20	19.6%
Various malignancies	19	18.6%
Gastro-intestinal tract cancers	12	11.8%
Prostate cancer	12	11.8%
Lung cancer	9	8.9%
Sarcoma	7	6.9%

Follow-up Schedule and Pain Score

First clinical follow-up was done 1 week after treatment to assess the patient status with particular emphasis on the pain level after radiosurgery. Further clinical evaluation and CT and/or MRI imaging studies were done 3, 6, 12, and 18 months after treatment. Any minute tumor progress or recurrence of a treated tumor during follow-up with imaging was classified as treatment failure. Distant recurrences were disregarded in this study. Missing clinical follow-up data were collected by phone calls. Each clinical evaluation included an assessment of the pain score. A 10-point pain scale visual analogue scale was applied.[9,10] Changes in prescribed analgesics were recorded.

Statistical Analysis and Outcome Assessment

The Stata/IC 10.0 software (Stata Corp., College Station, TX) was used for statistical analysis. The endpoints of the study were local tumor control, survival after radiosurgery, overall survival after diagnosis of the primary. These outcome parameters were estimated using the Kaplan-Meier method. Furthermore, the outcome was analyzed for significance using the log-rank test for patient characteristics (age, sex, KPS, tumor pain), tumor (primary tumor, spinal tumor level, number of spinal tumors), and treatment-related variables (previous fractionated radiation therapy, radiosurgical dose), corrected by Bonferroni method for multiple comparisons (baseline threshold of significance of 0.05 divided by 18 univariate tests, yielding an accepted threshold of $P = 0.002$).[11] Multivariate Cox proportional hazard analysis was used to assess the effect of patient characteristics and other prognostic factors of significance on survival after radiosurgery, with estimated hazards also reported.[11] Analysis of variance (ANOVA) was used to assess the influence of patient characteristics and other prognostic factors on the analgetic effect of radiosurgery. This ANOVA was restricted to patients with tumor associated pain. As appropriate, interval scaled variables like age and dose were transformed to either ordinal or nominal scale level to match the constraints of the statistical model. The differences in mean values were calculated with Student t test, using a threshold of 0.05.

■ Results

Within 14 months a total of 134 malignant spinal tumors in 102 patients were treated by single-fraction fiducial-free CKRS. Fifty-two (51%) patients had tumor-associated pain syndromes that were not due to vertebral instability. The median visual analogue scale pain score before treatment was 7 (range: 2–10; 95% CI: 6–7). To ablate the tumors a median marginal dose of 19.4 Gy (range: 15–24 Gy) was delivered to the 70% (range: 50%–85%) isodose. The dose level did not differ between patients with and without spinal pain syndromes. The median tumor volume for all 102 patients was 16.4 cm^3 (mean: 20.4 cm^3; range: 0.4 cm^3–64 cm^3), for pa-

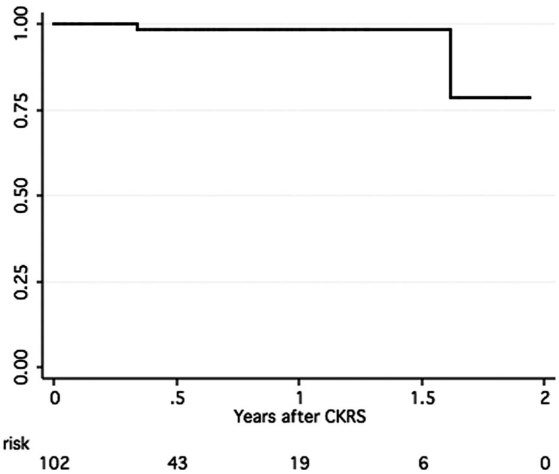

Figure 1. Cumulative local tumor control in patients (n = 102) with malignant spinal tumors after CyberKnife radiosurgery (Kaplan-Meier method).

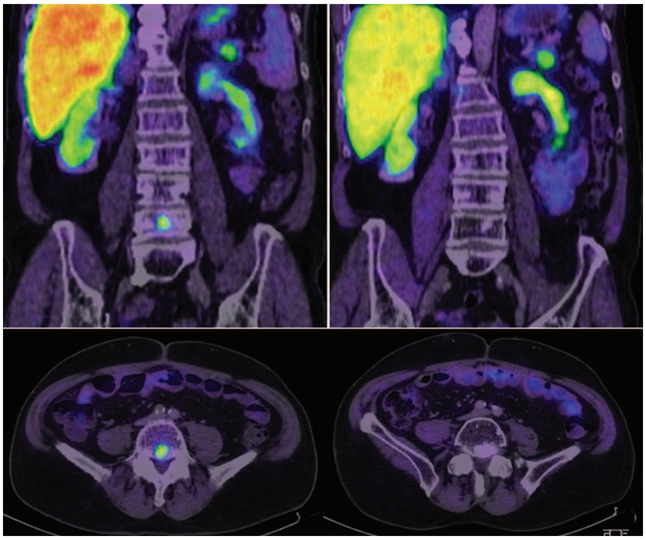

Figure 2. **A,** Cumulative survival after diagnosis of the primary in patients (n = 102) with malignant spinal tumors treated by CyberKnife radiosurgery (Kaplan-Meier method). **B,** Cumulative survival after radiosurgery in patients (n = 102) with malignant spinal tumors treated by CyberKnife radiosurgery (Kaplan-Meier method).

tients with pain 23.5 cm^3 ± 15.3 cm^3 (mean ± standard deviation; 95% CI: 19.3–27.7), and for patients without pain 17.0 cm^3 ± 15.6 cm^3 (mean ± standard deviation; 95% CI: 12.6–21.5). This difference of the mean tumor volumes was statistically significant ($P < 0.02$). No other statistically significant differences for treatment related parameters were detected when stratifying for patients with and without pain syndrome.

Follow-up information was verified for all patients. No acute side effects were observed except for 9 (9%) instances of nausea that responded well to symptomatic medication. Local treatment failures were observed in 2 patients; one had a malignant peripheral nerve sheath tumor in the thoracic spine (recurrence 19 months after radiosurgery), whereas another had a cervical melanoma metastasis (progress evident 4 months after radiosurgery). Local tumor control after 15 months was 98% (CI: 88.0–99.8) (Figures 1, 2). The statistical model failed to identify factors predictive of local tumor control; in particular, histology had no impact on tumor control.

Median survival was 1.4 years (CI: 1.2–1.6) after CKRS, and 18.4 years (CI: 15.1–23.4) years after the first diagnosis of the primary tumor (Figure 3A,B). Thus survival after CKRS covered approximately the last 10% of the total tumor survival time of the patients. log-rank tests of survival after radiosurgery showed equal functions in assessing the following variables: age ($P = 0.910$), sex ($P = 0.154$), tumor associated pain ($P = 0.098$), prior local fractionated radiation therapy ($P = 0.286$), primary tumor ($P = 0.159$), location of the spinal tumor ($P = 0.490$), number of treated spinal tumors ($P = 0.462$), radiosurgical dose ($P = 0.853$). However, KPS was significantly correlated with survival after radiosurgery ($P < 0.0001$). As summarized in Table 3, KPS remained the only independent predictor of survival after radiosurgery on Cox regression analysis (hazard ratio, 0.864, $P < 0.0001$, CI: 0.809–0.922).

Overall survival was significantly correlated with the primary tumor ($P < 0.0001$) in the log-rank test, but not on Cox regression analysis including patient characteristics, tumor, and treatment-related variables (data not shown). Five-years survival after diagnosis of the primary in breast cancer patients was 95% (CI: 70–99), in renal cancer 61% (CI: 30–81), in various other malignancies 81% (CI: 54–94), in gastrointestinal tract cancer 33% (CI: 3–70), in prostate cancer 83% (CI: 27–97), in lung cancer 48% (CI: 13–76), and in sarcoma 83% (CI: 27–97).

Concerning the patients with tumor related pain, after CKRS the median pain score was 1 (0–0; 95% CI: 4–6), significantly less ($P < 0.001$) than the pretreatment pain score (median 7; range 2–10; 95% CI: 6–7). Pain relief occurred as early as 1 hour and within 7 days after radiosurgery. Analgesics could be reduced in 10 patients or discontinued in 42 patients within a month after treatment. ANOVA identified the initial pain score as the only significant variable to predict pain reduction after spinal radiosurgery ($P < 0.03$) (Table 4). Three (3%) patients developed pain after radiosurgery. This symptom went along with local tumor recurrence after 3 to 6 months. No other patient developed pain after radiosurgery.

Twenty-two (21.6%) patients died from systemic tumor progression between 0.3 and 15.2 months after CKRS. There were no treatment-related deaths. Late complications after radiosurgery were found in 2 (2%) patients. One patient developed segmental neuropathy due to a circumscribed hemorrhage into a metastasis that had been treated by CKRS. This tumor was successfully resected *via* hemilaminectomy. No difficulties attributable to radiosurgery were encountered during this operation. Another patient developed vertebral instability

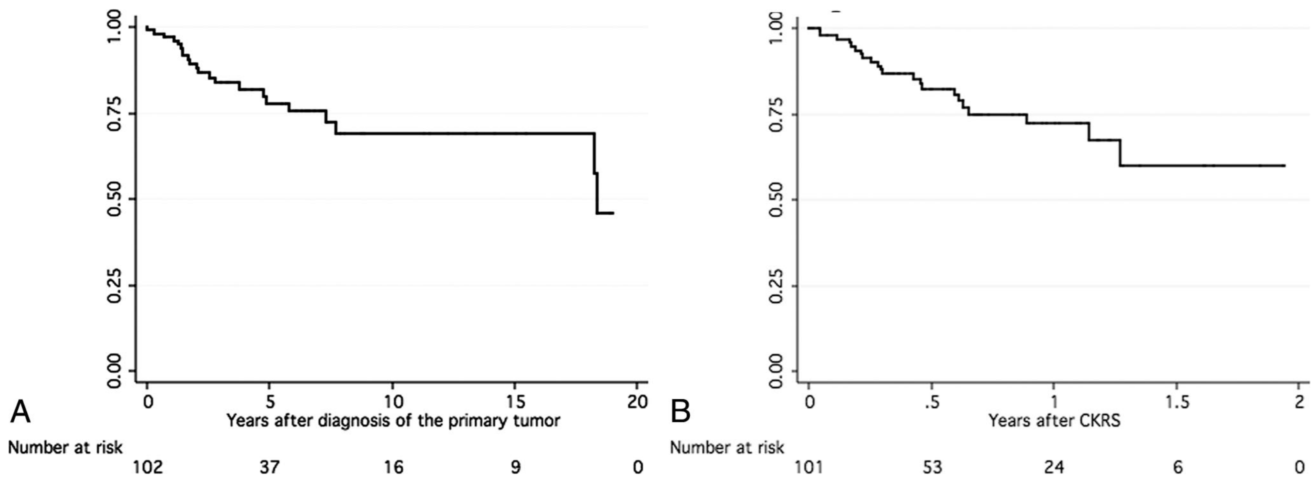

Figure 3. Patient example with follow-up (5 months) after CyberKnife radiosurgery for metastasis (L 4) from prostate cancer (left images = pre-CKRS, right = 5 months post-CKRS). Choline-PET CT becomes negative indicating successful treatment.

due to a pathologic fracture. This patient and 2 other in whom vertebral instability was anticipated underwent surgery for segmental stabilization after radiosurgery. No radiation damage of the spinal cord or the spinal nerve roots was observed.

Discussion

In most patients spinal metastases are first observed at an advanced stage.[12] The patients reported here are a selected series because their tumors were small and there were no more than 2 of them. Furthermore, the overall survival in this study group was comparatively long (15 years and more). Single session radiosurgical treatment yielded sustained tumor control, and in the half of the patients with tumor associated spinal pain syndromes the pain was effectively alleviated. Treatment efficacy and low toxicity significantly helped to maintain or even improve the functional status of the patients. The health threat conferred by spinal malignancies in the final stage of these patients' disease was eliminated by the noninvasive (*e.g.*, fiducial-free), single-session outpatient treatment that was delivered in only a few hours. This is an important feature of the present treatment approach because patients such as these frequently need further therapy (*e.g.*, chemotherapy or surgery); additional treatment is not delayed by radiosurgery.

Because fiducial-free tracking represents the latest advancement in CyberKnife technology for spinal applications, a comparison with previous and alternative methods is reasonable. Radiosurgery as an alternative to invasive surgery was applied to the patients of the current study because their tumors were small, did not cause myelopathy or paraplegia, and met the constraints of radiosurgery. Tumors requiring decompressive surgery were excluded. In this situation, the intention to treat the tumors with radiosurgery was to spare the patients the stress and the risk of open surgery. This surgical risk has been quantified in a recent Study of Patil *et al* by showing an in-hospital mortality rate of 5.6% and a complication rate of 21.9% after surgery for spinal metastasis.[13] How-

Table 3. Assessment of Patient Characteristics and Treatment Related Factors on Survival After Radiosurgery (Cox Proportional Hazard Model; n = 102)

Variable	HR	SE	z	P> z	[95% CI]
Age	0.987	0.017	−0.69	0.491	0.954–1.022
Sex	0.473	0.218	−1.62	0.106	0.191–1.171
KPS	0.864	0.028	−4.39	0.000	0.809–0.922
Pain	2.283	1.129	1.67	0.095	0.865–6.022
RT	0.436	0.256	−1.41	0.158	0.138–1.378
Primary	1.026	0.139	−0.19	0.846	0.786–1.339
Spine level	0.771	0.207	−0.96	0.336	0.455–1.308
T_{no}	1.748	0.743	1.31	0.189	0.759–4.025
D_{min}	1.217	0.158	1.51	0.131	0.943–1.571

HR indicates hazard ratio; SE, standard error; 95% CI, 95% confidence interval; P> z , significance if $P < 0.05$; KPS, Karnofsky performance score; Pain, patients with/without tumor associated pain; Primary, primary cancer; D_{min}, minimum tumor dose (Gy); T_{vol}, tumor volume (cm^3); T_{no}, no. treated tumors (1 or 2).

Table 4. Analysis of Variance in Patients (n = 52) With Tumor Associated Pain

Predictor	SS	*df*	MS	F	Prob >F
Model	214.489	25	8.5795	2.10	0.032
Sex	4.6421	1	4.6421	1.14	0.295
Age	0.2794	1	0.2794	0.07	0.795
KPS	5.0017	3	1.6672	0.41	0.748
Targets	4.1556	1	4.1556	1.02	0.322
VASi	88.3217	8	11.0402	2.71	0.025
Spine level	5.5110	3	1.8370	0.45	0.719
Primarius	40.095	6	6.6825	1.59	0.193
Dose	6.0192	1	6.0192	11.48	0.235
V10	2.0825	1	2.0825	0.51	0.481
Residual	106.029	26	4.0780		
Total	320.519	51	6.2846		

Test of predictors for pain reduction after radiosurgery. Predictor, parameter examined; SS, sum of squares; *df*, degrees of freedom; MS, mean square; F, F-value; Prob >F, statistical significance (*P*). Age young ≤57 yr vs. old >57 yr, KPS, 70, 80, 90, 100, Targets, no. tumors treated (1 or 2), VASi, pain score before radiosurgery (1, . . . 10), Spine level, spine levels treated (Table 1), Primarius, lesion histopathologies (Table 2), Dose, maximum tumor dose (19 Gy ≤/>19 Gy), V10, volume of tissue (cm^3) outside of the target receiving 10 Gy or more (50 cm^3 ≤/>50 cm^3).

ever, a combined treatment concept would be indicated if stabilization of the spine would be necessary. Osteosynthesis and kyphoplasty are feasible in combination with radiosurgery. The particular advantage of combining radiosurgery and minimally invasive kyphoplasty has already been published.[14] Whenever possible, radiosurgery should precede surgery with metallic implants. This guarantees optimal target visualization and a better chance to destroy the tumor. Otherwise metallic implants may make it difficult to delineate the tumor in CT and in MRI.

Single and multiple fraction radiotherapy is a palliative method for treating spinal metastases,[15] and in some cases can result in pain relief, preserved neurologic function, and tumor control.[16,17] However, and the efficacy of radiation therapy, and the duration of positive effects, are limited.[18] This therapy may be appropriate for patients with pronounced and advanced spinal metastasis but is disadvantageous for patients in better condition, similar to those reported here. Furthermore, the efficacy of fractionated radiation therapy is dependent on the radiosensitivity of the primary tumor.[18] Radiosurgery in the contrast by delivering necrotizing doses of radiation to metastatic tumors[1] is less dependent on the radiosensitivity of a target tumor.[1] We could reproduce this figure of radiosurgery in the present study.

Until recently, the use of the CyberKnife for spinal treatments required the invasive (*e.g.*, percutaneous) implantation of metallic seeds or bone screws to guarantee targeting with the mandatory submillimeter accuracy.[6,19–21] Several reports using CyberKnife and fiducial tracking in the treatment of benign and malignant spinal tumors have been published with convincing good results.[7,22–25] With the development of a fiducial-free skeletal structure tracking algorithm, completely noninvasive spinal radiosurgery with the CyberKnife became possible. First reports confirmed the same submillimeter accuracy of this software (Xsight, Accuray Inc.) as with fiducial-based targeting.[3,8] The present series is the largest to date on fiducial-free skeletal structure tracking and CKRS for spinal malignant tumors. Our results are in line with the previous studies in which fiducial tracking was used. For comparison, in the largest study with fiducial-based tracking an overall long-term improvement of pain was demonstrated in 86%, and a long-term radiographic control was achieved in 88% of the patients.[23] Furthermore, our results suggest, irrespective of the primary cancer, that spinal CKRS is especially valuable for cancer patients in good to excellent clinical condition with a comparatively long survival prospect, limited spinal metastases, and tumor-associated pain syndromes.

■ Conclusion

Single-fraction spinal radiosurgery with the CyberKnife is a completely noninvasive, safe, and effective treatment method for selected cancer patients. Patients with 1 or 2 small spinal tumors, and a comparatively long cancer survival time are particularly suited for this type of therapy. The short amount of time required to deliver this outpatient procedure allows it to fit well into oncological treatment concepts. Furthermore, in patients with tumor-associated pain syndromes the method provides significant pain reduction. Further studies are required to identify other patient groups who will profit from this innovative treatment method.

■ Key Points

- First report including more than 100 patients treated by fiducial-free frameless real-time image-guided single session radiosurgery in an outpatient setting.
- Patients with 1 or 2, small spinal malignant tumors, and a comparatively long cancer survival time were identified to be particularly suited for this type of therapy.
- In patients with tumor-associated pain quality of life was improved significantly.

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