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CLINICAL STUDY - PATIENT STUDY

Feasibility, safety, and outcome of frameless image-guided robotic radiosurgery for brain metastases

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Abstract We prospectively analyzed the safety and outcome of frameless image-guided robotic stereotactic radiosurgery (SRS) for treatment of brain metastases in patients that would have otherwise been treated with frame-based techniques. During a three-year period, 333 patients with 783 brain metastases of various histologies underwent 391 outpatient SRS procedures. Fifty-five percent of patients had multiple brain metastases. The median (mean) tumor volume was 1.0 cc (2.7 cc). The mean prescribed tumor dose was 18.5 Gy (±1.3 Gy). Local/distant tumor recurrences were treated by additional SRS for patients with stable systemic disease. Survival and freedom from local tumor recurrence was analyzed with the Kaplan–Meier method. Prognostic factors were obtained from the Cox proportional hazards model. System accuracy tests (end-to-end tests) were performed with a standard head phantom. Overall median survival was 12.2 months after SRS. The actuarial one-year local control rate was 95.2% (95% CI: 92.0–97.2); the distant brain tumor control rate was 67% (95% CI: 61.0–71.2). Most patients died from systemically progressing cancer (69%). A Karnofsky performance score (KPS) > 70 was related to prolonged survival in the univariate and multivariate analysis. Recursive partition analysis (RPA) classes I and II were related to prolonged survival in the univariate analysis. Twenty-one patients (6.3%) developed treatment-related neurotoxic effects; no patient died because of complications of SRS. Forty-five end-to-end tests documented a mean targeting accuracy of 0.48 ± 0.22 mm. Single-session, frameless robotic SRS is feasible, accurate, and safe in selected patients with brain metastases of various primary tumors. There seems to be no difference in patient selection, adverse effects, treatment outcomes, or system accuracy compared with frame-based SRS.

Keywords Frameless radiosurgery · Stereotactic radiosurgery · Radiosurgery · Brain metastases · Cyberknife

Introduction

Stereotactic radiosurgery (SRS) is widely used for local ablation of brain metastases. Local control has been reported to be above 90% in numerous retrospective and some prospective trials [1–11]. Most patients have been treated with frame-based stereotactic systems such as the Gamma Knife or dedicated stereotactic LINAC systems [4–7, 10, 11]. Recently, frameless image-guided robotic SRS has been introduced [12]. Technical accuracy comparable with that of conventional frame-based systems has been described [4, 13]. Even though brain metastases are the main indication for either frame-based or frameless SRS, clinical evidence for the local efficacy and safety of frameless single-session SRS has been mostly lacking until now [14, 15]. A few published preliminary reports describe the clinical outcomes of frameless intracranial radiosurgery for brain metastasis using externally fixed localization devices, conventional linear accelerators equipped with image-guided radiotherapy (IGRT) devices, or robotic image-guided radiosurgery (CyberKnife) [14–18]. Here we describe a single-center experience with the first 333 patients treated for brain metastases by single-session, frameless, image-guided robotic

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SRS using the same patient selection criteria and treatment conditions used in previous trials of frame-based technology [5, 11, 19].

Materials and methods

Between August 2005 and October 2008, 333 patients harboring 783 cerebral metastases from various primaries underwent 391 SRS procedures using the CyberKnife (Accuray, Sunnyvale, CA, USA). All patients were prospectively followed and archived in a digital database. Patients were sent from all over Germany and selected for radiosurgery treatment, by a dedicated tumor board of the University of Munich Hospital consisting of neurosurgeons, radiation oncologists, and physicians specializing in SRS, according to the following eligibility criteria:

(1) diagnosis of primary
(2) histological verification of brain metastases in uncertain cases by stereotactic biopsy
(3) maximum diameter of the tumors $\leq$3 cm
(4) probable life expectancy three months or longer
(5) Karnofsky performance score (KPS) score of 50 or higher
(6) extracranial tumor stable or in remission, with or without systemic therapy
(7) exclusion of meningeal or ependymal tumor spread by MRI and/or CSF examination

SRS was performed as an outpatient procedure. Gadolinium-enhanced MRI scans were used in addition to a dedicated thin-cut (1.2 mm slice thickness) CT investigation for treatment planning and follow-up examinations of all patients. The patients' heads were positioned during treatment using a custom-fitted face mask. Patient movements of up to 10 mm in translation and 1° in rotation (3° for yaw movements) were automatically corrected using the updated information of the image guidance system [12]. In clinical routine, we reposition the patient at translational offsets below the 10 mm threshold, whereas rotational limits are reached more frequently during treatment and depend heavily on the individual movement of the patient. Yaw corrections can not be corrected automatically and need to be adjusted manually within our configuration. We typically image before every single beam for the first 20 beams and then decide if it is safe enough to switch to imaging before every third beam which was done in about 90% of the cases treated.

Patient data were collected prospectively in a computerized database. Fifty-five percent of patients had multiple cerebral metastases (22%: two lesions, 12%: three lesions, 9%: four lesions, 4%: five lesions, and 7%: more than five lesions). For patients with multiple metastases, all tumors were treated in one treatment session. Surgery prior to SRS to resect large metastases not eligible for SRS occurred in 21% of patients. Whole-brain radiation therapy (WBRT) prior to SRS was not an exclusion criterion. Detailed patient and treatment characteristics are given in Tables 1 and 2. Nineteen of the 99 patients with lung cancer had small-cell lung cancer. Isocentric or conformal non-coplanar treatment planning techniques were chosen to match the tumor volume as accurately as possible. In cases of local or distant tumor recurrence, an additional SRS procedure was carried out if the patient was clinically stable and harbored no more than three new tumors. Asymptomatic radiation toxicity was defined as imaging

Table 1 Patient characteristics

Characteristics	No. of patients (%)	Median (range)
No. of patients	333	
Female	184 (55)	
Male	149 (45)	
Age (years)		60 (12–86)
KPS		90 (50–100)
Neurological deficits	133 (40)	
Total no. of brain metastases	783	
Tumor volume (cc)		1.0 (0.1–26.6)
No. of brain metastases/patient		2 (1–9)
Single	149 (44.7)	
Multiple	184 (55.3)	(2–9)
No. of brain metastases/RS		1 (1–9)
Site of primary tumor		
Non-small-cell lung cancer small-cell lung cancer	80 (24)	
Small-cell lung cancer	19 (5.7)	
GUT	53 (15.9)	
GIT	47 (14.1)	
Melanoma	37 (11.1)	
Breast	85 (25.5)	
Other	12 (3.6)	

Table 2 Treatment characteristics

Characteristics	No. of patients (%)	Mean ± SD
No. of SRS sessions/patient		
1	282 (84.7)	
2	43 (12.9)	
3	8 (2.4)	
Time to brain metastases (years)		3.9 ± 0.8
Chemotherapy	200 (60)	
WBRT	72 (21.6)	

changes, in the absence of neurological symptoms, in the T2 MRI sequence showing enlarged edema compared with the status before SRS. Typically, the treated tumors show a central hypointensity on T1 with the addition of contrast. Symptomatic or lethal effects were also scored. Side effects were considered due to either radiation toxicity to brain tissue or hemorrhages from treated metastases. Steroids were given in all cases, usually for 5–7 days after therapy (dexamethasone, 1–3 × 4 mg) depending on the size, location, and number of tumors. Steroids were reduced after one week depending on the neurological status.

Follow-up evaluation

Follow-up examinations were performed at three-month intervals after SRS until death or the date of closure of the study (October 1st, 2008). The development of new brain metastases or leukoencephalopathy associated with radiological findings (according to the National Cancer Institute's Common Toxicity Criteria version 2.0) was scored on the basis of serial MRI scans [20]. Local tumor progression was defined as a persistent radiographic increase of 25% or more in the size of a metastatic lesion (2D linear measurement). In cases where MRI could not discriminate between radiation toxicity and tumor recurrence C11-methionine PET imaging was performed. At each follow-up visit, functional status and neurologic toxic effects were scored. Systemic functional status was evaluated using the Karnofsky performance score (KPS) score. The KPS was used to define both improvement and deterioration. Whenever the KPS was better or worse than the preoperative findings, this was referred to as improved or deteriorated status, respectively. Otherwise, the status was considered stable. Local and distant recurrences were detected by MRI. Local recurrence was defined as the reappearance of a metastasis at exactly the same site as the first metastasis and distant recurrence was defined as the appearance of a new brain metastasis at a site different from that of the original metastasis. An acute toxic effect was defined as an event that arose within 90 days of SRS initiation and a late toxic effect was an event that occurred thereafter; both were identified on the basis of the central nervous system toxicity criteria listed in the Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring Criteria [21]. The cause of death was determined from medical records and from the referring physician's correspondence or supplementary phone calls. Cause of death was determined according to the prospective study protocol of Patchell et al. [22] patients with stable extracerebral disease and progressive neurological dysfunction, patients with severe neurological disability dying from intercurrent illness, and patients with progressive systemic and neurological disease were regarded as neurological deaths; otherwise a systemic death was assumed. Autopsy data were not available.

Statistical methods

The reference point for the study was the date of the SRS procedure. Endpoints are death and date of local recurrence. Length of survival and freedom from local recurrence were estimated with the Kaplan–Meier method [23]. Comparison of Kaplan–Meier curves was performed with the log-rank statistic. The prognostic value of the individual covariates was obtained from the Cox proportional-hazards model [24]. Variables used for univariate and multivariate analyses were dichotomized. The correlation between prognostic factors was analyzed using the chi-squared statistic. In the prognostic model the importance of each covariate was first tested univariately. Next, all variables were fitted together (full model). The "best" model contained only variables associated with the length of survival. The following variables were tested: age at SRS (>65 vs. ≤ 65 years); pretreatment KPS (≤ 70 vs. >70); number of brain metastases (single vs. multiple); prior WBRT (yes/no); surgery (yes/no); chemotherapy (yes/no); RPA class (I, II, or III); and latency from diagnosis of the primary tumor to development of cerebral metastasis (<1 vs. ≥ 1 year).

Accuracy testing

The total system accuracy of the CyberKnife is defined as the translational deviation of a spherical dose distribution delivered to a phantom, and includes the error compiled across the entire treatment chain of events (CT acquisition, planning, and image-guided delivery). For cranial treatments, it is determined using an anthropomorphic head-and-neck phantom, which contains an insert for an orthogonal set of radiochromic films. The complete procedure has recently been described in detail [25]. The total system accuracy was measured on a monthly basis.

Results

Follow-up information was available for all patients. The median follow-up period was seven months (3–36 months). The status of the primary tumor was classified as disseminated (RPA classes II/III) in 308 patients. Seventy-two patients (21.6%) were transferred to our institution after receiving WBRT (30–40 Gy). In patients that received prior WBRT, SRS was employed because of new tumor growth and/or detection of new tumors on MRI imaging. An SRS boost was typically not applied. Thirty-five patients received WBRT after SRS (10.5%) for treatment

of new multiple distant metastases in the brain. The diagnosis of brain metastasis was based on radiological findings and the primary tumor history. Thirty-six patients underwent stereotactic biopsy before SRS and 70 patients underwent surgical resection of tumors larger than 3 cm in diameter. Neurological symptoms, including all clinical symptoms such as headache, occulomotoric symptoms, seizures or focal neurological deficits, were present in 133 patients (40%) prior to SRS. All tumor locations in the brain were treated. In 44 cases the tumor was located in the brainstem. Treatment times ranged from 25 to 190 min, with a median treatment time of 65 min.

SRS treatment conditions

The median dose prescription to the tumor margin was 18 Gy (range, 15–24 Gy). The maximum and minimum median tumor doses were 27 Gy (range, 10.4–36.6 Gy) and 17 Gy (range, 7.5–22.7 Gy), respectively. The treatment volumes were prescribed to a median isodose of 70% (range, 50–85%). The median number of beams during treatment was 106 (range, 27–328). These conditions where chosen on the basis of suggested dose levels in the literature and according to our personal experience over the years [4, 5, 7, 19]. Patients received a slightly lower median dose to the tumor margin for recurrences after WBRT (18 vs. 19 Gy) and higher median doses for tumor histologies of melanoma and renal cell cancer (20 vs. 18 Gy).

Survival—prognostic factors

At the time of the last follow-up, 183 patients (55%) had died. The 6, 12, 18, and 24-month actuarial survival rates were 69.4% (95% CI: 64–74.2), 50.2% (95% CI: 44–56), 36.3% (95% CI: 29.9–42.7), and 27.7% (95% CI: 21.1–34.7), respectively. Fifteen patients (4.5%) died from progressive central nervous system disease (new distant metastases). Apart from 42 patients (12.6%) who had an unknown cause of death, all other patients died because of progressive systemic disease. Overall median survival was 12.2 months (Fig. 1). Patients with controlled systemic disease and no extracranial metastases (RPA class I) had a median survival time of 15.7 months (Fig. 2). A KPS > 70 was related to prolonged survival in the univariate and multivariate analysis. RPA classes I and II were related to prolonged survival in the univariate analysis. RPA was not included in the multivariate analysis because it is not independent of age and extracranial metastases. All other prognostic factors, including the number of treated metastases (Fig. 3) and prior WBRT, did not reach prognostic relevance (Table 3).

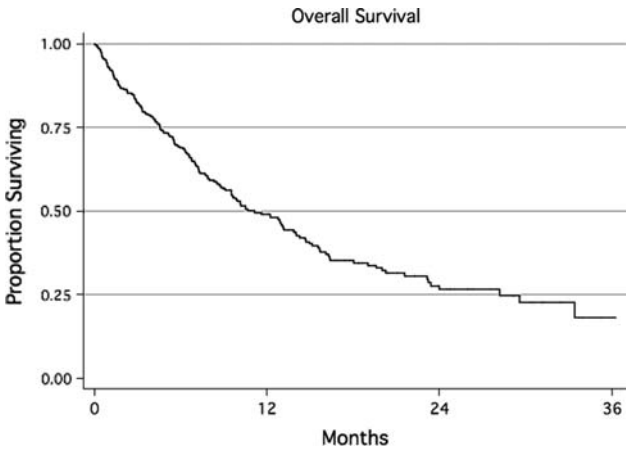

Fig. 1 Graph showing cumulative survival rates after robotic image-guided SRS for all 333 patients in this series

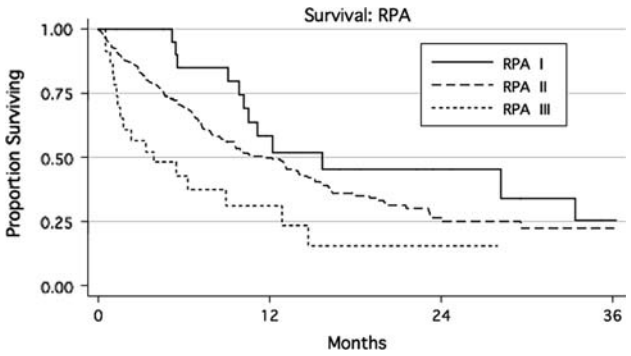

Fig. 2 Kaplan–Meier curves of patients of RPA classes I, II, and III. The difference was statistically significant only in the univariate analysis ($P = 0.0017$). Median survival of patients in classes I, II, and III was 15.7, 12.8, and 3.9 months, respectively

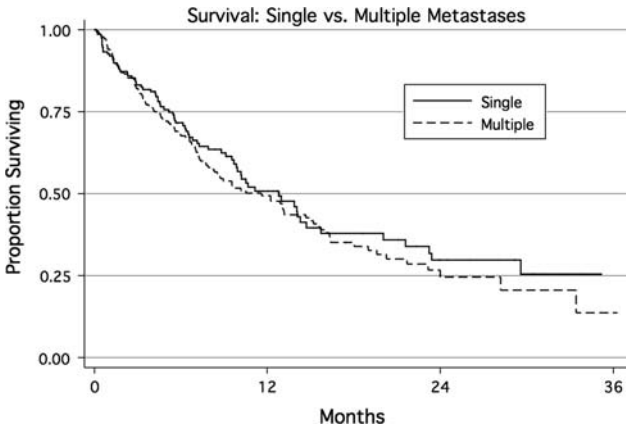

Fig. 3 Kaplan–Meier curves showing survival rates for patients harboring single or multiple brain metastases. The difference between the patients groups was not statistically significant ($P = 0.18$)

Treatment response

The actuarial local tumor control rates at 6, 12, 18, and 24 months were 99% (95% CI: 98–99.7), 95.2% (95% CI:

Table 3 Prognostic factors

Variable	No. of patients	MST (mos)	Log-rank *P*-value	Cox model *P*-value (exp (coef))
Age (years)			0.11	0.126 (0.78)
≤65	209	13		
>65	124	9.6		
KPS			<0.0001	<0.0001 (0.4)
≤70	60	5.5		
>70	273	14.3		
No. of metastases			0.4	0.21 (0.82)
Single	149	12.8		
Multiple	184	11.6		
WBRT			0.44	0.45 (1.15)
Yes	72	10.7		
No	261	12.2		
Surgery			0.5	0.9 (0.98)
Yes	70	14.7		
No	263	10.7		
Immuno/chemotherapy			0.16	0.05 (1.4)
Yes	200	10.5		
No	133	14.7		
RPA class			0.003	–[a]
I	25	15.7		
II	285	12.8		
III	23	3.9		
Latency period of brain metastases/ primary (years)			0.09	0.023 (1.48)
≤1	94	9.9		
>1	239	13		

[a] Cox analysis was not performed for RPA grade because the KPS had already been analyzed by Cox analysis and the RPA consists partly of the KPS grade

92–97.2), 92.1% (95% CI: 87.5–95) and 86% (95% CI: 77.5–91.5), respectively. Local recurrences were observed in 25 of the treated tumors. The 6, 12, 18, and 24-month actuarial distant tumor control rates in the brain were 78% (95% CI: 72.3–82.7.7), 64.7% (95% CI: 57.5–71.0), 55.9% (95% CI: 47.3–63.7) and 52% (95% CI: 42.4.5–60.8.5), respectively. SRS re-treatment was performed in 42 patients for new, distant metastases and in eight patients for local tumor recurrences. Up to three repeated SRS treatments were performed. Repeated SRS was only performed in patients with up to three new metastases.

Postoperative course

Of the 133 patients presenting clinical symptoms before SRS, 14 (10%) showed an improved KPS after SRS, 106 patients (80%) were stabilized, and 13 (10%) clinically deteriorated (because of treatment-related and non-treatment-related factors) at the first follow-up examination. Symptom improvement or progression occurred within a few days to a few weeks.

Table 4 Complications and cause of death after SRS for brain metastases

Factor	No. of patients (%)
Treatment related complications	52 (15.6)
Hemorrhage	4 (1)
Lethal	0
Symptomatic	1 (0.3)
Asymptomatic	3 (1)
Radiation toxicity	48 (14.4)
Lethal	0
Symptomatic	8 (2.4)
Asymptomatic	40 (12)
Deaths	183 (50)
Systemic death	126 (69)
Neurological death	15 (8)
Unknown	42 (23)

Causes of complications after SRS

Overall morbidity and mortality was 6.3% (21 patients) and 0%, respectively. Of these 21 patients, eight had worsened neurologic functions of preexisting neurological deficits (two patients: progressive hemiparesis, four patients: cerebellar symptoms, one patient: worsened visual field deficit, and one patient: aggravated facial palsy). New treatment-related deficits occurred in 13 patients (four patients: headache, eight patients: seizures, and one patient: pituitary insufficiency). A summary of post-treatment neurologic toxicity is given in Table 4. We did not find an association between complications and tumor volume, lesion number, or history of WBRT. The two patients with radiation necrosis suffered only from mild clinical symptoms (headache). Nine of the patients who received additional WBRT developed radiological leukoencephalopathy.

Radiation toxicity (perifocal edema) was the cause of new neurological deficits in eight patients. Radiation toxicity developed between 4 weeks and 20 months after SRS; symptoms such as seizures were treated with steroids and/or anticonvulsants in most cases. Two patients underwent surgery caused by space-occupying radionecrotic lesions. Asymptomatic radiation toxicity (typical imaging changes on T2 without clinical signs) was found in 40 patients. In four patients, intratumoral hemorrhages after SRS were detected. The tumor histologies were renal cell cancer in two cases and melanoma in two cases. The hemorrhages

where symptomatic in one case and not symptomatic in three cases.

System accuracy

Forty-one end-to-end phantom tests for cranial treatments were performed using an anthropomorphic head-and-neck phantom. The mean total targeting accuracy was 0.48 mm with a standard deviation of 0.22 mm.

Discussion

Stereotactically guided high-precision irradiation in a single dose (SRS) has demonstrated favorable treatment results for selected patients with brain metastases in several prospective and randomized trials [1, 2, 19]. SRS is attractive because of its low risk and minimal invasiveness. It can be used in conjunction with, or as an alternative to, other treatment methods and can be performed on an outpatient basis [11, 26, 27]. Multiple lesions can be treated at the same time, and re-treatments can be performed for local or distant recurrences [7, 11, 19, 28]. The vast majority of publications present outcomes of frame-based SRS. Non-invasive frameless SRS is becoming increasingly popular but, because of the limited number of reported treatment results on frameless SRS for brain metastases, the therapeutic impact remains unclear [14, 15]. We report here on a large patient series where SRS was applied using robotic image-guided frameless technology in patients with brain metastases from various histologies. All patients were prospectively analyzed and selected by an interdisciplinary tumor board for SRS treatment. Our objective was to assess the therapeutic impact of frameless SRS using the same selection criteria as those used for patients recently treated with frame-based techniques.

Treatment efficacy

A high percentage of local tumor control was achieved after frameless SRS in this study. The actuarial rate of local control for the 783 lesions treated with frameless SRS was 98, 95, 92, and 86% at 6, 12, 18 and 24 months, respectively. These rates compare favorably with other recently reported series using frameless and frame-based techniques. Using Novalis frameless IGRT, Breneman et al. [16] reported local control rates of 80 and 78% after 12 and 24 months, respectively. Using Gamma Knife radiosurgery, Bhatnagar et al. [29] treated patients with four or more intracranial metastases and Jawahar et al. [30] treated patients with lung metastases; both reported a 12-month local control rate of 71%. Furthermore, in our study freedom from distant failure in the brain (70%) was superior to that in other reports [2, 8]. We assume these results are related to the careful selection process for patients deemed suitable for SRS treatment.

Similar to our previous studies, SRS re-treatment was performed for all patients with local or new distant metastases (not more than three new tumors) to the brain and a stable systemic tumor status [7, 11, 19]. This concept of SRS salvage treatment has not yet been adequately investigated. Chen et al. [31] reported on 45 patients who underwent SRS salvage for new tumors out of 190 patients treated by initial SRS. They found that SRS salvage was a valuable means of treatment for tumor recurrence for patients who underwent previous treatment for brain metastases. Because of the lack of quality data, the role of SRS salvage therapy (as an alternative to WBRT) for distant tumor control deserves further prospective evaluation. Survival comparisons of retrospective studies are confounded strongly by selection biases. We found an overall median survival in the current study of 12 months, which was in accordance with overall survival rates reported by other authors after SRS either with or without WBRT, and surgery with WBRT [1, 2, 5, 7–9, 31–36].

Prognostic factors

The current analysis refers to a selected subpopulation with small brain metastases from various histologies. Similar to our previous trials, most of our patients (68%) were treated by SRS alone without additional WBRT before or after SRS [7, 11, 19]. SRS treatment planning and execution was comparable for all patients. The presence of multiple metastases had no prognostic impact for this selected patient population. Patients with multiple tumors (55%) experienced the same tumor control as those with a single lesion. Multiple metastases are, in most studies, correlated with an inferior prognosis, and these patients usually receive less aggressive treatment than those with singular lesions [6, 27]. Several retrospective studies and one randomized prospective trial have been published comparing patients treated with SRS who received WBRT with those who did not receive WBRT [2, 8, 35, 36]. These studies have generally shown that local and distant tumor control is poorer with the omission of upfront WBRT, but overall survival and the risk of neurological death is not altered [37]. Furthermore, the long-term adverse effects of WBRT on neurocognitive function are poorly understood and may not be negligible [38].

Complications

Eight patients with pre-existing deficits developed worsened neurologic symptoms after SRS and 13 patients developed new symptoms (mainly seizures and headache) between one and 20 months after SRS; these were controlled with

steroids and/or anticonvulsants in most cases. Forty patients showed asymptomatic radiation reactions on follow-up imaging (edema on T2 MRI imaging). No patients died of radiation-induced complications. Most importantly, patients undergoing multiple SRS procedures for local or distant re-treatment were not at higher risk of developing radiogenic complications compared with patients treated once. Two patients underwent surgery because of space-occupying radionecrotic lesions. Other authors describe similar complication rates after frameless and frame-based SRS, although we also scored transient edema (asymptomatic radiation toxicity) as treatment-related adverse events in this study [4, 14, 15]. Furthermore, our finding of a small risk of early or late toxicity after SRS in the current and recent trials accords well with data from the recent ASTRO evidence-based review of the role of SRS for brain metastases [37, 39].

Advantages and limitations of CyberKnife technology

There are several obvious advantages of frameless radiosurgery compared with traditional frame-based techniques, for example the complete non-invasiveness of the procedure, flexibility in scheduling the treatment process, and the possibility of spreading the treatment over several sessions in cases of multiple lesions. Fractionated treatments can also easily be implemented in selected cases [16]. These advantages, however, refer to all frameless technologies and are not exclusively related to CyberKnife technology. The CyberKnife offers a dedicated radiosurgery technology that is typically not used for conventional fractionation. Daily, routine quality-assurance checks are performed, but the system does not need to be physically readjusted for radiosurgery applications as conventional non-dedicated LINACs do. Because of the highly accurate image guidance with continuous tracking and correcting capabilities the lesions can be targeted with precision comparable with that of frame-based technologies. Periodic imaging is done with multiple planar stereoscopic X-rays during treatment (which exposes the patient to a low effective dose of the order of 0.2 mSv [40]). Treatment time depends on the size and configuration of the lesion and ranges between 20 and 90 min per lesion. Small spherical lesions can be treated quickly and straightforwardly using an isocentric planning technique (in addition to the standard non-isocentric, inverse treatment planning), similar to Gamma Knife treatment. The treatment of multiple lesions might require several hours; whether it is clinically justified to offer SRS and to treat all lesions in one session or to spread the treatment over two sessions is evaluated on an individual basis. In our experience, most patients tolerate even long treatments reasonably well as breaks can be taken during treatment, which makes this a more acceptable procedure.

System accuracy

The total system accuracy was checked monthly. Total system accuracy (the translational deviation of a spherical dose distribution delivered to a phantom) includes components of error encountered throughout the treatment chain, from CT acquisition to the end of image-guided delivery. For cranial treatments, a mean system accuracy of 0.48 ± 0.22 mm was verified over the described study period, which is in good agreement with the 0.44 ± 0.12 mm recently demonstrated for CyberKnife performance after commissioning [25]. This value is almost identical with the long-term accuracy of frame-based systems such as the Gamma Knife, which has been reported to be 0.48 ± 0.23 mm [41].

Conclusions

Single-session, frameless, image-guided robotic SRS is as safe and effective as frame-based SRS for local treatment of selected patients with singular and multiple brain metastases from various primary tumors. Outcome was particularly favorable in patients with a KPS > 70. Frameless salvage SRS for new distant metastases to the brain seems to be a feasible treatment option for selected patients and should be further studied in the framework of a prospective trial. The system's technical accuracy is comparable with that of conventional frame-based technologies.

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