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CLINICAL STUDY- PATIENT STUDY

Quality of radiosurgery for single brain metastases with respect to treatment technology: a matched-pair analysis

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Abstract *Objective* A comparison of treatment parameters and quality of clinical outcome in patients with single brain metastases treated with two different technologies for radiosurgery (Gamma Knife and CyberKnife). *Methods* Treatment parameters were statistically analyzed. Clinical outcome was assessed by matched-pair analysis based on the treatment device, differences in dose prescription, and the date of the treatment. Patients were matched according to their tumor size, age, gender, primary cancer, and Radiation Therapy Oncology Group score. Survival post-radiosurgery, local and distant tumor control, and complications were analyzed. Predictive factors were investigated. *Results* 423 single brain metastases were treated with Gamma Knife and 73 with CyberKnife. Tumor volumes were similar. The parameters minimum tumor dose, maximum tumor dose, prescription isodose volume, conformality index, homogeneity index, volume of tissue receiving a dose of 10 Gy or more were significantly larger in Gamma Knife group. Sixty-three patients were good matches. These showed the same pattern in parameters. Concerning the outcome analysis, only overall survival differed significantly between groups, twice as long with CyberKnife ($P < 0.03$). According to pooled data, dose was predictive of local failure, whole brain radiation therapy and chemotherapy were predictive of toxicity, the Radiation Therapy Oncology Group score was predictive of survival after radiosurgery, and date of treatment was predictive of overall survival. No factor predicted new brain metastases, including whole brain radiation therapy. *Conclusions* The most important result of this study was the finding that the obvious differences in treatment-related parameters between Gamma Knife and CyberKnife had no impact on the quality of the clinical outcome after radiosurgery. Survival time increased chronologically, presumably due to an intensified anti-cancer therapy in the more recent era of the CyberKnife treatments.

Keywords CyberKnife · Gamma Knife · Stereotactic radiosurgery · Stereotactic frame · Robotic surgery · Key indications of radiosurgery · Brain metastasis

Abbreviations

ARE	adverse radiation reaction
CFI	conformality index
CI	confidence interval
CK	CyberKnife
Dmax	maximum tumor dose
Dmin	minimum tumor dose
GK	Gamma Knife
PIV	prescription isodose volume
HI	homogeneity index
KPS	Karnofsky's performance score
Pt	Platinum
QA	quality assurance
RS	radiosurgery
RTOG	Radiation Therapy Oncology Group
Tvol	tumor volume
WBRT	whole brain radiation therapy
V10	volume of tissue receiving a dose of 10 Gy or more
V10net	V10 minus tumor volume

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Introduction

Lars Leksell described the concept of radiosurgery (RS) in 1951 [1]. The principle of radiosurgery is to destroy brain tumors with focussed ionizing radiation without harming surrounding healthy cerebral tissue. Since the 1970ies RS has become a very powerful and effective treatment method in neurosurgery. However, it took until 1987 when Sturm for the first time described the radiosurgical treatment of brain metastasis [2]. Within a few years after his publication cerebral metastases became an important and frequently treated key indication of RS [3].

Because high radiation doses in single fractions are used, quality assurance (QA) is an important concern in radiosurgery. QA refers to technical [4–7] and clinical issues [8–10]. It is now widely acknowledged that the principle of RS can be established with different technologies. However for many years the Leksell Gamma Knife (GK) has been regarded a standard device for RS. Its application has been limited to the intracranial space. GK RS requires a fixation of the patient's head in a rigid stereotactic frame to achieve submilimeter accuracy in dose delivery [7]. This is mandatory for intracranial RS. But, for the patients there is some discomfort associated with the fixation of a metallic frame. With the CyberKnife (CK) technology RS in the whole body became possible without the need to fix the head invasively for intracranial therapy [11]. Furthermore the characteristic advantages of radiosurgery (e.g., high efficacy, low risk, short time need) may confer an additional benefit to the patients when indications outside of the brain can be treated. Intracranial treatments however, continue to be a very important field of RS. Therefore the CK not only should show good treatment results in extracranial RS; it is also mandatory for the CK to meet the quality criteria of intracranial RS. In other words, RS in the brain using the CK should not be inferior to the GK therapy. It has already been published that the CK has the same sub-millimeter accuracy in intracranial and spinal RS as frame based technologies [12, 13]. However until now it has not been examined whether the clinical outcome after intracranial CK RS is equivalent to the results of GK RS.

We have used the GK over a period of more than 10 years for outpatient RS in more than 3,000 patients. In 2005 the CK replaced the GK in our outpatient RS service. The main reason to abandon the established GK technology was to use the possibility of full body RS offered by the CK, and for the patients with cerebral lesions to get rid of the occasionally cumbersome stereotactic frame. Against this background the purpose of this study was to compare the treatment parameters and the clinical results of GK and CK RS for single brain metastasis as an integral part of clinical QA.

Patients and methods

Patients were consecutively treated with the GK between October 1994 and June 2005. CK treatments were performed since July 2005. Patient treatments were included in this study until October 2007. All treatment parameters were stored prospectively in an electronic database. For this study those patients were selected who had radiosurgical treatment for a single cerebral metastasis. The following treatment related parameters were extracted from the database and comparatively analyzed: Volume of the brain metastasis (Tvol, cm^3), prescription tumor dose (Dmin, Gy), maximum tumor dose (Dmax, Gy), prescription isodose (isodose, %), prescription isodose volume (PIV, cm^3), total tissue volume receiving 10 Gy or more (V10, cm^3), tissue volume outside of the tumor receiving 10 Gy or more (V10 − Tvol = V10net, cm^3), conformality index (CFI), homogeneity index (HI). Tvol were derived from target definitition during the dose planning procedure. V10 was derived from dose-volume histograms calculated with the dose planning software. V10 can be regarded as a measure of dose concentration and V10net is useful to quantify the dose burden in the normal tissue adjacent to the treated metastasis. The CFI was the ratio of the tissue volume receiving the prescription isodose or more to the Tvol. The HI was the ratio of the Dmax to the Dmin.

Single cerebral metastases treated with the CK were matched in pairs to brain metastases treated with the GK according to Tvol, patient age, gender, primary tumor, and RTOG score. In order to qualify two metastases for matching, the difference in Tvol was kept below 10% or 0.25 cm^3 and the age difference of the patients was ≤5 years. Primary tumors had to fit pairwise according to the following groups: breast cancer, lung cancer, renal cell cancer, tumors of the genito-urinary (prostate, ovar), and the gastro-intestinal (colon, stomach) system, and a small group of rare other tumors. Gender and RTOG class [14, 15] had to fit perfectly. If no GK treated tumor could be identified to match a CK tumor according to these requirements, this lesion was excluded from the matched pairs. The patients harboring the machted pairs of brain metastases were grouped according to the treatment technology. The clinical outcome of the two groups was comparatively analyzed in respect to survival after RS, survival after diagnosis of the primary tumor (referred to as overall survival), local tumor control, distant treatment failure in the brain (indicating new cerebral metastases), radiological adverse radiation effects, complications not related to RS. The diagnosis of a radiation reaction was made based on the typical transient MRI appearance and taking into account predisposing factors like diabetes mellitus or history of WBRT. In ambiguous cases either

C11-mehtionine PET or stereotactic biopsy was used to clarify the situation. MRI follow up interval was 3 months in the first year after radiosurgery and later the interval was 6 months until death.

Treatment procedure

All radiosurgical treatments were performed in an outpatient setting according to an own standard protocol for GK RS [10] which has been adapted for CK RS. A Leksell GK Model B (Elekta Inc., Atlanta, GA, USA) and a CK (Accuray Inc., Sunnyvale, CA, USA) were used for RS. Imaging in all patients included high resolution contrast enhanced MRI; in general, at least a double dose of contrast media was given. Additional CT was used in all CK patients and in 10% of the GK procedures. For GK treatments a 1.0 T Siemens Expert scanner with a long and narrow gantry was used. This device has been proven to enable MRI significantly free of image distortions in order to allow dose planning without CT [7]. Imaging was performed after fixation of the stereotactic frame in GK procedures, and on the treatment day, or 1–5 days before RS in CK procedures. Dose delivery needed between 1 and 2 h. Differences in procedure time between GK and CK were not evaluated. Patients were discharged within 1 h after irradiation.

The GK is a frame-based RS device [16]. The therapeutic radiation is emitted by 201 min Cobalt-60 sources in a fixed array on a spherical segment and projecting to a single isocenter. Cobalt-60 is a radioactive isotope emitting photons of 1.17 and 1.33 MeV and a half-life of 5.3 years. The radioactive sources were replaced approximately after 6 years. The dose rate of the GK in this study was between 1.5 and 3 Gy/min. The GammaPlan Software (Elekta Inc., Atlanta, GA, USA) is able to calculate highly conformal dose plans with steep dose gradients. GammaPlan versions 2.01 to 5.3.2 were used. According to the dose plan treatment is delivered by sequentially scanning the tumor through the isocenter of the GK (multiple isocenter treatment). For spherical brain metastases one isocenter may be adequate for dose delivery. Single and multiple isocenter treatments lead to inhomogeneous dose distributions (high numerical value for HI).

The CK is a frameless, image-guided robotic RS system [11]. The therapeutic radiation is generated by a small linear accelerator (linac) mounted on the robotic arm. The dose rate (6 MeV Photon radiation) of the linac was either 3 Gy/min for the G3 or 6 Gy/min for the G4. A G4 CK was used in the last 4 months of the study period. Dose planning was performed with the Multiplan Software (Accuray Inc., Sunnyvale, CA, USA). Multiplan versions 1.3.2. to 1.6.4. were used. RS with the CK in the majority of cases applies a non-coplanar, non-isocentric treatment principle enabling a more homogeneous dose distribution (low numerical HI values) and a steep dose gradient. However, isocentric treatment similar to the GK is also possible; in this study, 3 CK tumors were treated isocentricly.

Statistical analysis

The Stata/IC 10.0 software package (Stata Corp. 4905 Lakeway Dr., College Station, TX 77845 USA) served for statistical analysis. The two-group mean comparison test and the Wilcoxon rank-sum test were used to investigate differences in clinical and treatment parameters with respect to the GK and CK group. To determine factors associated with or predictive of outcome after RS, analysis of variance and logistic regression, Kaplan–Meier survival estimates and the Cox proportional hazards model were used.

Results

A comparison of the radiosurgical treatment parameters of all patients with single cerebral metastases (423 GK procedures and 73 CK procedures) is given in Table 1. The tumor volume was 5.2 ± 5.5 cm^3 for the GK group and 5.1 ± 7.6 cm^3 for the CK group. There was no statistical difference between both groups in respect of tumor size. The minimum dose to the tumor margin was 19.4 ± 2.5 Gy in lesions treated by GK and 18.4 ± 1.5 Gy in lesions treated with the CK. This difference was statistically significant ($P < 0.0005$). The parameters Dmax, prescription isodose, and HI showed also statistically significant differences between the two treatment groups (Table 1). Smaller values for the CK group were measured concerning PIV (5.3 ± 7.9 cm^3 vs 7.4 ± 6.9 cm^3, $P < 0.02$), CFI (1.1 ± 0.3 vs 2.1 ± 3.3, $P < 0.005$), V10 (14.2 ± 15.7 cm^3 vs

Table 1 Comparison of treatment parameters in all patients (mean ± SD)

Technology	Gamma Knife	CyberKnife	Significance
Number of tumors	423	73	
Tvol (cm^3)	5.2 ± 5.5	5.1 ± 7.6	n.s.
Dmin (Gy)	19.4 ± 2.5	18.4 ± 1.5	$P < 0.0005$
Dmax (Gy)	37.3 ± 4.4	27.4 ± 3.5	$P < 0.0001$
Isodose (%)	53 ± 7	67 ± 5	$P < 0.0001$
PIV (cm^3)	7.4 ± 6.9	5.3 ± 7.9	$P < 0.02$
CI	2.1 ± 3.3	1.1 ± 0.3	$P < 0.005$
HI	1.9 ± 0.2	1.5 ± 0.1	$P < 0.0001$
V10 (cm^3)	19.0 ± 18.2	14.2 ± 15.7	$P < 0.02$
V10net (cm^3)	13.4 ± 13.2	8.5 ± 9.2	$P < 0.002$

Table 2 Comparison of dose parameters in matched-pair analysis (mean ± SD)

Technology	Gamma Knife	CyberKnife	Significance
Number of tumors	63	63	
Dmin (Gy)	19.5 ± 2.4	18.5 ± 1.2	$P < 0.001$
Dmax (Gy)	37.4 ± 4.6	27.4 ± 3.4	$P < 0.0001$
Isodose (%)	53 ± 7	67 ± 6	$P < 0.0001$
PIV (cm^3)	5.2 ± 4.6	3.6 ± 3.8	$P < 0.02$
CI	3.4 ± 7.6	1.1 ± 0.3	$P < 0.005$
HI	1.9 ± 0.2	1.5 ± 0.1	$P < 0.0001$
V10 (cm^3)	13.1 ± 11.6	10.6 ± 10.5	n.s.
V10net (cm^3)	9.2 ± 8.3	6.8 ± 7.2	$P < 0.05$

19.0 ± 18.2 cm^3, $P < 0.02$), and V10net (8.5 ± 9.2 cm^3 vs 13.4 ± 13.2 cm^3, $P < 0.002$).

63 pairs of tumors could be identified to meet exactly the constraints of the matched-pair model (Table 2). Follow up information was complete for all patients. The two groups represented 14.9% of the single metastases treated with the GK and 86.3% of the single metastases treated with the CK. In these patients the GK treatments were performed over a period of 8.9 years (from March 21st, 1996 until February 23rd, 2005), and the CK treatments over a period of 2.2 years (from July 22nd, 2005 until October 1st, 2007). The interval between the first diagnosis of the primary tumor and RS was 3.7 ± 4.8 years for the GK group and 4.2 ± 5.7 years for the CK group (difference not significant).

In order to give proof of the matching algorithm no statistical differences in the following parameters were found with respect to the technology used for RS (GK vs CK): Tumor volume (3.4 ± 3.6 cm^3 vs 3.3 ± 3.5 cm^3), age (59.4 ± 11.7 vs 59.7 ± 11.4), sex (38, 60% female), KPS (median 80 range 50–80), primary tumors, and RTOG score (Table 3). Furthermore, no statistically significant differences between the groups were found for the following parameters that were not used for matching: lesion side, confirmed histology of brain metastasis, WBRT before RS, chemo- or immunotherapy. However, in the CK group more metastases were located in the posterior fossa when compared to the GK group (24 vs 13, $P < 0.04$) (Table 3).

The following outcome results were found after RS with respect to the treatment modality and the time period in which RS was given (Table 4, Figs. 1, 2, 3, 4): Minimum follow up was 5 months after RS. About 58 (92%) patients died in the GK group and 38 (60%) in the CK group. None of the patients investigated in the matched pair analysis died from intracranial tumor progression alone. All deaths were due to general tumor progression or extracranial lethal events.

Table 3 Parameters of matched-pair analysis (mean ± SD)

Technology	Gamma Knife	CyberKnife	Significance
Number of tumors	63	63	
Matching parameters			
Tvol (cm^3)	3.4 ± 3.6	3.3 ± 3.5	n.s.
Patient age	59.4 ± 11.7	59.7 ± 11.4	n.s.
Sex (female/male)	38/25	38/25	n.s.
KPS (median, range)	80 (50–100)	80 (50–100)	n.s.
Primary cancers			n.s.
Lung	20 (32%)	20 (32%)	
Breast	16 (25%)	16 (25%)	
Kidney	7 (11%)	7 (11%)	
Melanoma	5 (8%)	5 (8%)	
Genito-urinary tract	5 (8%)	5 (8%)	
Gastro-intestinal tract	4 (6%)	4 (6%)	
Others	6 (10%)	6 (10%)	
RTOG score			n.s.
1	12 (19%)	12 (19%)	
2	38 (60%)	38 (60%)	
3	13 (21%)	13 (21%)	
General clinical parameters			
Lesion side			n.s.
Left	33	28	
Right	23	27	
Median	7	8	
Localisation of brain metastasis			
Supratentorial	50 (79%)	39 (62%)	$P < 0.04$
Infratentorial	13 (21%)	24 (38%)	
Brainstem	5 (8%)	10 (16%)	n.s.
Histology verified*	23 (37%)	26 (41%)	n.s.
WBRT before RS**	7 (11%)	14 (22%)	n.s.
Chemo-/Immunotherapy	31 (49%)	34 (54%)	n.s.
Platinum therapy	8 (13%)	9 (14%)	n.s.

* Histology of brain metastasis was verified prior to RS by stereotactic biopsy or resection of a cerebral metastasis

** Whole brain radiation therapy

Three local failures were recorded in each group. Using Kaplan–Meier statistics local tumor control 12 to 18 months after RS was 94.6% (CI: 98.6%–80.2%) after GK and 93.8% (CI: 98.6%–75.4%) after CK (n.s.). Pooling both groups to test treatment related factors associated with local recurrence in a Cox proportional hazard model, RS dose was the only significant variable (Dmax: $P < 0.04$; hazard ratio 8.6). Tumor volume, V10netto, CFI, and WBRT were without significance.

New brain metastases were recorded for 22 (35%) patients after GK treatment, and 15 (24%) patients after CK treatment (n.s.). Using Kaplan–Meier statistics distant cerebral tumor control (e.g., new brain metastases) 12 to 18 months after RS was 54.3% (CI: 68.4–37.4%) after GK

Table 4 Outcome of matched-pair analysis ($n = 63$ per group)

Technology	Gamma Knife	CyberKnife	Significance
Outcome parameter			
Lethal events	58 (92%)	38 (60%)	$P < 0.0001$°
Cerebral death	0	0	n.s.
Local failure	3	3	n.s.
Distant failure	22 (35%)	15 (24%)	n.s.
Salvage RS	15 (24%)	13 (21%)	n.s.
WBRT after RS	5	3	n.s.
Surgery for local failure	2	0	n.s.
No therapy for distant failure	4	3	n.s.
ARE	9 (14%)	14 (22%)	n.s.
Complications	2	3	n.s.
Survival (median, 95% CI, years)			
After RS	0.7 (0.5–1.2)	1.1 (0.8–1.9)	n.s.
After primary diagnosis	3.6 (2.4–4.0)	6.9 (3.1–11.3)	$P < 0.03$
Absence from			
Local failure (%, 95% CI)			
12–18 months	5.4 (1.4–19.8)	6.2 (1.4–24.6)	n.s.
Distant failure (%, 95% CI)			
18–24 months	45.7 (31.6–62.6)	41.3 (25.8–61.4)	n.s.
ARE (%. 95% CI)			
18 months	18.0 (8.4–36.5)	42.9 (25.5–65.6)	n.s.

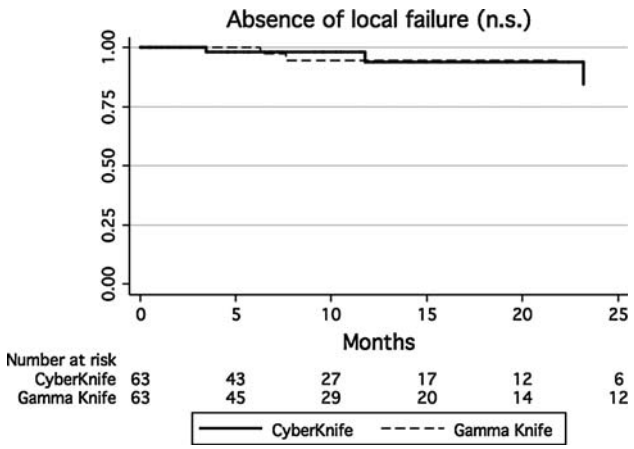

Fig. 1 Local tumor control in brain metastases treated by radiosurgery (absence of local failure; Gamma Knife versus CyberKnife; Kaplan–Meier estimates)

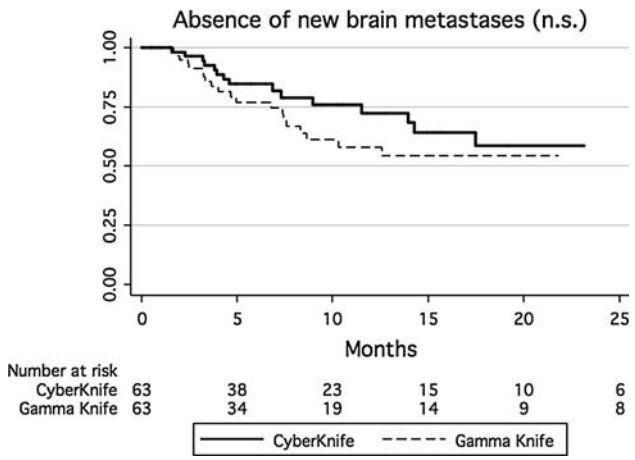

Fig. 2 Distant tumor control in brain metastases treated by radiosurgery (absence of new cerebral metastases; Gamma Knife versus CyberKnife; Kaplan–Meier estimates)

and 58.7% (confidence interval: 74.2–38.6%) after CK (n.s.). Pooling both groups in a multivariate Cox proportional hazard model no factor could be identified to correlate with the observation of new brain metastases. In particular whole brain radiation therapy (WBRT) did not decrease the incidence of new brain metastases after RS.

There were statistically no differences between both groups concerning other treatments for cerebral metastases after RS (e.g., salvage RS, WBRT, surgery).

Adverse radiation reactions were found in 9 (14%) tumors treated with the GK and in 14 (22%) after CK treatment (n.s.). Symptomatic ARE caused epileptic fits in 5 GK patients and in 6 CK patients. Pooling both groups in a multivariate Cox proportional hazard model age, WBRT, and chemotherapy with Platinum compounds were significant prognostic factors ($P < 0.05$). The highest level of significance ($P < 0.001$) and a very high hazard ratio of

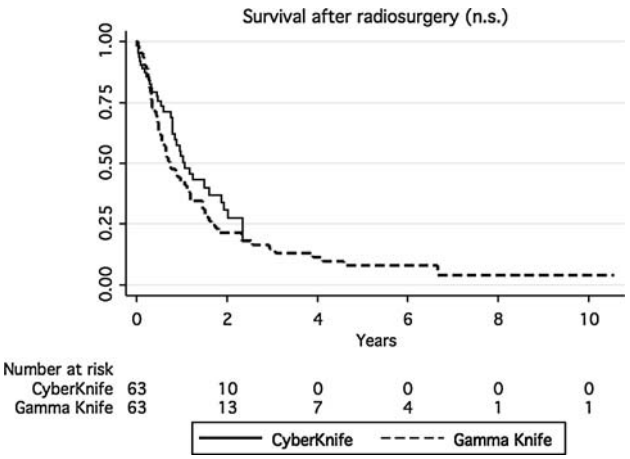

Fig. 3 Survival after radiosurgery for single cerebral metastasis (Gamma Knife versus CyberKnife; Kaplan–Meier estimates)

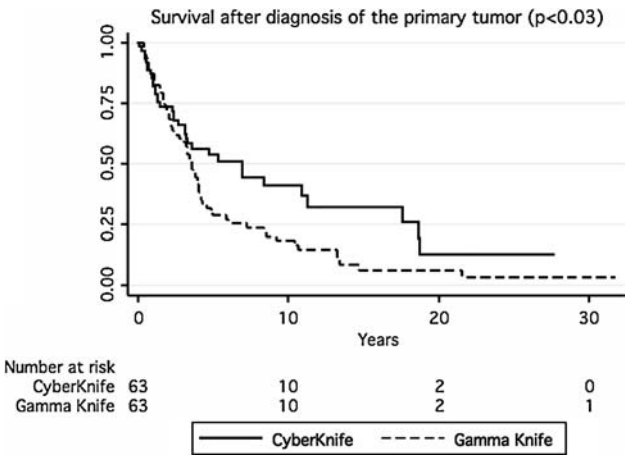

Fig. 4 Overall survival after first diagnosis of the primary tumor for radiosurgically treated single cerebral metastasis (Gamma Knife versus CyberKnife; Kaplan–Meier estimates)

10.2 were found for the combination of WBRT and Platinum therapy. Other complications not related to RS were observed in two GK patients and in five CK patients (n.s.).

Median survival was 0.7 years (range 0.5–1.2) after GK and 1.1 years (range 0.8–1.9) after CK RS (n.s.). Pooling both groups in a multivariate Cox proportional hazard model the extracranial tumor status (RTOG score) [14, 15] was the only significant variable found associated with survival after RS ($P < 0.04$; hazard ratio 1.4).

Median overall survival (after first diagnosis of the primary tumor) was 3.6 years (range 2.4–4.0) after GK and 6.9 years (range 3.1–11.3) after CK RS ($P < 0.03$). In multiparametric survival modeling the time period (e.g., the CK period) was the only significant factor associated with prolonged overall cancer survival ($P < 0.02$; hazard ratio 1.7).

Discussion

This study is a new contribution to our series of publications in which we investigated the emerging role of outpatient RS for cerebral metastasis since we introduced the GK in Germany in October 1994 [17–23].

In general, cerebral metastasis has become a frequently treated key indication of RS [3] and there is also progress in clinical oncology and medical technology. Therefore as an integral part of our clinical QA [10], aim of this study was to compare the results of outpatient RS for single cerebral metastases with respect to treatment technology, potential differences in dose prescription, and the period of time in which RS was performed. In July 2005 a CK in our service replaced the GK after a period of more than 10 years.

The GK is a frame based standard RS device mainly for intracranial indications [16] while the CK represents an innovative frame-less, image-guided robotic technology for whole body RS [11]. While the accuracy of dose delivery has already been shown to be equivalent for both systems [12, 13], dose planning and by that the dose distribution in the target tissue may be different for both therapeutic devices [24]. With the GK a single or multiple isocenter treatment (with coplanar array of 201 Cobalt-60 sources) is used resulting in a highly conformal but inhomogeneous dose distribution and high central tumor dose [24, 25]. In brain metastasis the characteristic dose inhomogeneity of the GK theoretically may be advantageous. It could help to minimize local tumor recurrences because the necrotic or hypoxic core of metastases harboring particularly radio-resistant tumor cells is receiving a very high dose of radiation [26]. On the contrary, with the CK a more homogeneous dose distribution is generated due to its non-isocentric non-coplanar treatment geometry and its highly flexible dose planning software [24, 27]. This feature could potentially give rise to a higher local recurrence rate in tumors with a radio-resistant core when compared to the GK. In this investigation we were actually able to confirm the theoretical assumptions concerning the physical dose distribution. In the total study cohort and in the tumors selected for matched-pair analysis statistically highly significant evidence of higher dose homogeneity and lower central dose was found in tumors treated with the CK as compared to the GK. Likewise the minimum tumor dose was significantly lower in the CK group as compared to the GK group. However the absolute numerical difference in this dose parameter was small (around 1 Gy or 5%).

Further significant differences between the GK and the CK treatments were found for the variables CFI, V10, and V10net. Concerning the issue of radiation protection but not the clinical outcome the results obtained with these parameters were significantly in favor of the CK treatment.

Healthy brain tissue was exposed to less radiation when compared to the GK treatment. This difference applies to therapeutically used dosages. Therefore in regard of radiation protection our data outweigh a recent communication in which in an experimental setting very low peripheral doses for the CK were larger than those measured for the comparable GK brain treatment [28].

The parameters CFI, V10, and V10net in approximation describe the dose concentration to the target tumor and the dose burden to surrounding healthy tissue. Theoretically a high CFI and a large V10 and V10net could be correlated with better local tumor control because tumor cells (invisible on MRI) infiltrating adjacent brain tissue, although outside of the planning target volume, are more likely to still receive a potentially cytotoxic dose of radiation. On the other hand, V10 has been described to predict the risk of intracranial RS [29]. Actually a recent study on RS for single metastases showed that by adding a 2 mm margin to the radiosurgical target (e.g., increasing PIV, V10 and V10net) no increase in local tumor control or survival was achieved. Instead more severe complications were found [30]. Taking our treatment data into account we therefore could have expected to find a higher rate of adverse radiation effects and perhaps a better local tumor control in the patients treated with the GK. However, this could not be established. In this regard the quality of treatment outcome was maintained with the CK when compared to the GK.

Pooling the data of both treatment groups allowed identifying predictive factors of the outcome endpoints of the study. This was mainly done to assess potential selection bias in our patients in comparison with other similar radiosurgical studies. Survival after RS, local and distant cerebral tumor control as well as toxicity were in general agreement with other similar studies on RS for brain metastases [31–33]. We found the radiosurgical dose was predictive of local failure; this is rational because it reflects a well-known dose-response relationship in radiation therapy. WBRT and in particular the combination of WBRT and Pt chemotherapy were found to be predictive factors of neurotoxicity. This is a quite new important result in regard of treatment QA and it is worthwhile to be further investigated. Furthermore, this result adds to a controversy about the role of WBRT in addition to RS. In the present study WBRT did not correlate with risk reduction for new distant brain metastases. This is in line with our previous publications on RS for cerebral metastases [17–23] but not with a recently published randomized controlled trial (and some other studies) in which WBRT in addition to RS significantly reduced cerebral recurrences [34]. This comparative figure may hint on a special patient selection in our service. However, since the GK and the CK group were balanced in this respect and salvage RS for new brain metastases was equally applied in both group, the issue deserves no further discussion in this place. Well accepted and once more reproduced in this study was the fact that the RTOG score is a predictor of survival after RS. This is a serviceable finding in order to select patients who may best benefit from RS.

The most important result of this study, however, was the finding that the obvious differences in treatment related parameters between GK and CK had no impact on the clinical outcome and the quality of the treatment results after RS. Negative expectations concerning dose homogeneity and dose concentration were not met. On the contrary, the two groups of patients experienced an indistinguishable clinical outcome after RS irrespective of the technology used for treatment. This result clearly is in favor of the reproducibility of the treatment principle of RS if appropriate technology is used and the physical and clinical QA criteria are respected. More generally speaking similar results could also be expected for other sophisticated radiosurgical technologies when staying within the constraints of this study. The full body applicability of the CK [12, 13, 35–37] is not at the expense of inferior intracranial treatment quality when compared to the dedicated intracranial RS technology of the GK.

In a relatively short time cerebral metastasis has emerged as a high-volume key indication of RS. Therefore after changing the technology it was reasonable to perform the present study as a part of our QA. Brain metastases are discrete and often spherical on imaging, thus representing attractive and easily to treat targets with any radiosurgical technology. Other important radiosurgical indications like vestibular schwannoma or skull base meningioma because of their irregular shape are more challenging to treat. Therefore we are planning similar studies comparing the quality of radiosurgery with respect to treatment technology in these indications.

Unexpectedly we found a significantly longer overall survival for the CK group while the interval between first diagnosis of the primary cancer and the RS and the survival after RS was similar in both groups. The result could reflect a general therapeutic progress in oncology pertaining to patient cohorts with similar characteristic to ours. A selection bias pertinent to factors that are not accounted for in this study could also explain this observation. Unfortunately the available information does not allow a convincing explanation of this unexpected result and further studies on this subject are needed.

Conclusion

With a matched-pair analysis we for the first time were able to prove that identical quality of clinical results in a key indication of RS, namely single brain metastases, can be

achieved with the GK and the CK. Furthermore we could show that the radiosurgical dose can be better tailored to the target with the CK than with the GK. This result, a more homogeneous dose distribution, and a lower peripheral dose represent an advantage of the CK in regard of the radiation protection. Furthermore, we could repeat our results concerning the concept of primary RS without the addition of WBRT and salvage RS for recurrent lesions. This is important as we found that WBRT significantly added to neurotoxicity after RS either alone or even more in combination with Platinum therapy. This issue and the observation of an increase in overall cancer survival time in the CK period underlines the importance of advances in treatment technology and the need of distinguished oncological concepts including outpatient RS. Further studies on this topic are warranted.

References

1. Leksell L (1951) The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 102:316–319
2. Sturm V, Kober B, Hover KH, Schlegel W, Boesecke R, Pastyr O, Hartmann GH, Schabbert S, zum Winkel K, Kunze S et al (1987) Stereotactic percutaneous single dose irradiation of brain metastases with a linear accelerator. Int J Radiat Oncol Biol Phys 13:279–282
3. Smith ML, Lee JY (2007) Stereotactic radiosurgery in the management of brain metastasis. Neurosurg Focus 22:E5. doi:10.3171/foc.2007.22.3.6
4. Flickinger JC, Lunsford LD, Kondziolka D, Maitz A (1993) Potential human error in setting stereotactic coordinates for radiosurgery - implications for quality assurance. Int J Radiat Oncol Biol Phys 27:397–401
5. Hartmann GH (1994) Quality assurance programme on stereotactic radiosurgery. Acta Neurochir Suppl (Wien) 62:98–100
6. Treuer H, Hoevels M, Luyken K, Gierich A, Kocher M, Muller RP, Sturm V (2000) On isocentre adjustment and quality control in linear accelerator based radiosurgery with circular collimators and room lasers. Phys Med Biol 45:2331–2342. doi:10.1088/0031-9155/45/8/318
7. Mack A, Czempiel H, Kreiner HJ, Durr G, Wowra B (2002) Quality assurance in stereotactic space. A system test for verifying the accuracy of aim in radiosurgery. Med Phys 29:561–568. doi:10.1118/1.1463062
8. Schell MC, Kooy H (1994) Stereotactic radiosurgery quality improvement: interdepartmental collaboration. Int J Radiat Oncol Biol Phys 28:551–552. doi:editorial;comment
9. Shaw E, Kline R, Gillin M, Souhami L, Hirschfeld A, Dinapoli R, Martin L (1993) Radiation Therapy Oncology Group: radiosurgery quality assurance guidelines. Int J Radiat Oncol Biol Phys 27:1231–1239
10. Muacevic A, Jess-Hempen A, Tonn JC, Wowra B (2004) Clinical quality standards for gamma knife radiosurgery–the Munich protocol. Acta Neurochir Suppl (Wien) 91:25–32
11. Adler JR Jr, Chang SD, Murphy MJ, Doty J, Geis P, Hancock SL (1997) The Cyberknife: a frameless robotic system for radiosurgery. Stereotact Funct Neurosurg 69:124–128. doi:10.1159/000099863
12. Chang SD, Main W, Martin DP, Gibbs IC, Heilbrun MP (2003) An Analysis of the Accuracy of the CyberKnife: A Robotic Frameless Stereotactic Radiosurgical System. Neurosurgery 52:140–147. doi:10.1097/00006123-200301000-00018
13. Yu C, Main W, Taylor D, Kuduvalli G, Apuzzo ML, Adler JR Jr (2004) An anthropomorphic phantom study of the accuracy of Cyberknife spinal radiosurgery. Neurosurgery 55:1138–1149. doi:10.1227/01.NEU.0000141080.54647.11
14. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG, Byhardt R (1997) Recursive Partitioning Analysis (RPA) of Prognostic Factors in Three Radiation Therapy Oncology Group (RTOG) Brain Metastases Trials. Int J Radiat Oncol Biol Phys 37:745–751. doi:10.1016/S0360-3016(96)00619-0
15. Gaspar LE, Scott C, Murray K, Curran W (2000) Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 47:1001–1006. doi:10.1016/S0360-3016(00)00547-2
16. Arndt J (1993) Focussed gamma radiation. The Gamma Knife. In: Phillips MH (ed) Physical aspects of stereotactic radiosurgery. Plenum Press, New York, pp 87–128
17. Muacevic A, Kreth FW, Horstmann GA, Schmid-Elsaesser R, Wowra B, Steiger HJ, Reulen HJ (1999) Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. J Neurosurg 91:35–43
18. Muacevic A, Kreth FW, Mack A, Tonn JC, Wowra B (2004) Stereotactic radiosurgery without radiation therapy providing high local tumor control of multiple brain metastases from renal cell carcinoma. Minim Invasive Neurosurg 47:203–208. doi:10.1055/s-2004-818511
19. Muacevic A, Kreth FW, Tonn JC, Wowra B (2004) Stereotactic radiosurgery for multiple brain metastases from breast carcinoma. Cancer 100:1705–1711. doi:10.1002/cncr.20167
20. Muacevic A, Siebels M, Tonn JC, Wowra B (2005) Treatment of brain metastases in renal cell carcinoma: radiotherapy, radiosurgery, or surgery? World J Urol 23:180–184
21. Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW (2007) Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. J Neurooncol 87:299–307
22. Wowra B, Muacevic A, Jess-Hempen A, Tonn JC (2004) Safety and efficacy of outpatient gamma knife radiosurgery for multiple cerebral metastases. Expert Rev Neurother 4:673–679. doi:10.1586/14737175.4.4.673
23. Wowra B, Siebels M, Muacevic A, Kreth FW, Mack A, Hofstetter A (2002) Repeated gamma knife surgery for multiple brain metastases from renal cell carcinoma. J Neurosurg 97:785–793
24. Yu C, Jozsef G, Apuzzo ML, Petrovich Z (2003) Dosimetric comparison of CyberKnife with other radiosurgical modalities for an ellipsoidal target. Neurosurgery 53: 1155–1162; Discussion 1162–1153
25. Flickinger JC, Lunsford LD, Wu A, Maitz AH, Kalend AM (1990) Treatment planning for gamma knife radiosurgery with multiple isocenters. Int J Radiat Oncol Biol Phys 18:1495–1501
26. Leith JT, Cook S, Chougule P, Calabresi P, Wahlberg L, Lindquist C, Epstein M (1994) Intrinsic and extrinsic characteristics of human tumors relevant to radiosurgery: comparative cellular radiosensitivity and hypoxic percentages. Acta Neurochir Suppl (Wien) 62:18–27
27. Collins SP, Coppa ND, Zhang Y, Collins BT, McRae DA, Jean WC (2006) CyberKnife radiosurgery in the treatment of complex skull base tumors: analysis of treatment planning parameters. Radiat Oncol 1:46. doi:10.1186/1748-717X-1-46

28. Petti PL, Chuang CF, Smith V, Larson DA (2006) Peripheral doses in CyberKnife radiosurgery. Med Phys 33:1770–1779. doi:10.1118/1.2198173
29. Voges J, Treuer H, Sturm V, Buchner C, Lehrke R, Kocher M, Staar S, Kuchta J, Muller RP (1996) Risk analysis of linear accelerator radiosurgery. Int J Radiat Oncol Biol Phys 36:1055–1063. doi:10.1016/S0360-3016(96)00422-1
30. Nataf F, Schlienger M, Liu Z, Foulquier JN, Gres B, Orthuon A, Vannetzel JM, Escudier B, Meder JF, Roux FX, Touboul E (2008) Radiosurgery With or Without A 2-mm Margin for 93 Single Brain Metastases. Int J Radiat Oncol Biol Phys 70:766–772. doi:10.1016/j.ijrobp.2007.11.002
31. Auchter RM, Lamond JP, Alexander E, Buatti JM, Chappell R, Friedman WA, Kinsella TJ, Levin AB, Noyes WR, Schultz CJ, Loeffler JS, Mehta MP (1996) A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. Int J Radiat Oncol Biol Phys 35:27–35. doi:10.1016/S0360-3016(96)85008-5 see comments
32. Fernandez-Vicioso E, Suh JH, Kupelian PA, Sohn JW, Barnett GH (1997) Analysis of prognostic factors for patients with single brain metastasis treated with stereotactic radiosurgery. Radiat Oncol Investig 5:31–37. doi:10.1002/(SICI)1520-6823(1997)5:1<31::AID-ROI5>3.0.CO;2-L
33. Yamanaka K (1999) Prognostic factors for brain metastasis from lung cancer after gamma knife radiosurgery. Osaka City Med J 45:45–59
34. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N, Kobashi G (2006) Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 295:2483–2491. doi:10.1001/jama.295.21.2483
35. Ho AK, Fu D, Cotrutz C, Hancock SL, Chang SD, Gibbs IC, Maurer CR Jr, Adler JR Jr (2007) A Study of the Accuracy of Cyberknife Spinal Radiosurgery Using Skeletal Structure Tracking. Neurosurgery 60:147–156. doi:10.1227/01.NEU.0000249248.55923.EC
36. Muacevic A, Drexler C, Wowra B, Schweikard A, Schlaefer A, Hoffmann RT, Wilkowski R, Winter H, Reiser M (2007) Technical description, phantom accuracy, and clinical feasibility for single-session lung radiosurgery using robotic image-guided real-time respiratory tumor tracking. Technol Cancer Res Treat 6:321–328
37. Muacevic A, Staehler M, Drexler C, Wowra B, Reiser M, Tonn JC (2006) Technical description, phantom accuracy, and clinical feasibility for fiducial-free frameless real-time image-guided spinal radiosurgery. J Neurosurg Spine 5:303–312. doi:10.3171/spi.2006.5.4.303