Kim DG, Lunsford LD (eds): Current and Future Management of Brain Metastasis.
Prog Neurol Surg. Basel, Karger, 2012, vol 25, pp 201–209

CyberKnife Radiosurgery for Brain Metastases

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Abstract

Classic radiosurgery is a neurosurgical treatment concept for single-fraction irradiation of cerebral lesions not amenable to open surgery. Until recently it has been realized mainly by frame-based technologies (Gamma Knife; stereotactic linear accelerators). The CyberKnife described in 1997 is an image-guided frameless robotic technology for whole-body radiosurgery. It can be used for classic single-fraction radiosurgery and for hypofractionated treatments. The CyberKnife treatment procedure is completely non-invasive and can be repeated throughout the body if necessary. Brain metastases are an important and frequently treated indication of modern radiosurgery. Data concerning radiosurgical treatment of brain metastases with the CyberKnife are reviewed. Scientific evidence shows that the full-body applicability of the CyberKnife is not at the expense of an inferior intracranial treatment quality when compared to standard frame-based technology. The clinical results of CyberKnife single-fraction radiosurgery are in line with the published literature. The attractive therapeutic profile of CyberKnife radiosurgery is reflected by a high tumor control and a low toxicity and the repeatability of the treatments for recurrent metastases. Although hypofractionated treatments (in 3–5 fractions) of brain metastases have been performed with the CyberKnife to treat large metastases, the clinical significance of this new radiosurgical concept is unclear and requires further study. A new approach is to treat the resection cavity with radiosurgery after surgical removal of brain metastases. In this concept radiosurgery replaces fractionated radiation therapy as an adjunct to surgery. The initial results are very promising. The CyberKnife has been established as a modern non-invasive technology for intra- and extracranial radiosurgery. It adds to the oncological armamentarium and confers upon radiosurgery a greater emphasis as an oncological treatment concept.

In 1951 the concept of radiosurgery was defined by Lars Leksell [1]. During the following decades different radiosurgery systems have been developed. The pioneering work of Leksell and his colleagues resulted in the construction of the Leksell Gamma Knife [2]. Other groups adapted linear accelerators for radiosurgical application [3–5]. In 1997, John Adler described a new frameless robotic system for radiosurgery, the CyberKnife® Robotic Radiosurgery System (Accuray Incorporated, Sunnyvale, Calif., USA) [7]. Over time it was demonstrated that the goals of radiosurgery, to deliver high, ablative radiation doses with maximal dose fall-off outside the treatment volume, could generally be achieved using these different technologies. However, consistently high treatment quality can only be delivered when every single treatment respects the physical and biological limits of radiosurgery. Depending on the treatment technology, variability in the dose-planning parameters exists which may have an impact on the clinical outcome. Therefore, it seems appropriate to comparatively assess clinical outcomes obtained with different treatment technologies. In this chapter we review clinical outcomes of an important radiosurgical application, the treatment of brain metastases, with the CyberKnife technology, and compare it with previous data from studies involving other technologies.

Within a few years after the first specific publication by Sturm and colleagues [5] cerebral metastases became a frequently treated key indication of radiosurgery. Scientific evidence accumulated since has established radiosurgery as an important tool in the local management of brain metastases [6]. CyberKnife users have contributed to this evidence, enough to assess whether technical capabilities and clinical outcomes of Cyberknife radiosurgery are comparable to other radiosurgery devices for this application. A primary advantage of the CyberKnife system is its image-guided targeting system, as opposed to frame-based targeting. This allows the CyberKnife to be used for whole-body radiosurgery. Here we review on our own research and other published studies, and conclude that this advantage is not at the expense of reduced treatment quality for this classic indication of radiosurgery, brain metastases.

The CyberKnife Technology

The CyberKnife is a system [7] for whole-body radiosurgery. In this contribution only the intracranial application of the system shall be reviewed (fig. 1). The CyberKnife System consists of a 6 MV X-band linear accelerator mounted on a computer-controlled robotic manipulator capable of movement in 6 d.f. [7, 8]. Depending on the system version, the linear accelerator emits a dose rate between 3 and 10 Gy/min. There is a set of spherical tungsten collimators (range of apertures, 5–60 mm) and a circular lamellar collimator with variable aperture (Iris™ Variable Aperture Collimator; Accuray Inc.). For treatment of a brain metastasis either a single or several fixed collimators [9] or the Iris collimator [10] can be used. Integral to the CyberKnife is a dedicated image-guidance system which acquires low energy X-ray images during treatment (fig. 1). Exact patient positioning is automatically or semi-automatically accomplished by a 5-axis patient couch in earlier system versions. Newer versions include a robotic couch positioning system which aligns patients precisely with 6 degrees of freedom. Target displacements caused by patient

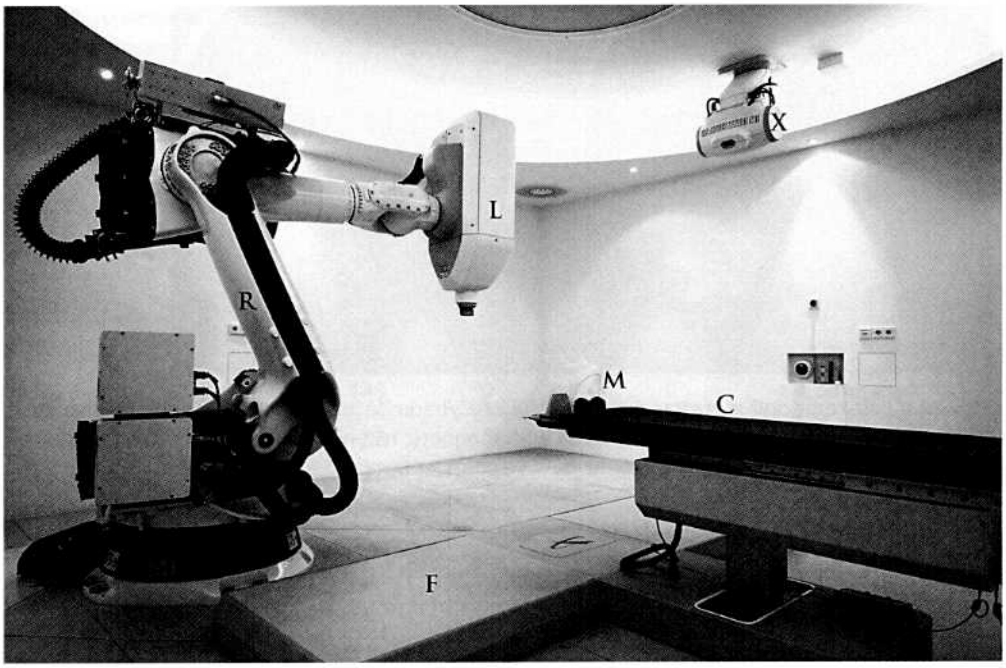

Fig. 1. The CyberKnife System and its components. C = patient couch; M = head support and thermoplastic mask; X = X-ray tube; F = X-ray detectors; R = robotic arm; L = linear accelerator.

movements during treatment are automatically corrected for by the system. For cerebral indications a 6-dimensional skull tracking algorithm is applied; this software uses the bony anatomy of the skull as a reference to continually track intracranial targets and to automatically correct for translational and rotational target shifts during radiation delivery. Stereoscopic X-ray images acquired during treatment are co-registered with a set of images digitally reconstructed radiographs (DRRs) from the dose planning computed tomography (CT). A displacement vector is calculated by matching pairs of stereoscopic live images (obtained during treatment) with DRRs. The robot corrects the actual treatment position by taking into account the displacement vector. The CyberKnife system has the same sub-millimeter accuracy as frame-based technologies [11–14]. For dose planning, digital image information from CT, magnetic resonance (MR) and/or positron emission tomography (PET) can be used. There is a specific dose planning software, MultiPlan® (Accuray Inc., Sunnyvale, Calif., USA). For treatment of brain metastases a nonisocentric or isocentric planning method can be used (fig. 2a, b). With the CyberKnife the total treatment dose can be delivered using 100 or more beams in a single session (as in the classic concept of radiosurgery [1]) or in up to 5 fractions (reflecting the recent modified concept [15]). During treatment, a thermoplastic mask provides comfortable restraint of the patient's head.

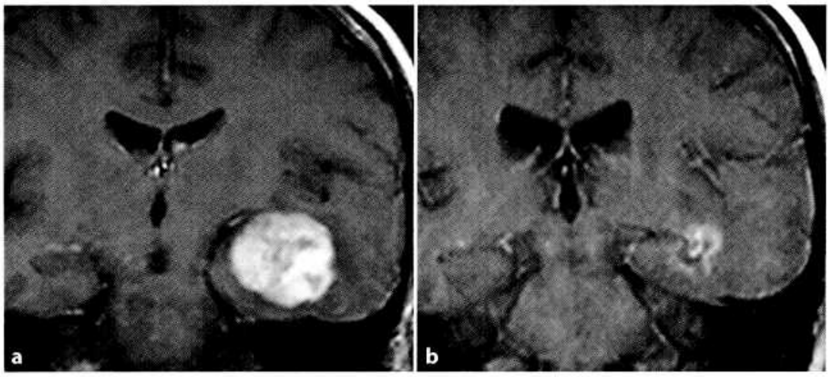

Fig. 2. **a** Left temporal metastasis at the time of Cyberknife treatment (magnetic resonance T_1-weighted Gd-enhanced) **b** Follow up-study with magnetic resonance image after 9 months: remission of the treated metastasis with some reactive contrast uptake.

Clinical Experience

Radiosurgery plays a significant role in the modern management of brain metastases [6]. The majority of patients have been treated with either the Gamma Knife or stereotactic linear accelerators. In radiosurgical series, the treatment of brain metastases accounts for 25% or more of all intracranial indications treated. In our Gamma Knife era (October 1994 to June 2005, 10 years) 926 of 2,714 patients were treated for brain metastases (34%). With the CyberKnife, extracranial radiosurgery became available. In the first 5 years since July 2005, we treated 2,430 patients with the new technology, 1,898 for intracranial indications, and 512 for cerebral metastases (21% of all cases; 27% of intracranial indications). This indicates that the substitution of the Leksell Gamma Knife by a CyberKnife in June 2005 had no impact on the absolute numbers of patients (around 100 per year) which we treat radiosurgically for brain metastases.

Today, there is some published experience in treating brain metastases with the CyberKnife [16–19] (table 1a, b). In 2002 the first publication on CyberKnife stereotactic irradiation for metastatic brain tumors was published by Shimamoto et al. [18]. The authors did not find severe side effects and concluded that stereotactic irradiation with the CyberKnife for metastatic brain tumors is effective and safe, and the dose should be at least 24 Gy. Nishizaki et al. [17] examined the role of CyberKnife radiosurgery/radiotherapy for brain metastases of multiple or large-size tumors. Their conclusion was that despite the fact they had treated an unfavorable group of patients with large tumors, the results for survival and tumor control rates were comparable to those of other published series. Furthermore, they stated that the CyberKnife provides the advantage of allowing for fractionated treatment for multiple or large-size tumors [17]. In 2009, four reports were published, one by Hara

Table 1. a Review of published studies on CyberKnife radiosurgery for brain metastases

1st author, reference, year	n patients n metastases	Dose fractions Gy	Tumor control toxicity
Shimamoto [18], 2002	48	9–30	high >24 Gy
	77	not available	no severe
Soltys [27], 2007	72	15–30	86%
	76 cavities	1–5	7 (3 necrosis)
Nishizaki [17], 2006	71	7.8–30.1	83%
	148	1–3	no permanent
Hara [16], 2009	62	14–24	87%
	145	1	6%
Muacevic [13], 2009	333	17–22	95.2%
	783	1	6.3%
Wang [19], 2009	40	18–36	94.1%
	68	1–5	14/40
Wowra [20], 2009	63	17–22	95%
	63	1	5%

et al. [16], another by Wang et al. [19], and two by our group [13, 20]. Hara et al. [16] found that CyberKnife radiosurgery provided excellent local control with acceptable toxicity in patients with melanoma or renal cancer brain metastases. Initial CyberKnife radiosurgery alone appeared to be a reasonable option, as survival was dictated by systemic disease.

In our first publication on the use of the CyberKnife for treatment of brain metastases, we examined the quality of radiosurgery with respect to treatment technology [20]. A matched-pair analysis was performed on patients with single brain metastases. Patients were treated with either the Gamma Knife or the CyberKnife. A strict matching algorithm was applied defining two clinically and oncologically very similar groups. Tumor volumes, location, and histology were equal in both groups. Patient ages, gender, and tumor status were also well matched. Concerning the radiosurgical treatment parameters, the largest difference between both groups was found for dose homogeneity, which was greater for CyberKnife, and correspondingly the maximal tumor dose, which was greater for Gamma Knife. These parameters are representative of the ways the Gamma Knife and the CyberKnife are used; with the Gamma Knife multiple isocentric shots are used to cover a target

Table 1. b Review of studies on CyberKnife radiosurgery for brain metastases (selected abstracts presented at CyberKnife Society meetings 2008–2010*)

1st author, year	n patients n metastases	Dose fractions Gy	Tumor control toxicity
McLaughlin, 2008[a]	18	24	89%
	18	1	4 acute, no late
McLaughlin, 2008	10	24–30	88%
	17	1–3	4 acute, no late
Kim, 2009	31	20–30	93.6%
	50	1–3	1 necrosis
Gagnon, 2010	215	17.5–20.4	lung cancer worse
	215	1–2	
Inoue, 2010	580	10–40	88.9%
		1–10	3 severe
Rhodes, 2010	70	18–22	high
	115	1	
Stacy, 2010[a]	23	25	93%
		5	no major

* For review, see: http://www.cksociety.org/). [a]CyberKnife radiosurgery to tumor bed after resection; nonresected additional metastases in patients.

with the radiosurgical field, while with the CyberKnife mostly a noncoplanar, nonisocentric dose plan is applied. The clinical outcome between both treatment groups was essentially identical. No difference in tumor control, toxicity, or survival after radiosurgery was observed. Only overall cancer survival was significantly longer in the patients treated with the CyberKnife, presumably due to more effective systemic anticancer therapy in the more recent era of the CyberKnife. It was also shown that the full-body applicability of the CyberKnife is not at the expense of inferior intracranial treatment quality when compared to the standard treatment technology of the Gamma Knife [20].

In our second publication, the results obtained in the first 3 years of using the CyberKnife to treat brain metastases were evaluated [13]. Both with respect to the number of patients and number of metastases treated, this represents the largest series on single-fraction radiosurgery for brain metastases with the CyberKnife published so far. The actuarial local tumor control rate at 12 and 24 months was 95.2 and 86%

respectively. This is in line with the radiosurgical literature [6]. The rate of distant, new cerebral metastases was 30%, pretty low when compared to the radiosurgical literature [21], but the figure corresponded well to our experience with the Gamma Knife [22–24]. Whole-brain radiotherapy was not a prognostic factor when combined with CyberKnife radiosurgery.

After surgical resection, adjuvant whole brain radiation reduces the risk of local recurrence of a brain metastasis [25]. This has been a recognized standard of care. Radiosurgery is typically regarded as a therapeutic alternative to surgery but not as an adjunct treatment option like fractionated radiation therapy. Recently however, retrospective studies with the Gamma Knife [26] and with the CyberKnife [27] (Stacy, table 1b; McLaughlin, table 1b) showed that treating the resection cavity provided effective local control of the tumor after resection (73–93%) with acceptable toxicity (5.4–9.2%). Although some details of this new adjunct therapeutic concept have to be refined, the available results are promising and in favor of replacing whole-brain radiation therapy with a postoperative radiosurgical boost to the resection cavity in selected patients.

The results of Wang et al. [19], in their study on hypofractionation with the CyberKnife, were that they got improved clinical outcomes by higher dosage per fraction. In their hands, the CyberKnife was an appropriate and valid treatment for brain metastasis [19]. The studies of Nihizaki [17] and Wang [19] included hypofractionated treatments while Hara et al. [16] and our series [13, 20] were on classic single fraction radiosurgery only. Hypofractionated treatment of brain metastases according to the extended definition of radiosurgery [15] was also addressed in several oral communications (table 1b). Inoue and colleagues used hypofractionation for large tumors. In their study Gagnon's group found that hypofractionation improved local control in brain metastases from lung cancer but not in brain metastases from nonlung histologies. The authors stated that their finding would be consistent with a previously reported high alpha/beta value in lung metastases which would argue for a higher total dose (Gagnon, table 1b). Summarizing hypofractionated treatment of brain metastases with the CyberKnife there is little evidence to support this concept so far and further studies are necessary.

Conclusion

The CyberKnife has been established as a modern non-invasive technology for intra- and extracranial radiosurgery. Its full-body applicability is not at the expense of inferior intracranial treatment quality. The treatment results in brain metastases are in line with the published literature on frame-based technologies. In the treatment of metastatic disease, it adds to the oncological armamentarium and gives radiosurgery a higher emphasis in oncological treatment concepts.

Acknowledgement

We are grateful to David Schaal for his editorial support.

References

1 Leksell L: The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 1951;102:316–319.

2 Arndt J: Focussed gamma radiation: the Gamma Knife; in Phillips MH (ed): Physical Aspects of Stereotactic Radiosurgery. New York, Plenum Press, 1993, pp 87–128.

3 Betti OO, Galmarini D, Derechinsky V: Radiosurgery with a linear accelerator: methodological aspects. Stereotact Funct Neurosurg 1991;57:87–98.

4 Colombo F, Benedetti A, Pozza F, et al: External stereotactic irradiation by linear accelerator. Neurosurgery 1985;16:154–160.

5 Hartmann GH, Schlegel W, Sturm V, et al: Cerebral radiation surgery using moving field irradiation at a linear accelerator facility. Int J Radiat Oncol Biol Phys 1985;11:1185–1192.

6 Smith ML, Lee JY: Stereotactic radiosurgery in the management of brain metastasis. Neurosurg Focus 2007;22:E5.

7 Adler JR Jr, Chang SD, Murphy MJ, et al: The CyberKnife: a frameless robotic system for radiosurgery. Stereotact Funct Neurosurg 1997;69:124–128.

8 Kuo JS, Yu C, Petrovich Z, Apuzzo ML: The CyberKnife stereotactic radiosurgery system: description, installation, and an initial evaluation of use and functionality. Neurosurgery 2003;53:1235–1239; discussion 1239.

9 Poll JJ, Hoogeman MS, Prevost JB, et al: Reducing monitor units for robotic radiosurgery by optimized use of multiple collimators. Med Phys 2008;35:2294–2299.

10 Echner GG, Kilby W, Lee M, et al: The design, physical properties and clinical utility of an iris collimator for robotic radiosurgery. Phys Med Biol 2009;54:5359–5380.

11 Chang SD, Main W, Martin DP, Gibbs IC, Heilbrun MP: An analysis of the accuracy of the CyberKnife: a robotic frameless stereotactic radiosurgical system. Neurosurgery 2003;52:140–147.

12 Yu C, Main W, Taylor D, et al: An anthropomorphic phantom study of the accuracy of CyberKnife spinal radiosurgery. Neurosurgery 2004;55:1138–1149.

13 Muacevic A, Kufeld M, Wowra B, Kreth FW, Tonn JC: Feasibility, safety, and outcome of frameless image-guided robotic radiosurgery for brain metastases. J Neurooncol 2010;97:267–274.

14 Takakura T, Mizowaki T, Nakata M, et al: The geometric accuracy of frameless stereotactic radiosurgery using a 6D robotic couch system. Phys Med Biol 2010;55:1–10.

15 Barnett GH, Linskey ME, Adler JR, et al: Stereotactic radiosurgery—an organized neurosurgery-sanctioned definition. J Neurosurg 2007;106:1–5.

16 Hara W, Tran P, Li G, et al: CyberKnife for brain metastases of malignant melanoma and renal cell carcinoma. Neurosurgery 2009;64:A26–A32.

17 Nishizaki T, Saito K, Jimi Y, et al: The role of CyberKnife radiosurgery/radiotherapy for brain metastases of multiple or large-size tumors. Min Invas Neurosurg 2006;49:203–209.

18 Shimamoto S, Inoue T, Shiomi H, et al: CyberKnife stereotactic irradiation for metastatic brain tumors. Radiat Med 2002;20:299–304.

19 Wang ZZ, Yuan ZY, Zhang WC, You JQ, Wang P: Brain metastasis treated with CyberKnife. Chin Med J (Engl) 2009;122:1847–1850.

20 Wowra B, Muacevic A, Tonn JC: Quality of radiosurgery for single brain metastases with respect to treatment technology: a matched-pair analysis. J Neurooncol 2009;94:69–77.

21 Aoyama H, Shirato H, Tago M, et al: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295:2483–2491.

22 Muacevic A, Kreth FW, Horstmann GA, et al: Surgery and radiotherapy compared with Gamma Knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. J Neurosurg 1999;91:35–43.

23 Wowra B, Siebels M, Muacevic A, et al: Repeated Gamma Knife surgery for multiple brain metastases from renal cell carcinoma. J Neurosurg 2002;97:785–793.

24 Muacevic A, Wowra B, Siefert A, et al: 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 2008;87:299–307.
25 Patchell RA, Tibbs PA, Regine WF, et al: Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998;280:1485–1489.
26 Mathieu D, Kondziolka D, Flickinger JC, et al: Tumor bed radiosurgery after resection of cerebral metastases. Neurosurgery 2008;62:817—823, discussion 823–814.
27 Soltys SG, Adler JR, Lipani JD, et al: Stereotactic radiosurgery of the postoperative resection cavity for brain metastases. Int J Radiat Oncol Biol Phys 2008;70:187–193.

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