
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.

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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

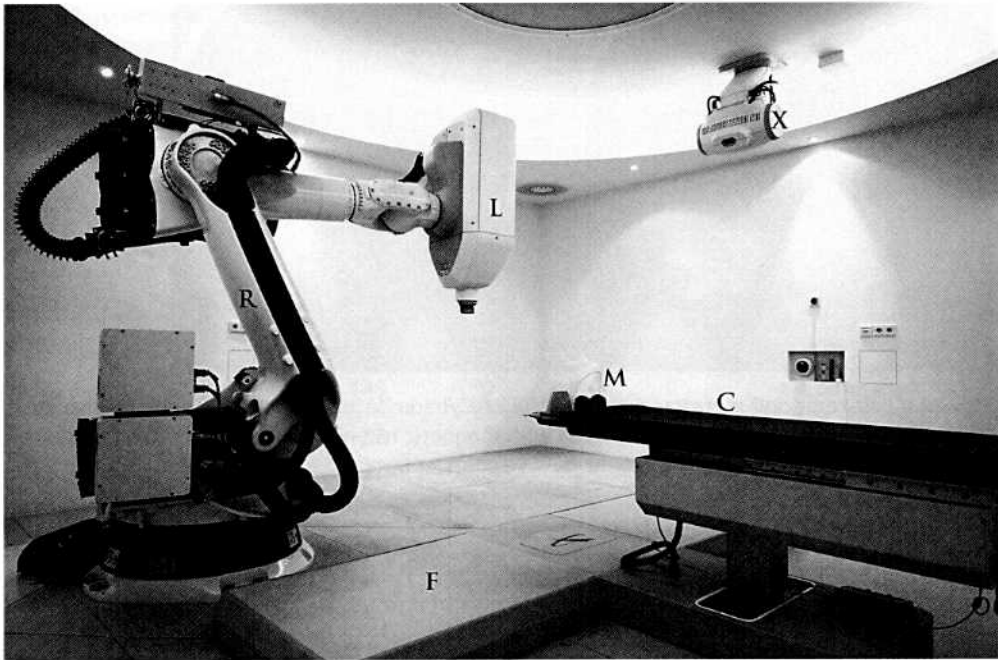


Fig. 1. The CyberKnife System and its components. C = patient couch; M = head support and the thermoplastic mask; X = X-ray tube; F = X-ray detectors; R = robotic arm; L = linear accelerator.

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.

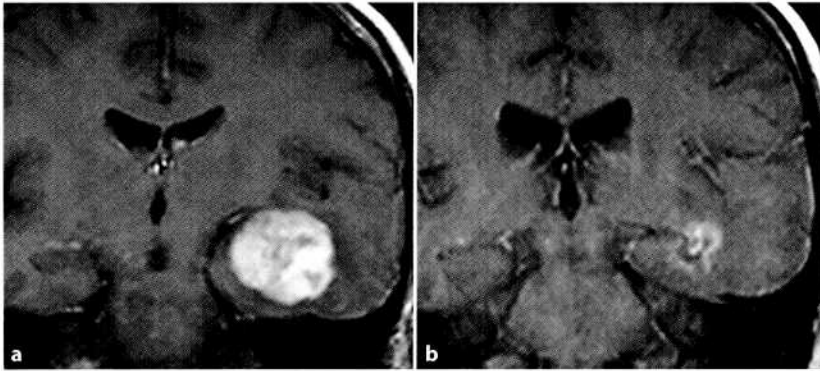


Fig. 2. **a** Left temporal metastasis at the time of Cyberknife treatment (magnetic resonance T₁-weighted Gd-enhanced) **b** Follow up-study with magnetic resonance image after 9 months: remission of the treated metastasis with some reactive contrast uptake.

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

