

# Treatment of Brain Metastases Using Gamma Knife Radiosurgery – The Gold Standard

a report by

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Annually, about 4,300 patients per million people present with cancer. According to conservative estimates about 8.5% of cancer patients will develop brain metastases,<sup>1</sup> yet there is no general management strategy dealing with this situation. Treatment options include fractionated whole-brain radiotherapy (WBRT), microsurgical resections,<sup>2</sup> radiosurgery with either Linac® or Gamma Knife® or, in some instances, supportive care only. Large retrospective studies demonstrate that the effect of conventional fractionated radiotherapy is limited, with a particularly negative prognosis for patients with multiple metastases or older patients. Furthermore, fractionated radiotherapy involves lengthy hospitalisation plus potential side effects, thereby affecting the patient's quality of life.

Cerebral metastases often cause the leading symptoms in cancer, therefore their local control is particularly important. Single-session Gamma Knife radiosurgery under local anaesthesia is the least invasive active and effective therapy for brain tumours and can be carried out without interrupting the systemic treatment or the eventual planned surgery of a primary cancer. Active and effective treatment of brain metastases has been shown to be important for the survival and quality of life.<sup>3,4</sup>

The Gamma Knife principle is based on the mechanical focusing of 201 radiation sources, resulting in an extremely limited irradiated volume. By the addition of several focuses (isocentres), virtually any geometrical structure can be matched, thereby allowing the exclusive irradiation of the target within the brain, i.e. the metastasis in the current context. The Gamma Knife provides a steep radiation dose fall-off. This specific gradient in 3D guarantees that the surrounding tissue is exposed to only limited radiation and consequently is 'protected' against undesired radiation effects. The 3D precision of the radiation focus and dose gradient is unmatched by other technologies. These physical characteristics of radiosurgery allow treatment in one single session. Compared with radiosurgery, no study of conventional fractionated WBRT has shown superior results in terms of local control, quality of life or survival.

## Conventional Fractionated Radiotherapy

Fractionated WBRT is a common conventional treatment for brain metastases;<sup>3</sup> however, the results are disappointing. The results of WBRT for cerebral metastases have been summarised in a retrospective analysis of several Radiation Therapy Oncology Group (RTOG) studies consisting of 1,200 patients. Eighty per cent of patients were divided into recursive partitioning analysis (RPA) classes II and III with a median survival of fewer than 4.2 months.<sup>5</sup> Another three recent large retrospective studies of patients with brain metastases treated with conventional fractionated radiotherapy revealed a median survival of 2.9–4 months.<sup>6–8</sup> A large German retrospective study with 916 patients who had been operated on and treated with fractionated WBRT

showed a median survival of 3.4 months.<sup>9</sup> The subgroup of older patients (>65 years of age) with multiple brain metastases (and uncontrolled primary cancer) survived only 1.2 months with conventional radiotherapy.<sup>9</sup> Therefore, conventional fractionated radiotherapy can not be considered sufficiently effective in the treatment of cerebral metastases.

## Gamma Knife Radiosurgery

Gamma Knife radiosurgery is highly effective even for brain metastases that are otherwise resistant to conventional fractionated external-beam radiation therapy. Gamma Knife treatment is carried out in one session (one day) under local anaesthesia and causes low physical stress to the patient. The necessary precision requires a stereotactic magnetic resonance imaging (MRI) study before radiosurgery and a stereotactic frame fixation during treatment. Generally, prescription doses of 18–22Gy are applied in Gamma Knife treatment of cerebral metastases. Doses are expressed as 'minimum' or 'prescription doses', reflecting the dose applied to the tumour periphery. This very often corresponds to the 50% isodose, resulting in an inhomogenous dose distribution within the tumour, with a maximum dose ranging between 36 and 50Gy. It has been shown that this lack of dose homogeneity is irrelevant for the outcome.

It is crucial to understand how Gamma Knife radiosurgery compares with microsurgery in the local control of metastases and prognosis. Three retrospective studies suggest that the two techniques are equivalent in terms of local control of the treated brain tumour.<sup>10–12</sup> A recent prospective randomised study compared the efficacy of radiosurgery of brain metastases with the combined effect of open microsurgery plus WBRT.<sup>13</sup> The minimally invasive approach with Gamma Knife radiosurgery provided equally good results to the invasive combination of open tumour resection and conventional radiotherapy with regard to survival, neurological death rates and freedom from local recurrence. Radiosurgery was associated with a shorter hospital stay, less frequent and shorter-duration steroid application and lower frequency of toxicities. Improved scores for role functioning and quality of life were seen six weeks after radiosurgery.<sup>13</sup> Therefore, the therapeutic effect of Gamma Knife radiosurgery can be considered as equivalent to that of standard surgical approaches.

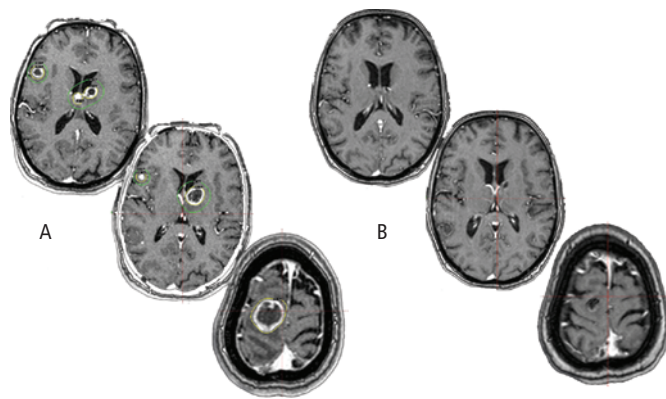
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**Table 1: Results of Recently Published Larger Series After Gamma Knife Radiosurgery of Cerebral Metastases**

		Single or Multiple	Number of Patients	Local Tumour Control (%)
Mathieu et al., 2007 <sup>28</sup>	Melanoma	Both	244	86.2
Gaudy-Marqueste et al., 2006 <sup>23</sup>	Various	Both	106	83.7
Pan et al., 2005 <sup>30</sup>	Lung	Both	191	84–94 (volume-dependent)
Gerosa et al., 2005 <sup>24</sup>	Lung	Both	504	One-year local control: 94%
Simonová et al., 2003 <sup>36</sup>	Various	Both	400	90
Hasegawa et al., 2003 <sup>25</sup>	Various	Both	172	87
Sheehan et al., 2002 <sup>34</sup>	Lung	Both	273	84
Chen et al., 1999 <sup>15</sup>	Various	Both	190	89

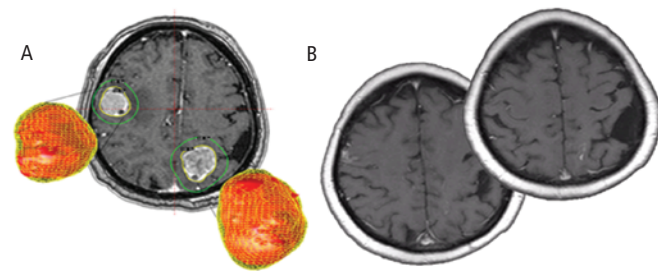
**Figure 1: Patient with Breast Cancer and Multiple Cerebral Metastases**



Combination of Gamma Knife radiosurgery for the larger and critically located tumours (prescription dose 19Gy) with conventional whole-brain radiotherapy (WBRT) due to general tumour spreading.

A: Magnetic resonance imaging with contrast enhancement during Gamma Knife treatment. B: Follow-up three months later.

**Figure 2: Patient with Multiple Brain Metastases of Lung Cancer**



A: 3D dose plan for Gamma Knife radiosurgery of the frontal and parietal metastasis (prescription dose 18Gy). B: Follow-up two months after radiosurgery demonstrates significant response with only minimal remnants detected at the original tumour site.

Recently, after a level I–III evidence-based review of the role of radiosurgery for brain metastases, the American Society for Therapeutic Radiology and Oncology (ASTRO) stated that for selected patients with up to four small brain metastases the addition of a radiosurgery boost to WBRT improves brain control compared with WBRT alone.<sup>14</sup> However, evidence is lacking as to whether conventional radiotherapy actually provides a benefit in combination with radiosurgery. Several recent studies comprising more than 950 radiosurgically treated patients have not documented any differences in survival or local tumour control when fractionated WBRT was omitted.<sup>15–17</sup> However, without affecting prognosis and survival, the rate of new cerebral metastases seems to be reduced when WBRT is applied.<sup>16</sup> So far, there is no evidence that fractionated WBRT increases either local control or survival for patients who have been treated with Gamma Knife.

However, if needed in individual cases, the two methods can be combined<sup>18</sup> (see *Figure 2*).

Multiple radiosurgical sessions are considered less invasive and require only a short hospitalisation period. Therefore, the current strategy for radiosurgically treated Swedish patients with brain metastases does not include prophylactic WBRT.<sup>19</sup> Patients who develop further tumours after initial radiosurgery are treated with several sessions of radiosurgery. WBRT is applied only in cases with a more general tumour spread when the disease in the brain can no longer be considered local. The clinical results support this regimen, which seems beneficial compared with series after WBRT.<sup>5–7,20</sup> A prospective randomised study of patients with multiple brain metastases failed to demonstrate a survival benefit of conventional fractionated radiotherapy over radiosurgery.

A wide range of retrospective and a few prospective studies with more than 4,800 studied patients with brain metastases treated with radiosurgery have provided consistent and reproducible results with an average local tumour control between 84 and 97% (see *Figure 1*).<sup>10,12,15,17,21–38</sup> *Table 1* shows a selection of larger current Gamma Knife studies. A recent prospective randomised study documents a benefit for functional stability and quality of life for radiosurgically treated patients.<sup>39</sup>

The number of patients with multiple metastases treated with radiosurgery is constantly increasing. A recently published series compared the outcome of patients with multiple metastases after radiosurgery or WBRT in a retrospective analysis.<sup>40</sup> The group of patients who had received only WBRT survived 6.6 months; patients in the radiosurgical group had a documented median survival time (MST) of 12.5 months.<sup>40</sup> A European Gamma Knife study in a series of 97 patients with a median of three metastases demonstrated local control in 94%.<sup>41</sup> Survival has been found independent of the numbers of lesions treated.<sup>21,42</sup>

One of the few prospective randomised studies compared the effects of a radiosurgical boost in patients with multiple brain metastases. Treatment with WBRT alone resulted in local failure at one year in 100%. Boost radiosurgery increased the local control considerably, resulting in only 8% local failures. The median time to local failure was six months after WBRT alone in comparison with 36 months after WBRT plus radiosurgery.<sup>43</sup>

Another multi-institutional study analysed the prognosis of patients treated with radiosurgery plus WBRT.<sup>32</sup> The MST for the entire radiosurgical series of 502 patients was 10.7 months. The addition of radiosurgery significantly improved results compared with the median survival observed in the RTOG RPA analysis for patients treated

with WBRT alone.<sup>32</sup> The prospective, randomised RTOG study 9508 stated significant differences of survival for patients with solitary metastases and for younger patients with an advantage for radiosurgically treated patients.<sup>39</sup> The RTOG study compared the outcome when radiosurgery was used as a boost after fractionated WBRT. The final interpretation that “WBRT and stereotactic radiosurgery should, therefore, be standard treatment for patients with a single unresectable brain metastasis and considered for patients with two or three brain metastases” is certainly remarkable since this study<sup>39</sup> is the first prospective, randomised study that documented both increased local control and increased quality of life in patients treated with stereotactic radiosurgery boost.

The complication rate after radiosurgery is low. The risk of development of adverse radiation effects has been shown to be related to the irradiated volume. A typical example of the impact of the irradiated tumour volume on the risk of complications is shown in the RTOG

protocol 90-05.<sup>18</sup> Among other results, the study demonstrates that tumours with a diameter between 21 and 40mm were significantly more likely to develop serious neurotoxicity compared with tumours with a diameter <20mm. Therefore, generally only metastases with a tumour diameter <30mm are accepted for radiosurgery.

### Summary

Gamma Knife radiosurgery provides a highly effective method of treating cerebral metastases with reliable and predictable local tumour control in the brain. Thereby, the minimally invasive approach with radiosurgery provides the time needed to treat the systemic cancer. When the established radiosurgical criteria concerning dose and tumour volumes are applied, the risk of adverse radiation effects or local recurrences is low. The addition of WBRT after Gamma Knife radiosurgery does not seem to optimise local tumour control or survival, but can be safely applied when needed in case of a more general tumour spread. ■

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