

HTA-Report | Summary

## Medical and health economic assessment of radiosurgery for the treatment of brain metastasis

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### Introduction

Radiotherapy for patients suffering from malignant neoplasms has developed greatly during the past decades. Stereotactic radiosurgery (SRS) is one important radiotherapeutic option which is defined by a single and highly focussed application of radiation during a specified time interval. One of its important indications is the treatment of brain metastases. The equipment that is used for radiosurgery is quite expensive in terms of purchase and maintenance costs.

### Research questions

The objective of this Health Technology Assessment (HTA) is to summarise the current literature concerning the treatment of brain metastasis and to compare SRS as a single or additional treatment option to alternative treatment options with regard to their medical effectiveness/efficacy, safety and cost-effectiveness as well as their ethical, social and legal implications.

To investigate these objectives, the following research questions will be addressed.

### Medical research questions

What are the effectiveness/efficacy and safety of SRS alone compared to alternative therapeutic approaches in the treatment of brain metastases?

What are the effectiveness/efficacy and safety of SRS in combination with other therapeutic options compared to alternative therapeutic approaches in the treatment of brain metastases?

What are the effectiveness/efficacy and safety of SRS alone or as combined treatment compared to alternative therapeutic approaches, depending on certain prognostic factors, such as e. g. number and localisation of brain metastases, RPA-class (RPA = Recursive partitioning analysis) or systemic disease status)?

What are the effectiveness/efficacy and safety of SRS compared to alternative therapeutic approaches depending on the chosen radiosurgery system?

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### **Economic research questions**

1. How does the cost-effectiveness of radiosurgery compare to treatment-alternatives?
2. What is the cost-effectiveness of different treatment-combinations that involve radiosurgery?
3. From a healthcare-providers perspective, what is the economic efficiency of radiosurgery?
4. Which health-economic decisions does the existing evidence imply?
5. What is the budgetary effect of those decisions?

### **Ethical research question**

To what extent can the access to this technology be ensured for the German population?

### **Methods**

Relevant publications are identified by means of a structured search of databases accessed through the German Institute of Medical Documentation and Information (DIMDI) on 08.08.2007. In addition, a manual search of identified reference lists is conducted. The former includes the following electronic resources:

DAHTA; INAHTA (NHS-CRD-HTA); NHSEED; CDAR94 (NHS-CRD-DARE); CDSR93 (Cochrane Library); ME00 (MEDLINE); EM00 (EMBASE); CB85 (AMED); BA90 (BIOSIS Previews); MK77 (MEDIKAT); CCTR93 (Cochrane Library – Central); GA03 (gms); SM 78 (SOMED); CV72 (CAB Abstracts); II78 (ISTPB + ISSHP); ED93 (ETHMED); AZ72 (GLOBAL Health); AR 96 (Deutsches Ärzteblatt); ME0A (MEDLINE Alert); EA08 (EMBASE Alert); IS90 (SciSearch); CC00 (CCMed); IN73 (Social SciSearch); KR03 (Karger Publisher Database); KL97 (Kluwer Publisher Database); SP97 (Springer Publisher Database); SPPP (Springer Publisher Database PrePrint); TV01 (Thieme Publisher Database).

The present report includes German and English literature published between January 2002 and August 2007. The search parameters can be found in the appendix. Target population are patients with brain metastasis. The methodological quality of included studies is assessed using standardised quality checklists and rated according to the criteria recommended by the Scottish Intercollegiate Guidelines Network Grading Review Group (SIGN).

### **Results**

Of 1,495 publications 15 medical studies meet the inclusion criteria. Overall study quality is limited and with the exception of two RCT and two meta-analyses only historical cohort studies are identified. Apart from the outcome survival, reporting of outcome measures is highly variable between studies. None of the identified studies investigates the quality of life of patients undergoing certain treatment regimes. Stu-

dies with high methodological quality provide evidence, that whole-brain radiation therapy (WBRT) in addition to SRS and SRS in addition to WBRT is associated with improved local tumour control rates and neurological function. Only in patients with single brain metastasis, RPA-class 1 and certain primary tumour entities, this combination of SRS and WBRT is associated with superior survival compared to WBRT alone. Studies report no significant differences in adverse events between treatment groups. Four additional retrospective cohort studies report improved local tumour control associated with SRS compared to neurosurgery (NS). This does not, however, result in improved survival of patients treated radiosurgically. Methodologically less rigorous studies provide no conclusive evidence with regard to medical effectiveness and safety, comparing SRS to WBRT, or hypofractionated stereotactic radiotherapy (HCSRT).

Two studies which compared different radiosurgical systems reported no difference in effectiveness and safety between Gamma Knife and Linac-based systems (LINAC = Linear accelerator).

Of the 320 economic publications that are identified within the searched databasis four are found to be eligible for this report. One more publication is identified through a manual search. The five reports consist of three original studies and two Canadian HTA. None of these studies is a complete health economic evaluation. The quality of the studies is quite variable. The only results that can be reported concern the economic efficiency of alternative equipment for the treatment. One study compares the cost of a Gamma Knife and an adapted linear accelerator within an Australian setting for different indications. The authors thereby assume equal effectiveness of the alternatives. The calculations show, that economic efficiency depends to a great extent on the number of patients treated. In case that the two alternative equipments are used solely for SRS the Gamma Knife might be more cost-efficient. In case the adapted linear accelerator can be used to treat other patients as well, it is most likely that it is also the cost-efficient alternative. One HTA states similar costs for a Gamma Knife and a dedicated linear accelerator, while an adapted version is cheaper. The decision for the hardware can be influenced by the need for a certain precision in the treatment near sensitive areas. No reports concerning newer alternatives such as the CyberKnife are identified.

The same holds for ethical, legal and social aspects.

## Discussion

Overall, quantity and quality of identified studies are limited. The identified studies indicate that the prognosis of patients with brain metastases is despite highly developed and modern treatment regimes still poor and that survival is limited. Considering the addressed research questions, conclusive evidence with regard to the effectiveness of identified interventions is only available for the combined treatment of SRS and WBRT compared to SRS or WBRT alone, respectively. Combined treatment is in both cases associated with improved local tumour control and neurological function. However, only in certain subgroups

of patients, this results in improved survival compared to WBRT. Due to the availability of only less rigorous studies, there is only some evidence for superior local tumour control of SRS compared to NS. This improved tumour control does not result in gains in survival, however. On the other hand, there is insufficient evidence to directly compare SRS with WBRT, or HCSRT. It should be further noted, that none of the identified studies investigates the quality of life in patients undergoing presented interventions.

Furthermore, two studies provide some evidence that there is no difference in effectiveness/efficacy and safety between Gamma Knife and Linac-based systems. The evaluation of newer and less invasive radiosurgery systems is currently not available, however.

The efficiency of different equipments depends on the number and indications of the patients treated. One publication compares the costs for radiosurgery with a Gamma Knife and with a linear accelerator for different indications. Thereby the authors assume equal effectiveness for the alternatives, acknowledging that this is still to be confirmed. If dedicated systems can be used to their full capacity, it can be suggested, that these systems are more cost-efficient. If the system needs to be used for other indications in order to reach full capacity, it is very likely that adapted linear accelerators are advantageous in terms of economic efficiency. Overall costs are reported to be comparable for dedicated linear accelerators and Gamma Knife, while adapted systems seem to be cheaper. No reports concerning newer alternatives such as the CyberKnife are identified. Resulting from the advice of using the equipment at full capacity wherever possible, is the ethical problem of an equal and easy access to this technology for the whole population.

## Conclusion

On the basis of identified evidence, it can be concluded that the combination of SRS and WBRT is associated with improved local tumour control and at least over the initial 24 months with improved neurological function compared to SRS or WBRT alone. However, only in patients with single metastasis there is strong evidence that this results in improved survival compared to WBRT alone. A direct comparison of SRS and WBRT as up front treatment in methodologically rigorous studies is currently not available. The choice of treatment regimen, SRS, WBRT or combined treatment therefore depends on outcome measures, considered relevant, and also on certain patient characteristics which are associated with improved outcome under specific treatments. Comparing SRS and NS, there is some evidence that SRS is associated with superior tumour control. It does not result in superior survival, however. Methodologically rigorous studies are therefore warranted to investigate SRS compared to WBRT or NS and to investigate the quality of life in patients undergoing different treatment regimes. Further, the evaluation of newer and less invasive radiosurgery systems is to be awaited.

From the economic literature, conclusions can only be drawn referring to the type of equipment used. Economic efficiency depends to a great extent on the capacity at which the system can be utilized. A high number of patients gives rise to an advantage for dedicated systems. Lower patient counts favour adapted systems because of their possible flexibility. Studies concerning other alternatives such as the CyberKnife are desirable. Overall more studies, also concerning comparisons of different therapies or combinations of therapies and especially studies suited for the German health system are recommendable.