NHS
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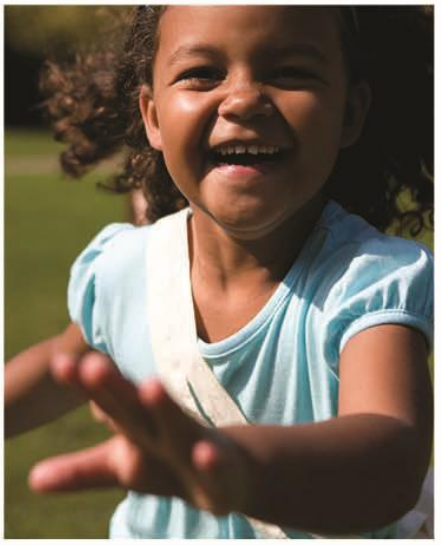
Clinical Commissioning Policy: Stereotactic Radiosurgery / Radiotherapy for Cerebral Metastases



April 2013

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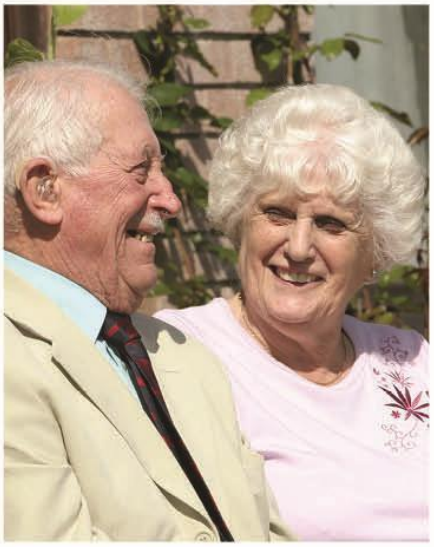

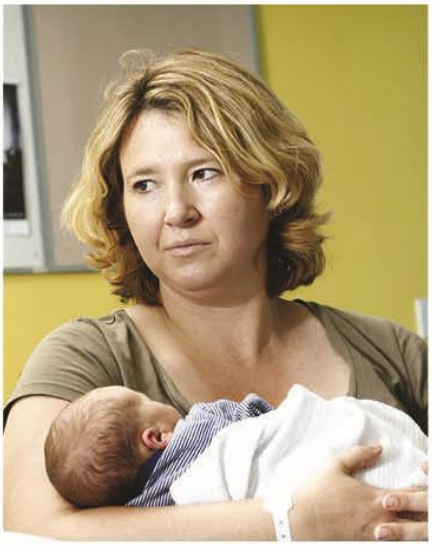

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NHS Commissioning Board

Clinical Commissioning Policy: Stereotactic Radiosurgery / Radiotherapy for Cerebral Metastases

First published: April 2013

Prepared by the NHS Commissioning Board Clinical Reference Group for

Stereotactic Radiosurgery

First published April 2013
Published by the NHS Commissioning Board, in electronic format only.

Contents

Policy Statement

The NHS Commissioning Board (NHS CB) will commission stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) for the treatment of cerebral metastases in accordance with the criteria outlined in this document.

In creating this policy the NHS CB has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

The NHS CB has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012.The NHS CB is committed to ensuring equality of access and non-discrimination, irrespective of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex (gender) or sexual orientation. In carrying out its functions, the NHS CB will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which they are responsible, including policy development, review and implementation.

Plain Language Summary

Cerebral metastases are tumours in the brain that result from the spread of cancer cells from a primary site outside of the brain. Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) destroys abnormal tissues in the brain by the administration of a strong and highly focused dose of radiation.

There is sufficient evidence of the effectiveness of SRS/SRT to support use in a small subset of patients with cerebral metastases within defined criteria. Microsurgery sometimes followed by whole brain radiotherapy remains the standard for large tumours in accessible anatomical positions. Radiosurgery provides a relatively safe and effective alternative for those with good performance status, controllable systemic disease and low volume metastatic disease. It is appropriate for clinicians to consider SRS for a small subset of patients where there is evidence of effectiveness for SRS, and where conventional surgery is contra-indicated or the risk of functional disability would be increased through surgery.

Information on the outcome of treatments for patients who receive SRS/SRT will be collected and considered when this policy is reviewed.

1. Introduction

The basic principle of stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) is the elimination of a functional disorder, or destruction of abnormal tissues, by administration of a strong and highly focused dose of radiation. The procedure allows radiation to be limited to the target area and thus helps spare the surrounding tissues as much as possible stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT)

For the purpose of this policy the term “SRS” is used to mean treatment given as a single dose, and “SRT” as a hypofractionated treatment of not more than 5 fractions. This policy applies to both of these approaches. Commissioning arrangements for fractionated treatments or larger tumour volumes utilising a larger number of fractions are beyond the remit of this policy.

SRS/SRT is a highly conformal radiotherapy treatment to a precisely delineated target volume, delivered using stereotactic localisation techniques. A multidisciplinary team of neurosurgeons, neurooncologists and neuroradiologists should be involved in SRS case selection, treatment planning and delivery.

This policy considers the use of SRS/SRT compared to standard therapy for patients with cerebral metastases and sets criteria which identify patients in which SRS/SRT should be considered.

2. Definitions

Cerebral Metastases

Cerebral metastases are tumours in the brain that result from the spread of metastatic cancer cells from a primary site outside of the brain. The term can be used interchangeably with *brain metastases* and this policy covers all such metastases.

Any primary malignant tumour can spread to the brain. However cerebral metastases most commonly result from melanoma and cancers of the lung, breast, kidney and colon. It is estimated that 30-40% of people with cerebral metastases present with a single lesion and the remainder with multiple lesions (Lohr et al, 2001). In patients with cancer that is or has become systemic, cerebral metastases are thought to occur in 20-40% (Linskey et al, 2010), however rates appear to be increasing as treatments for primary cancers improve life expectancy.

Life expectancy for patients with brain metastases is low. Historically, in patients only treated with corticosteroids, estimated median survival time is one to two months and six months for those undergoing whole brain radiation therapy (WBRT) (Andrews et al, 2004). Studies suggest that further survival and improved quality of life may be possible where localised radiological and surgical approaches are used.

In patients with brain metastases, death may be attributable to the brain metastases in approximately 40% of cases (Stafinski et al, 2006) but, in the majority of cases, overall survival is likely to be determined by the extent of extra-cranial disease.

Stereotactic Radiosurgery (SRS) and Stereotactic Radiotherapy (SRT)

The basic principle of stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) is the elimination of a functional disorder, or destruction of abnormal tissues, by administration of a strong and highly focused dose of radiation. The procedure allows radiation to be limited to the target area and thus helps spare the surrounding tissues as much as possible.

SRS/SRT is a highly conformal radiotherapy treatment to a precisely delineated target volume, delivered using stereotactic localisation techniques. A multidisciplinary team of neurosurgeons, neuro-oncologists and neuroradiologists should be involved in SRS case selection, treatment planning and delivery.

Patients of all ages may benefit from SRS/SRT. The treatment is usually carried out with the patient awake and therefore the patient needs to be compliant. Young children and non-compliant adults can be treated using sedation or general anaesthesia.

Stereotactic radiosurgery and stereotactic radiotherapy can be provided using one of several technologies. The SRS/SRT service specification to which this policy relates covers SRS/SRT whether delivered by Gamma Knife, Cyberknife or any other linear accelerator-based technology. Departments wishing to provide such service should have access to technologies with up-to-date dose planning.

Karnofsky Performance Status (KPS) Scale

The Karnofsky Performance Status (KPS) scale was developed to evaluate the usefulness of chemotherapeutic agents for cancer. It represents a patients' functional ability to do normal activities, their ability to do active work and their need for assistance. The KPS score has been used to inform clinical decisions, as a criterion for inclusion or stratification in randomised trials and as a measure of response to treatment. It may also be considered to be a measure of a patient's quality of life. The scale for assessment of KPS is given in Appendix 1.

Recursive Partitioning Analysis (RPA)

KPS scoring is helpful to provide general information on a patient's functional ability and current quality of life. However, it is not specific to any type of cancer and does not necessarily reflect patient prognosis. In order to make a prediction of survival time for patients with brain metastases, other factors need to be taken into account.

Recursive partitioning analysis (RPA) is a scoring system that has been used for predicting overall patient prognosis for patients with brain metastases (see Appendix 2). It incorporates information on primary tumour control, the presence of other (in addition to brain) metastases, age and KPS. It was developed by analysis of factors that influenced patient prognosis in three large trials (Gaspar et al,1997) and has subsequently been validated in different populations. It has been promoted as a suitable stratification factor for clinical trials. Although useful in assessing the evidence, RPA classification is not suitable for use as a criterion for identifying patients suitable for routine funding, as it is partly based on the age of the patient. Within the NHS a patient cannot be excluded from access to a treatment purely on the basis of age.

3. Aim and Objectives

The aim of this policy is to:

- Identify robust evidence of clinical effectiveness, safety and cost effectiveness to support the use of SRS/SRT for patients with cerebral metastases
- If the evidence is sufficiently robust, to identify the clinical criteria to be used to identify suitable patients to be considered for SRS/SRT treatment

4. Criteria for commissioning

Patients meeting <u>all</u> of the following eight criteria will be routinely funded for SRS/SRT:

- All patients must have undergone prior assessment by the local multi-disciplinary team (MDT). The selection of patients for SRS/SRT must be made by an MDT with an understanding of the systemic and neurological disease processes and must include consideration of surgical treatment if appropriate.
- In centres where SRS/SRT is delivered, referral may be made directly to the SRS MDT. In centres where there is no local SRS service, referral should be initially to the local neuro-science MDT, who can decide on the appropriateness of onward referral to an agreed SRS centre.
- All patients being considered for SRS /SRT must be discussed by the specialist MDT at the stereotactic treatment centre and must have both specialist neurosurgery and specialist oncology input. SRS/SRT must not be recommended without the collective agreement of the MDT to ensure that the criteria regarding systemic disease and prognosis are fulfilled and that there is clarity about the place of SRS/SRT in the patient's overall management plan.
- Patients must have a Karnofsky Performance Status (KPS) ≥ 70
- The diagnosis of cancer must be established and there must be absent or controllable primary disease.
- Pressure symptoms which would be best relieved by surgery are excluded.
- Pre-treatment scans must not show a tumour volume of more than 20cc. This will usually mean that no individual tumour has a diameter in excess of 3cm.
- The MDT has confirmed that the patient's life expectancy from extracranial disease is expected to be greater than 6 months

SRS/SRT may be used to treat new lesions in patients where SRS/SRT has previously been effective provided:

- A period of three months has elapsed since the last SRS/SRT treatment AND the above eight criteria are all met AND
- The disease specific cancer MDT has reviewed the patient and confirmed the appropriateness of further SRS/SRT

Repeat treatment of lesions previously treated with SRS/SRT will only be supported if:

- A period of six months has elapsed since the last SRS/SRT treatment AND Criteria 1 to 8 above are all met AND
- The disease specific cancer MDT has reviewed the patient and confirmed the appropriateness of further SRS/SRT

5. Patient pathway

The service specification for SRS/SRT describes the detail of the care pathways and describes the key aspects of SRS/SRT services being commissioned, and should be referred to in conjunction with this policy.

Treatment options for cerebral metastases depend on the size, position and number of cerebral metastases and the prognosis due to extracranial disease. The management options are:

- Best supportive care, including steroids for symptomatic relief
- Whole brain radiotherapy (WBRT)
- Surgical resection of cerebral metastases +/- WBRT
- SRS /SRT alone
- WBRT plus SRS/SRT

WBRT may be given as a palliative measure on its own, or as an adjunct to surgical resection or SRS. Patients may have more than one treatment modality, depending on their disease course.

Patients in all groups usually also receive treatment with corticosteroids for the relief of symptoms related to intra-cerebral swelling and tumour effects.

For patients with progressive systemic disease and/or poor performance status, palliative WBRT or supportive management with dexamethasone alone is considered the most appropriate treatment. This applies to the majority of patients with cerebral metastases.

Patients with a solitary brain metastasis in a surgically accessible location that is causing clinically significant mass effect, who otherwise have no or stable systemic disease and a good performance status, should be considered for palliative surgical resection prior to WBRT.

Surgery followed by WBRT has shown to significantly improve both the survival time and the quality of life of patients in this category, when compared to treatment with WBRT alone. However, WBRT is also known to cause neuro-cognitive toxicity and in selected cases may be reserved for relapse where focal treatment options are not suitable.

The role of single fraction SRS in the primary treatment of cerebral metastases is an area of ongoing investigation. It is considered particularly useful for patients whose brain metastases are of small volume and surgically inaccessible, without high risk of new deficit. SRS uses non-invasive technology, so the risks involved are reduced over conventional surgery to offer a broad range of benefits:

- No incisions mean minimal discomfort
- Less risk of postoperative complications
- Shorter recovery period
- Patients return home the same day
- Nearby healthy brain tissue is seldom affected
- May use local anaesthetic or sedation (for adults) for maximum patient comfort (children are anaesthetised.
- Usually only one treatment versus many over several weeks

Similarly for external beam radiotherapy the movement to SRS could reduce the number of daily attendances from 15-20 to a single visit, with less impact on the healthy brain tissue and improving patient experience by minimising hospital attendances. There are also patients who currently are not suitable for surgery or external beam radiotherapy, due to the positioning of the tumour or mass, who may now have a treatment option available.

6. Governance arrangements

The service specification for SRS/SRT describes the care pathways and key aspects of SRS/SRT services being commissioned, and should be referred to in conjunction with this policy.

7. Epidemiology and needs assessment

Estimation of the number of patients who might benefit from treatment with SRS/SRT requires identification of the types of patients in whom it is effective (and more effective than alternative treatment options). This is likely to be influenced by a variety of factors.

RPA scoring has been used for predicting overall patient prognosis for patients with brain metastases (see Appendix 2).In studies of patients with brain metastases, 3-39% of patients fell into class I (best prognosis) whilst 33-72% fell into class II and 33-50% fell into class III (worst prognosis) (Andrews et al, 2004) .Typical survival times for patients in RPA classes I, II and III may be around nine, four and two months respectively. If patients classified as RPA class 1 are considered suitable for SRS this puts the proportion of patients with cerebral metastases who would be suitable for SRS at between 3 and 39%.

Although the RPA analysis can be useful it does not take into account patient-specific factors e.g. if SRS treatment were confined to patients of RPA grade 1, all patients aged >65 would be ineligible regardless of their performance status or the natural history of their disease. For this reason, it has been superseded in publications by Sperduto (Int J Rad Oncolo Biol Phy 2008 and 2010), which takes account of primary disease site and other factors. Median survival in this series of 4259 patients was 13.2 – 18.7 months for those in the most favourable prognostic groups.

An analysis of 1500 patients with cerebral metastases was carried out by the Yorkshire and Humber SCG and included in a report to the National SCG Directors Group in 2009. This analysis calculated that 11.5% of the 1500 cases were suitable for SRS. It has been estimated that there are ~15,000 patients diagnosed with cerebral metastases in England each year (population of 50 million) and assuming that 11.5% of these patients will be eligible for SRS and this would equate to 1,725 patients each year. However other estimates suggest an incidence of brain metastases of around 14 or 15 per 100,000 population per year. For an incidence of 15 per 100,000 population with 11.5% suitable for SRS, this would equate to ~860 patients in England each year.

Given the variety of determining factors it is hard to get a robust estimate of the numbers of individuals likely to be eligible for SRS/SRT for the treatment of cerebral metastases. Over time growth in numbers is expected as greater control of systemic disease is achieved in more people and therefore more become eligible for treatment. There will need to be ongoing review of the number of individuals referred for SRS for cerebral metastases to ensure that appropriate individuals are being offered treatment.

8. Evidence Base

Evidence can be graded according to the robustness of the study design, giving an indication of the degree to which the evidence should be relied upon when making clinical decisions. The grades of evidence range from level 1 (the most robust) to level 4 (the least robust). The diagram in Appendix 3 outlines the levels of evidence.

In summary, the evidence suggests that, in selected patients with brain metastases, SRS/SRT effectively increases overall survival and functional capacity when used in addition to non-localised treatment (WBRT)). The size and number of metastases are likely to have an impact on potential survival gain. In appropriate patients, median overall survival may be extended by about two months. These effects are likely to vary widely between patients, and be highly dependent on the extent of extracranial disease. SRS/SRT does not appear to be associated with additional adverse events or additional impairments in neurological function compared to standard treatment.

The evidence base for use of SRS/SRT for newly diagnosed cerebral metastases was reviewed by the American Society for Therapeutic Radiology and Oncology (ASTRO) and again by Linskey at al (Linskey et al, 2010; Liskey et al Erratum, 2010). The key findings are reproduced from Linskey et al below:

SRS plus WBRT vs. WBRT alone

Level 1: Single-dose SRS along with WBRT leads to significantly longer patient survival compared with WBRT alone for patients with single metastatic brain tumours who have a KPS ≥ 70.

Level 1: Single-dose SRS along with WBRT is superior in terms of local tumour control and maintaining functional status when compared to WBRT alone for patients with 1–4 metastatic brain tumours who have a KPS ≥ 70.

Level 2: Single-dose SRS along with WBRT may lead to significantly longer patient survival than WBRT alone for patients with 2–3 metastatic brain tumours.

Level 3: There is class III evidence demonstrating that single-dose SRS along with WBRT is superior to WBRT alone for improving patient survival for patients with single or multiple brain metastases and a KPS < 70.

SRS plus WBRT vs. SRS alone

Level 2: Single-dose SRS alone may provide an equivalent survival advantage for patients with brain metastases compared with WBRT + single-dose SRS. There is conflicting class I and II evidence regarding the risk of both local and distant recurrence when SRS is used in isolation, and class I evidence demonstrates a lower risk of distant recurrence with WBRT; thus, regular careful surveillance is

warranted for patients treated with SRS alone in order to provide early identification of local and distant recurrences so that salvage therapy can be initiated at the soonest possible time.

Surgical Resection plus WBRT vs. SRS ± WBRT

Level 2: Surgical resection plus WBRT, vs. SRS plus WBRT, both represent effective treatment strategies, resulting in relatively equal survival rates. SRS has not been assessed from an evidence-based standpoint for larger lesions (>3 cm) or for those causing significant mass effect (>1 cm midline shift).

Level 3: Underpowered class I evidence along with the preponderance of conflicting class II evidence suggests that SRS alone may provide equivalent functional and survival outcomes compared with resection + WBRT for patients with single brain metastases, so long as ready detection of distant site failure and salvage SRS are possible.

SRS alone vs. WBRT alone

Level 3: While both single-dose SRS and WBRT are effective for treating patients with brain metastases, single-dose SRS alone appears to be superior to WBRT alone for patients with up to three metastatic brain tumours in terms of patient survival advantage.

Using total tumour volume rather than size or number of tumours as a commissioning criterion

Applying a cut-off for the number of cerebral metastases above which patients will not be routinely funded for SRS is problematic. This approach excludes some patients who have a higher number of small tumours but who would be likely to respond well to SRS treatment. Many RCTs have selected patients with between 1 and 3 metastases and restricted patients to those with tumours no larger than 3cm in diameter. Thus the evidence base focuses on this group. Total tumour volume is a more holistic assessment of the tumour burden and this policy uses tumour volume as one of the commissioning criteria rather than size or number of tumours.

The decision to use SRS/SRT must balance the likely benefits against the risk of complications and side effects including radionecrosis. Evidence suggests that radionecrosis becomes more likely as the total brain volume treated increases (Minniti et al, 2011). An upper limit of 20cc has been identified as a reasonable cut-off point for SRS (Ernst-Stecken et al, 2006). When using SRS, the total brain volume being treated must not exceed 20cc. A total volume of 20cc could accommodate a single tumour of approximately 3.2cm diameter, or a number of smaller tumours.

Comparison of modes of SRS delivery

The current evidence does not show a significant difference in effectiveness and safety of LINAC, CyberKnife or Gamma Knife SRS for the treatment of brain metastases.

Cost-effectiveness

There is a lack of evidence addressing the cost-effectiveness of SRS/SRT compared to other treatment options in a UK setting. However, there is some evidence that the overall costs, including ancillary treatment and readmission costs are lower for patients treated with SRS/SRT than by microsurgery (Wallis et al, 2003) In 1997 Mehta et al. determined a cost/benefit estimation for conventional fractionated radiotherapy (RT), surgery and radiosurgery (RS) for patients with single brain metastases. The cost per life year of median survivorship was $16,250 for RT alone, $13,729 for RS plus RT, and $27,523 for resection plus RT. Hence, according to this study a surgical resection resulted in a 1.8-fold increase in cost, compared to radiosurgery (Mehta et al, 1997) A similar American comparative cost analysis found that the cost per life year gained for radiosurgery was 30% lower than for surgical resection (Rutigiano et al, 1995).

9. Rationale behind the policy statement

- The evidence regarding the effectiveness and safety of SRS/SRT for treating cerebral metastases has been used as a basis for this commissioning policy.
- SRS/SRT can be used to treat cerebral metastases where the positioning makes surgical resection inappropriate. Similar levels of tumour control are seen between SRS/SRT and surgical resection.
- Routine funding is restricted to those where a likely benefit from SRS/SRT has been robustly demonstrated. Individuals with better prognosis from extra cranial disease benefit more from SRS/SRT treatment. Routine funding is restricted to individuals with total tumour volume cerebral metastases of no more than 20cc.
- A number of clinical factors affect whether a person will benefit from SRS/SRT or whether other treatment options are more appropriate. Any SRS/SRT treatment decision must be made by an IOG compliant CNS tumours neuroscience unit based MDT.
- There is no available robust estimate of the cost effectiveness of SRS/SRT for treatment of cerebral metastases and ongoing monitoring of numbers and outcomes needs to be undertaken.

10. Mechanism for funding

From April 2013 the NHS CB will be responsible for commissioning Stereotactic Radiosurgery in line with this policy on behalf of the population of England.

11. Audit Requirements

Audit requirements will include the following data items for each patient:

- Karnofsky Performance Status
- Estimated total tumour volume (cc)
- No. of tumours
- Size of largest tumour
- Dose
- Fractionation
- Treatment outcome

12. Documents which have informed this policy

- 2012/13 NHS Standard Contract: Service Specification Contract NSSD 8 Neurosciences (adult0 (subsection 4.1 Neurosurgery) Stereotactic radiosurgery and stereotactic radiotherapy
- National Institute for Health and Clinical Excellence. Improving outcomes for people with brain and other CNS tumours. London: NICE, 2006.
- National Institute for Health and Clinical Excellence. Advanced breast cancer: diagnosis and treatment. London: NICE, 2009.

13. Links to other policies

This policy follows the principles set out in the ethical framework that governing the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of Review

April 2015

15. Abbreviations

CK	Cyber Knife
GK	Gamma Knife
HTA	Health technology assessment
KPS	Karnofsky Performance Status
LINAC	Linear Accelerator
MDT	Multi-disciplinary team
NICE	National Institute for Health and Clinical Excellence
RPA	Recursive partitioning analysis
RCT	Randomised controlled trial
SCG	Specialised Commissioning Group
SRS	Stereotactic Radiosurgery
SRT	Stereotactic Radiotherapy
WBRT	Whole brain radiotherapy

References

- The American Society for Therapeutic Radiology and Oncology (ASTRO) Evidence-based review of the role of radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys.* 2005 Sep 1;**63**(1):37-46.

- Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004; **363**(9422):1665-1672.

- Banfill et al. Stereotactic radiosurgery for the treatment of brain metastases: impact of cerebral disease burden on survival. *British Journal of Neurosurgery*, 2012;**26**(5):674-8.

- Chang EL, Wefel JS, Hess KR, et al. .Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;**10**(11):1037-44. Epub 2009, Oct 2.

- Ernst-Stecken et al Phase II trial of hypofractionated stereotactic radiotherapy for brain metastases: Results and toxicity. *Radiotherapy and Oncology*, 2006;**81**:18–24.

- Fahrig et al Hypofractionated Stereotactic Radiotherapy for Brain Metastases Results from Three Different Dose Concepts Strahlenther Onkol 2007;183:625–30.

- Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*, 1997;**37**(4):745-51.

- Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *Int J Radiat Oncol Biol Phys* 2000; **47**(4):1001-1006.

- Kocher et al Adjuvant Whole-Brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC *J Clin Oncology*, 2011;**29** no. 222952-26001 Study.

- Lal et al Economic impact of stereotactic radiosurgery for malignant intracranial brain tumors. *Expert Rev Pharmacoecon Outcomes Res.* 2011;**11**(2):195-204.

- Linskey ME, Andrews DW, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline. *Journal of Neuro-Oncology* 2010; **96**(1):45-68.

- Linskey ME, Andrews DW, Asher AL et al.Erratum to: The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*m, 2010;**96**:69–70. DOI 10.1007/s11060-009-0099-7.

- Lohr F, Pirzkall A, Hof H, et al. Adjuvant treatment of brain metastases. *Semin Surg Oncol*, 2001;**20**(1):50-56.

- Mehta M, Noyes W, Craig B, et al. A cost-effectiveness and cost-utility analysis of radiosurgery vs. resection for single-brain metastases. *International journal of radiation oncology, biology, physics* 1997;**39**(2): 445-54.

- Minniti et al Stereotactic radiosurgery for brain metastases:analysis of outcome and risk of brain radionecrosis. *Radiation Oncology*, 2011;**15**;6:48.

- Rutigliano MJ, Lunsford LD, Kondziolka D, et al. The cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors. *Neurosurgery* 1995;**37**(3): 445-53; discussion 53-5.

- Stafinski T, Jhangri GS, Yan E, Menon D. Effectiveness of stereotactic radiosurgery alone or in combination with whole brain radiotherapy compared to conventional surgery and/or whole brain radiotherapy for the treatment of one or more brain metastases: a systematic review and meta-analysis. *Cancer Treatment Reviews* 2006; **32**(3):203-213.

- Silvia Scoccianti , Umberto Ricardi. Treatment of brain metastases: Review of phase III randomized controlled trials Radiotherapy and Oncology. *Radiotherapy and Oncology*, 2012;**102**:168–179.

- Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol*. 1984;**2**(3):187-193.

- Wellis G, Nagel R, Vollmar C, Steiger HJ. Direct costs of microsurgical management of radiosurgically amenable intracranial pathology in Germany: an analysis of meningiomas, acoustic neuromas, metastases and arteriovenous malformations of less than 3 cm in diameter. *Acta Neurochirurgica* 2003;**145**(4): 249-55.

Appendix 1: Karnofsky Performance Status Scale

Condition	Performance Status %	Comments
A. Able to carry on normal activity and to work. No special care is needed.	100	Normal. No complaints. No evidence of disease.
	90	Able to carry on normal activity. Minor signs or symptoms of disease.
	80	Normal activity with effort. Some signs or symptoms of disease.
B. Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed.	70	Care of self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
C. Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled. Requires special care and assistance.
	30	Severely disabled. Hospitalization is indicated although death not imminent.
	20	Hospitalization necessary, very sick active supportive treatment necessary.
	10	Moribund. Fatal processes progressing rapidly.
	0	Dead.

Reproduced from Schag et al, 1984

Appendix 2: Classifications of Recursive Partitioning Analysis

	Class 1	Class 2	Class 3
KPS	**≥70**	**≥70**	**<70**
Primary status	Controlled	Uncontrolled	
Age (y)	<65	≥65	
Extra-cranial disease status	Brain only	Brain plus other sites	

Appendix 3: Grades of evidence