



Overview

New Developments in Intracranial Stereotactic Radiotherapy for Metastases

M.B. Pinkham^{*†}, G.A. Whitfield^{*‡}, M. Brada[§]^{*} Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK[†] School of Medicine, University of Queensland, Brisbane, Australia[‡] The University of Manchester, Manchester Academic Health Science Centre, The Christie NHS Foundation Trust, Manchester, UK[§] University of Liverpool, Department of Clinical and Molecular Cancer Medicine and Academic Radiotherapy Unit, Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK

Received 2 December 2014; received in revised form 16 December 2014; accepted 22 January 2015

Abstract

Brain metastases are common and the prognosis for patients with multiple brain metastases treated with whole brain radiotherapy is limited. As systemic disease control continues to improve, the expectations of radiotherapy for brain metastases are growing. Stereotactic radiosurgery (SRS) as a high precision localised irradiation given in a single fraction prolongs survival in patients with a single brain metastasis and functional independence in those with up to three brain metastases. SRS technology has become commonplace and is available in many radiation oncology and neurosurgery departments. With increasing use there is a need for appropriate patient selection, refinement of dose-fractionation and safe integration of SRS with other treatment modalities. We review the evidence for current practice and new developments in the field, with a specific focus on patient-relevant outcomes.

© 2015 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.

Key words: Brain metastases; Gamma knife; Review; Stereotactic radiosurgery; Stereotactic radiotherapy

Statement of Search Strategies Used and Sources of Information

Searches for original and review articles were conducted on Pubmed, Cochrane and Google Scholar databases. Relevant clinical trials registered on ClinicalTrials.gov were identified. General search terms included 'stereotactic radiosurgery', 'stereotactic radiotherapy', 'gamma knife', 'Cyberknife' and 'brain metastases'. Focused searches incorporating 'prognostic index', 'brainstem', 'histology', 'melanoma', 'renal cell carcinoma', 'sarcoma' and 'radio-resistant' with the general terms were also carried out. Individual bibliographies were reviewed for additional relevant references.

Author for correspondence: M. Brada, University of Liverpool, Department of Clinical and Molecular Cancer Medicine and Academic Radiotherapy Unit, Clatterbridge Cancer Centre NHS Foundation Trust, Bebington, Wirral, CH63 4JY, UK. Tel: +44-151-482-7793; Fax: +44-151-482-7621.

E-mail address: michael.brada@liverpool.ac.uk (M. Brada).

Introduction

Brain metastases develop in 10–20% of patients diagnosed with cancer [1–4], with non-small cell lung cancer (NSCLC), breast cancer, melanoma, renal cell carcinoma (RCC) and colorectal carcinoma the most common primary tumours [2,5]. Prognosis varies according to primary tumour type, age, performance status, number of brain metastases and extracranial disease status. The recursive partitioning analysis (RPA) [6] and graded prognostic assessment (GPA) [7] are the best known prognostic indices.

The principal treatment in average prognosis patients with multiple brain metastases is whole brain radiotherapy (WBRT) with a median survival in the region of 4–6 months [6,7]. In the absence of randomised studies, the survival gain of WBRT is not known. Patients with poor prognosis disease without WBRT have a median survival of 1–2 months [8,9]. In selected better prognosis patients, local therapy in the form of stereotactic radiosurgery (SRS) or

surgery is used with the aim of improving outcome. SRS refers to high precision conformal radiotherapy given in a large, single fraction. We review the evidence for current and evolving SRS practice and the effect on patient-relevant clinical outcomes.

Evidence Base for Current Stereotactic Radiosurgery Practice

SRS is a non-invasive alternative to surgery for single brain metastases where data suggest improved overall survival and disease control in patients with single brain metastases undergoing surgery and WBRT compared with WBRT alone in two studies (median survival 10 versus 4–6 months) [10,11], while not confirmed in a third study [12]. Limited information suggests that outcomes are comparable for patients with a single brain metastasis undergoing surgery or SRS, but the only randomised trial comparing the two modalities closed early due to poor accrual [13]. SRS is suggested to be more cost-effective than surgery for brain metastases [14–17], but evidence addressing this in the UK is lacking [18].

The principal aims of treatment of metastatic disease regardless of its site are to improve the duration and the quality of survival. The Radiation Therapy Oncology Group (RTOG) 9508 randomised trial compared SRS and WBRT with WBRT alone in adults with one to three brain metastases up to 3–4 cm diameter and Karnofsky performance status ≥ 70 [19]. The trial showed improved overall survival with SRS in patients with a single brain metastasis (median survival 6.5 versus 4.9 months) and in patients of RPA class I (i.e. age < 65 years, Karnofsky performance status ≥ 70 , no extracranial disease: median survival 11.6 versus 9.6 months), but not for patients with two to three brain metastases. Greater functional independence and reduced steroid use at 6 months was seen in all patients treated with SRS [19,20]. Consequently, the evidence that SRS improves patient-relevant outcomes is for patients with up to three brain metastases, good performance status and controlled extracranial disease.

In the initial trials of SRS and surgery, WBRT was part of the treatment of brain metastases. Subsequent trials evaluating the role of WBRT showed a lack of overall survival or functional benefit by adding WBRT to surgery or SRS [21–23]. Although the addition of WBRT improves intracranial disease control, this is of uncertain clinical value and may adversely affect quality of life [24]. High quality data on neurocognition are lacking as few trials have included sensitive neurocognitive tests. One phase III trial suggested a neurocognitive benefit from the addition of WBRT to SRS using the mini-mental state examination [25], which has poor discriminatory power. A smaller randomised trial noted a detrimental effect of WBRT using more sensitive measures at the 4 month time point, although differences in overall survival between the arms may confound this interpretation [26].

Post-treatment surveillance with magnetic resonance imaging (MRI) is commonly carried out in patients suitable

for further salvage (SRS, surgery and/or WBRT) and is recommended by some expert groups [27], but high-level evidence that early (pre-symptomatic) intervention is beneficial in terms of overall survival, quality of life or neurocognition is lacking.

Stereotactic Radiotherapy and Stereotactic Radiotherapy Techniques

SRS initially used stereotactic localisation technology to accurately define the position of the target using Cartesian coordinates relative to a fixed point of reference generally in the form of a neurosurgical-type frame. As technology and high-precision radiotherapy has evolved, many SRS techniques no longer depend on stereotaxy, but the terminology remains.

Treating small targets with multiple, non-coplanar beams creates high dose conformity to the target and steep dose gradients that minimise dose to nearby normal structures (Figure 1). Although previous trials did not mandate the use of MRI [19,22], the precision of delivery required is such that target localisation with thin slice contrast-enhanced MRI accurately co-registered with thin slice planning computed tomography is now usual. Patient intra- and interfraction motion is minimised with firm immobilisation using fixed invasive neurosurgical-type or relocatable frames [28]. Alternatively, less precise mask immobilisation may be combined with on-treatment imaging (such as orthogonal kV) [29,30] provided accurate initial set-up and acceptable intrafraction motion (generally ≤ 1 mm) can be shown.

SRS is increasingly marketed by manufacturers and SRS providers as a potentially more effective treatment for patients with even large numbers of brain metastases. However, evidence for patients with more than three brain metastases is lacking and SRS use in the USA tends to relate to the availability of equipment and socio-economic factors [31,32]. It is unclear how this variability relates to other patient, disease and provider characteristics.

Considerable emphasis is placed on the equipment used to deliver SRS. These include a multi-headed cobalt unit (Gamma Knife[®]), a robotic arm-mounted linear accelerator (Cyberknife[®]) and a conventional modern linear accelerator (linac) that can be employed using fixed-field conformal or intensity-modulated radiotherapy (IMRT) beams or arcing IMRT (on conventional linac or with dedicated Tomotherapy[®] equipment).

Although differences between the technologies do exist, most are of questionable clinical significance and no clear advantage has been shown for any single technique. Comparative technical evaluation requires the assessment of a number of planning metrics, including target dose conformity, dose homogeneity, dose gradient, normal tissue doses, organ at risk doses and time to deliver the treatment. Although some techniques have been compared using a few of the metrics, no comprehensive comparison has been independently carried out looking at all the parameters. Claimed advantages for one parameter in one technique

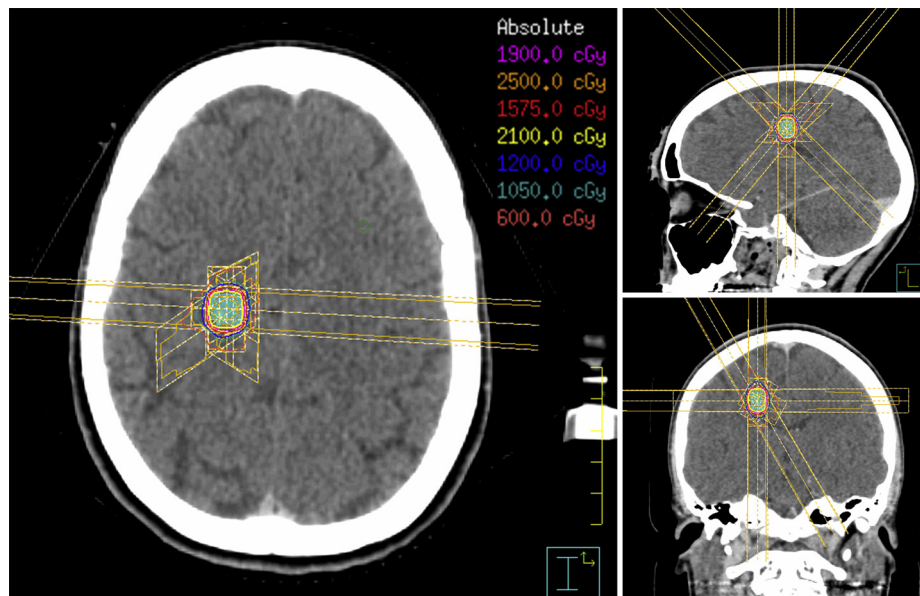


Fig 1. Illustration of the dose distribution achieved with stereotactic radiosurgery in axial (left), sagittal (top right) and coronal (bottom right) planes. 21 Gy to the 80% isodose (yellow line) was delivered using a linear accelerator with fixed-field conformal beams. The volume receiving 12 Gy (dark blue line) and 6 Gy (orange line) is small.

tend to be balanced by advantages in other parameters for an alternative technique and the expertise of the operator and department infrastructure will probably be the main determinant of the quality of treatment delivery. The ultimate test of the technologies is efficacy assessed using clinically relevant outcomes. There are no randomised studies comparing outcome after treatment for brain metastases by SRS technology used and retrospective comparisons are biased by patient selection. The only objective data available come from RTOG 9508, where both Gamma Knife and linac SRS were permitted for the treatment of brain metastases and overall survival outcomes were equivalent [19].

There have been few, if any, recent technical advances in the delivery of SRS that are likely to alter patient outcomes. With the increasing although unvalidated use of SRS for multiple brain metastases, approaches of simultaneous integrated boost using rotating IMRT techniques [33] are being explored as an alternative to multiple isocentre SRS and as an alternative to WBRT. The advantage in terms of normal brain sparing in comparison with multiple isocentre SRS is unclear, but the techniques offer a faster, more streamlined treatment delivery and it therefore becomes a more accessible and potentially more cost-effective alternative that requires appropriate testing, particularly in comparison with WBRT. The emergence of hippocampal avoiding-WBRT (HA-WBRT) as a putative method to reduce the deleterious effects of WBRT on neurocognitive function and quality of life [34] may lead to the re-evaluation of established treatment paradigms for brain metastases. The effect of HA-WBRT on neurocognitive function and quality of life in patients with one to four brain metastases after SRS or surgery will be assessed in a phase II randomised trial (ClinicalTrials.gov identifier NCT02147028).

Current Stereotactic Radiosurgery Practice in the UK

Up to 1725 patients with brain metastases may be eligible to receive SRS in England each year [18]. Surgery is preferred to SRS for larger metastases, those associated with significant mass effect or when histopathology is required. Suitable patients with up to 20 cm³ total brain metastasis volume can be offered SRS [18]. The commissioning criteria in the National Health Service in England are given in [Table 1](#).

Typical SRS doses range from 15 to 24 Gy at the periphery of the target volume and are adjusted based on tumour

Table 1

National Health Service commissioning criteria for stereotactic radiosurgery and stereotactic radiotherapy for metastatic intracranial disease

All of the following criteria must be met:

- Selection of patients by local multidisciplinary team with understanding of the systemic and neurological disease processes and neurosurgical options, as well as discussion by the specialist stereotactic radiosurgery multidisciplinary team;
- Karnofsky performance status ≥ 70 ;
- Established diagnosis of cancer;
- Absent or controllable primary disease;
- Estimated life expectancy from extracranial disease ≥ 6 months;
- Total tumour volume ≤ 20 cm³*

Adapted from [18]. Note that additional criteria apply in the context of retreatment.

* Perfectly spherical lesions 1, 2, 3 and 3.5 cm in diameter have volumes of 0.5, 4.2, 14.1 and 22.4 cm³.

size, location and proximity to organs at risk [19,22,35,36]. There are differences in methodology of dose prescription specific to technologies. For example, using a linac, the multileaf collimator is used to shape the prescription isodose to the target volume and the dose is typically prescribed to the 80–90% isodose. By contrast, as the Gamma Knife has a range of fixed diameter collimators, the dose is typically prescribed to the 50–80% isodose covering the target. This leads to greater dose inhomogeneity within the target, but a steeper initial dose fall off outside the prescription isodose.

Although there is a suggestion of improved tumour control with higher radiation doses, this is based on retrospective series in which the effect of dose and tumour size are confounded [37]. Late central nervous system toxicity (grade ≥ 3) is uncommon. Radiation necrosis is reported in 3–6% of patients receiving SRS with WBRT [19,21] and can mimic tumour progression clinically and radiologically. The non-invasive diagnosis and treatment of radiation necrosis is challenging [38].

Management after SRS is not clearly defined and policies on MRI surveillance vary. One current policy is follow-up with 3 monthly contrast-enhanced MRI for 2 years in patients who have not received WBRT previously. The value of such an intensive surveillance policy in what is largely a palliative situation remains unclear, but enables early intervention for pre-symptomatic recurrence.

Modernising Patient Selection for Stereotactic Radiosurgery

In the era of increasingly effective therapies and more frequent imaging surveillance, there are expectations of providing more effective therapy for brain metastases than achieved with WBRT. Incidental screen-detected and asymptomatic lesions have become more common and are seen in patients with lower disease burden. More patients are therefore candidates for SRS and it is not clear whether the conclusions from prior data should be generalised across all primary sites, histologies and molecular subtypes. It is also not certain if data from patients with symptomatic brain metastases with competing risks from intracranial and extracranial disease are applicable for the screen-detected population.

Although in previous trials the number of brain metastases was the principal selection criterion for SRS, the number detected on MRI is technique dependent [39]. It is suggested that for small volume disease, the number of lesions treated using Gamma Knife without WBRT may not correlate with outcome [40], although this is based on selected series of patients. The total brain metastasis volume in some retrospective studies correlates better with local control [41,42], distant intracranial control [42] and overall survival [41–44] after SRS than brain metastasis number. However, it remains to be shown whether patients with more than three brain metastases benefit from resource-intensive SRS compared with WBRT and high-quality randomised studies are required to ensure

evolving changes in practice are fully assessed before their routine introduction.

A range of prognostic indices have been proposed to predict overall survival in patients with brain metastases for the purposes of clinical decision-making and stratification into clinical trials [6,7,45–50]. The RPA classification [6] is not tumour type-specific and predates the routine use of SRS. The diagnosis-specific GPA (ds-GPA) is disease specific [45]; although it may not fully reflect outcomes incorporating modern systemic therapies and is affected by selection biases [51], it has undergone some independent validation [41,52,53] and can identify patients with the worst prognosis [54] best managed with palliative intent. In a post-hoc analysis of the RTOG 9508 data, predominantly of NSCLC patients (and excluding breast cancer), ds-GPA scores of 3.5–4.0 identified a subgroup with up to three brain metastases and an apparent overall survival benefit from SRS [55] although the validity in such a retrospective stratification in a highly selected group of patients is uncertain. Prognostic indices reflecting current treatment approaches may better define disease and treatment-specific prognosis, although they are not a substitute for prospective studies defining the appropriate treatment for each patient subgroup.

Considerations in Dose Selection for Stereotactic Radiosurgery and Stereotactic Radiotherapy

The SRS dose prescribed is generally determined by the brain metastasis size and the presumed risk of injury to the surrounding normal tissues. The accepted maximum tolerated doses for brain metastases were defined in the RTOG 9005 dose escalation trial as 24, 18 and 15 Gy to the isodose encompassing the contrast-enhancing disease (gross tumour volume) without further expansion for lesions ≤ 20 , 21–30 and 31–40 mm, respectively, although these data were determined from a mixture of disease types and previous radiotherapy doses [35]. Depending on the technology and immobilisation used, some centres isotropically expand the gross tumour volume by 1–2 mm; however, it must be borne in mind that the risk of radionecrosis increases with the volume of brain receiving at least 12 Gy [36,56–58]. Lower SRS prescription doses are associated with a lower risk of complications at the cost of reduced local control [37,59] and are used for larger brain metastases and lesions within or close to eloquent locations, such as the brainstem and optic apparatus.

Patients with brainstem metastases were previously excluded from trials due to concerns regarding toxicity [19,21,22]. Patients with small brainstem metastases have been treated to marginal doses of 13–18 Gy (using varying isodoses as above) with acceptable risk of toxicity [60–65], although the risk increases with lesions >1 cm³ [61,65].

An alternative local treatment to SRS for larger, inoperable brain metastases or those in eloquent locations is fractionated/hypofractionated stereotactic radiotherapy (SRT) aiming to improve the therapeutic ratio. Prospective [66–68] and larger retrospective series [69–75] suggest comparable outcomes for SRS and SRT using doses in the

range 24–30 Gy in three fractions [66,69,75], 30–35 Gy in four to five fractions [67,68,70,72,75] and 35–40 Gy in seven to 10 fractions [70,71]. The number of patients with large brain or brainstem metastases in each cohort was generally low or not clearly reported and analyses of toxicity and functional outcomes according to size and location were limited to provide reliable safety and efficacy data of any given dose-fractionation schedule. Data on the use of SRT for inoperable metastases >3–4 cm are limited and it has not been shown to be preferable to WBRT.

Brain metastases from melanoma, RCC and sarcoma have been considered as radioresistant when treated with conventionally fractionated radiotherapy, although the data are not fully validated [76]. On the theoretical basis that radioresistant disease has a low α/β ratio, lower dose SRS may be preferred to SRT for large lesions, although this remains an unproven hypothesis not currently tested. Similar consideration has been applied to recurrent brain metastases.

Sequencing of Stereotactic Radiosurgery with Targeted Agents

The emergence of targeted agents in molecular subtypes of NSCLC, breast cancer, RCC and melanoma offers new treatment options for patients with brain metastases. Direct randomised comparisons of the efficacy of targeted agents with SRS in enriched populations have not been carried out and the optimal sequencing is not defined. Nevertheless, it is reasonable to consider potentially effective systemic therapy as first-line treatment for asymptomatic brain metastases, reserving SRS and/or WBRT for salvage. Disease-specific trials comparing systemic therapy with systemic therapy plus SRS are of interest, although difficult to mount due to limited patient numbers and preconceived ideas of the efficacy of the different approaches.

SRS and WBRT have been combined with temozolomide and erlotinib separately in an unselected population of patients with one to three brain metastases from NSCLC. Contrary to expectation, the use of erlotinib was associated with a trend to inferior overall survival compared with radiotherapy alone, presumed to be due to the increased toxicity [77]. As novel systemic therapies become available, concomitant administration during brain irradiation without prior testing may lead to unexpected toxicities when agents are administered in close sequence with [78,79] or after SRS [80,81]. Although this should not preclude investigation of combined therapies in appropriate subpopulations, this may require novel study design and vigilant post-marketing reporting to provide sufficient toxicity data.

Combining Stereotactic Radiosurgery or Stereotactic Radiotherapy with Surgery

After surgery, the addition of WBRT reduces the risk of recurrence and neurologic death, but does not improve

overall survival or functional independence [22,82]. Although SRS or SRT to the excision cavity could be exploited as an alternative to WBRT to reduce the risk of local recurrence [68,83–86], patient-relevant benefit is uncertain and should be shown in randomised studies. Resected metastases larger than 3 cm with superficial dural or pial involvement are more liable to recur [83], as are subtotally resected lesions, although these are challenging lesions to treat with SRS. Postoperative SRS is being compared with WBRT in a phase III randomised trial (ClinicalTrials.gov identifier NCT01372774). The role of cavity SRS or SRT compared with observation alone after surgery with salvage treatment when needed has not been examined. Cavity dynamics [87,88] and difficulties with target delineation make treatment with SRS or SRT in the postoperative period challenging. The option of SRS or SRT before surgery may overcome some of these technical problems and may lead to a reduction in tumour size, although it may alter the risks of surgery and further evaluation is required [89].

Future Studies

Although SRS is an established treatment option in the management of one to three small volume brain metastases, a number of uncertainties remain. Previous trials have incorporated heterogeneous groups of patients. The end points studied did not always translate into patient-relevant outcomes and were largely applicable to symptomatic, heavily pre-treated patients.

Future studies should focus on the quality and duration of survival, rather than only radiological measures of local disease control that are of uncertain relevance to patients. Large mixed-histology trials without stratification are no longer appropriate; multicentre efforts are therefore needed to achieve a statistically sound disease-specific population size.

SRS competes with novel targeted therapies and future studies will need to address the integration of systemic therapies with SRS or SRT. Studies of the toxicity of combined treatments pose as yet unresolved challenges to study design where the expected toxicities are seen beyond the median life expectancy.

In the enthusiasm for high-technology treatment approaches to metastatic disease embodied in SRS, it is important not to lose focus on patient-relevant outcomes and future studies should include relevant functional (including neurocognitive) and quality of life end points. In this context it remains important to consider surveillance as an alternative to intervention in patients with disease of presumed indolent or unknown natural history and in patients with a poor prognosis where focus on intracranial disease may not be of relevance to the patient.

Conclusion

In fit patients with controlled extracranial disease, the place of SRS to improve overall survival in those with a

single brain metastasis and the duration of functional independence in those with up to three metastases is established. The role of SRS and SRT in other patients continues to evolve. High-quality studies are needed to clarify areas of uncertainty that remain regarding patient selection, dose-fractionation and integration with other therapies.

References

- [1] Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneaun FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol* 2004;22(14):2865–2872.
- [2] Schouten LJ, Rutten J, Huvneers HAM, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* 2002;94(10):2698–2705.
- [3] Walker AE, Robins M, Weinfeld FD. Epidemiology of brain tumors: the national survey of intracranial neoplasms. *Neurology* 1985;35(2):219–226.
- [4] Davis FG, Dolecek TA, McCarthy BJ, Villano JL. Toward determining the lifetime occurrence of metastatic brain tumors estimated from 2007 United States cancer incidence data. *Neuro-Oncology* 2012;14(9):1171–1177.
- [5] Johnson JD, Young B. Demographics of brain metastasis. *Neurosurg Clin N Am* 1996;7(3):337–344.
- [6] 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):745–751.
- [7] Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys* 2008;70(2):510–514.
- [8] Horton J, Baxter DH, Olson KB. The management of metastases to the brain by irradiation and corticosteroids. *Am J Roentgenol* 1971;111(2):334–336.
- [9] Langley RE, Stephens RJ, Nankivell M, et al. Interim data from the Medical Research Council QUARTZ Trial: does whole brain radiotherapy affect the survival and quality of life of patients with brain metastases from non-small cell lung cancer? *Clin Oncol* 2013;25(3):e23–e30.
- [10] Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322(8):494–500.
- [11] Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys* 1994;29(4):711–717.
- [12] Mintz AH, Kestle J, Rathbone MP, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1996;78(7):1470–1476.
- [13] Muacevic A, Wowra B, Siefert A, Tonn J-C, Steiger H-J, Kreth FW. 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(3):299–307.
- [14] Vuong DA, Rades D, van Eck ATC, Horstmann GA, Busse R. Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: stereotactic radiosurgery versus surgical resection. *Clin Neurol Neurosurg* 2013;115(3):276–284.
- [15] Caruso JP, Moosa S, Fezeu F, Ramesh A, Sheehan JP. A cost comparative study of Gamma Knife radiosurgery versus open surgery for intracranial pathology. *J Clin Neurosci* 2015;22(1):184–188.
- [16] Rutigliano MJ, Lunsford LD, Kondziolka D, Strauss MJ, Khanna V, Green M. The cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors. *Neurosurgery* 1995;37(3):445–453. discussion 453–455.
- [17] Mehta M, Noyes W, Craig B, et al. A cost-effectiveness and cost-utility analysis of radiosurgery vs. resection for single-brain metastases. *Int J Radiat Oncol Biol Phys* 1997;39(2):445–454.
- [18] NHS Commissioning Board Clinical Reference Group for Stereotactic Radiosurgery. *Clinical Commissioning Policy: Stereotactic Radiosurgery/Radiotherapy for Cerebral Metastases*. Reference: NHSCB/D05/P/d NHS Commissioning Board 2013.
- [19] Andrews DW, Scott CB, Sperduto PW, 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.
- [20] Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. *Cochrane Database Syst Rev* 2012;9. CD006121.
- [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(21):2483–2491.
- [22] Kocher M, Soffiotti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 2011;29(2):134–141.
- [23] Tsao MN, Lloyd N, Wong RKS, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev* 2012;4. CD003869.
- [24] Soffiotti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol* 2013;31(1):65–72.
- [25] Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* 2007;68(5):1388–1395.
- [26] 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):1037–1044.
- [27] Tsao MN, Rades D, Wirth A, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol* 2012;2(3):210–225.
- [28] Gill SS, Thomas DG, Warrington AP, Brada M. Relocatable frame for stereotactic external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 1991;20(3):599–603.
- [29] Rosenfelder NA, Corsini L, McNair H, et al. Achieving the relocation accuracy of stereotactic frame-based cranial radiotherapy in a three-point thermoplastic shell. *Clin Oncol* 2013;25(1):66–73.

- [30] Verbakel W, Lagerwaard FJ, Verduin AJE, Heukelom S, Slotman BJ, Cuijpers JP. The accuracy of frameless stereotactic intracranial radiosurgery. *Radiother Oncol* 2010;97(3):390–394.
- [31] Halasz LM, Weeks JC, Neville BA, Taback N, Punglia RS. Use of stereotactic radiosurgery for brain metastases from non-small cell lung cancer in the United States. *Int J Radiat Oncol Biol Phys* 2013;85(2):e109–116.
- [32] Hodgson DC, Charpentier A-M, Cigsar C, et al. A multi-institutional study of factors influencing the use of stereotactic radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys* 2013;85(2):335–340.
- [33] Levegrün S, Pöttgen C, Wittig A, Lübcke W, Abu Jawad J, Stuschke M. Helical tomotherapy for whole-brain irradiation with integrated boost to multiple brain metastases: evaluation of dose distribution characteristics and comparison with alternative techniques. *Int J Radiat Oncol Biol Phys* 2013;86(4):734–742.
- [34] Gondi V, Pugh SL, Tome WA, et al. Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol* 2014.
- [35] Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 2000;47(2):291–298.
- [36] Lawrence YR, Li XA, el Naqa I, et al. Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys* 2010;76(Suppl. 3):S20–S27.
- [37] Wiggenraad R, Verbeek-de Kanter A, Kal HB, Taphoorn M, Vissers T, Struikmans H. Dose-effect relation in stereotactic radiotherapy for brain metastases. A systematic review. *Radiother Oncol* 2011;98(3):292–297.
- [38] Chao ST, Ahluwalia MS, Barnett GH, et al. Challenges with the diagnosis and treatment of cerebral radiation necrosis. *Int J Radiat Oncol Biol Phys* 2013;87(3):449–457.
- [39] Hanssens P, Karlsson B, Yeo TT, Chou N, Beute G. Detection of brain micrometastases by high-resolution stereotactic magnetic resonance imaging and its impact on the timing of and risk for distant recurrences. *J Neurosurg* 2011;115(3):499–504.
- [40] Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLKG0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014;15(4):387–395.
- [41] Likhacheva A, Pinnix CC, Parikh NR, et al. Predictors of survival in contemporary practice after initial radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys* 2013;85(3):656–661.
- [42] Baschnagel AM, Meyer KD, Chen PY, et al. Tumor volume as a predictor of survival and local control in patients with brain metastases treated with Gamma Knife surgery. *J Neurosurg* 2013;119(5):1139–1144.
- [43] Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. *Int J Radiat Oncol Biol Phys* 2006;64(3):898–903.
- [44] Chen JC, Petrovich Z, O'Day S, et al. Stereotactic radiosurgery in the treatment of metastatic disease to the brain. *Neurosurgery* 2000;47(2):268–279. discussion 279–281.
- [45] Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012;30(4):419–425.
- [46] Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys* 1999;43(4):795–803.
- [47] Weltman E, Salvajoli JV, Brandt RA, et al. Radiosurgery for brain metastases: a score index for predicting prognosis. *Int J Radiat Oncol Biol Phys* 2000;46(5):1155–1161.
- [48] Lorenzoni J, Devriendt D, Massager N, et al. Radiosurgery for treatment of brain metastases: estimation of patient eligibility using three stratification systems. *Int J Radiat Oncol Biol Phys* 2004;60(1):218–224.
- [49] Rades D, Dziggel L, Haatanen T, et al. Scoring systems to estimate intracerebral control and survival rates of patients irradiated for brain metastases. *Int J Radiat Oncol Biol Phys* 2011;80(4):1122–1127.
- [50] Golden DW, Lamborn KR, McDermott MW, et al. Prognostic factors and grading systems for overall survival in patients treated with radiosurgery for brain metastases: variation by primary site. *J Neurosurg* 2008;109(Suppl.):77–86.
- [51] Chamberlain MC, Silbergeld DL. Is graded prognostic assessment an improvement compared with radiation therapy oncology group's recursive partitioning analysis classification for brain metastases? *J Clin Oncol* 2012;30(26):3315–3316. author reply 3316–3317.
- [52] Nieder C, Andratschke NH, Geinitz H, Grosu AL. Diagnosis-specific graded prognostic assessment score is valid in patients with brain metastases treated in routine clinical practice in two European countries. *Med Sci Monit* 2012;18(7):CR450–CR455.
- [53] Villà S, Weber DC, Moretones C, et al. Validation of the new Graded Prognostic Assessment scale for brain metastases: a multicenter prospective study. *Radiat Oncol* 2011;6:23.
- [54] Rodrigues G, Gonzalez-Maldonado S, Bauman G, Senan S, Lagerwaard F. A statistical comparison of prognostic index systems for brain metastases after stereotactic radiosurgery or fractionated stereotactic radiation therapy. *Clin Oncol* 2013;25(4):227–235.
- [55] Sperduto PW, Shanley R, Luo X, et al. Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation therapy versus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the Graded Prognostic Assessment (GPA). *Int J Radiat Oncol Biol Phys* 2014;90(3):526–531.
- [56] Korytko T, Radivoyevitch T, Colussi V, et al. 12 Gy gamma knife radiosurgical volume is a predictor for radiation necrosis in non-AVM intracranial tumors. *Int J Radiat Oncol Biol Phys* 2006;64(2):419–424.
- [57] Blonigen BJ, Steinmetz RD, Levin L, Lamba MA, Warnick RE, Breneman JC. Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2010;77(4):996–1001.
- [58] Minniti G, Clarke E, Lanzetta G, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. *Radiat Oncol* 2011;6:48.
- [59] Chang EL, Hassenbusch SJ, Shiu AS, et al. The role of tumor size in the radiosurgical management of patients with ambiguous brain metastases. *Neurosurgery* 2003;53(2):272–280. discussion 280–281.
- [60] Kawabe T, Yamamoto M, Sato Y, et al. Gamma Knife surgery for patients with brainstem metastases. *J Neurosurg* 2012;117(Suppl.):23–30.
- [61] Kased N, Huang K, Nakamura JL, et al. Gamma knife radiosurgery for brainstem metastases: the UCSF experience. *J Neurooncol* 2008;86(2):195–205.
- [62] Koyfman SA, Tendulkar RD, Chao ST, et al. Stereotactic radiosurgery for single brainstem metastases: the Cleveland clinic experience. *Int J Radiat Oncol Biol Phys* 2010;78(2):409–414.

- [63] Kelly PJ, Lin YB, Yu AYC, et al. Linear accelerator-based stereotactic radiosurgery for brainstem metastases: the Dana-Farber/Brigham and Women's Cancer Center experience. *J Neurooncol* 2011;104(2):553–557.
- [64] Lin C-S, Selch MT, Lee SP, et al. Accelerator-based stereotactic radiosurgery for brainstem metastases. *Neurosurgery* 2012;70(4):953–958. discussion 958.
- [65] Kilburn JM, Ellis TL, Lovato JF, et al. Local control and toxicity outcomes in brainstem metastases treated with single fraction radiosurgery: is there a volume threshold for toxicity? *J Neurooncol* 2014;117(1):167–174.
- [66] Manning MA, Cardinale RM, Benedict SH, et al. Hypofractionated stereotactic radiotherapy as an alternative to radiosurgery for the treatment of patients with brain metastases. *Int J Radiat Oncol Biol Phys* 2000;47(3):603–608.
- [67] Ernst-Stecken A, Ganslandt O, Lambrecht U, Sauer R, Grabenbauer G. Phase II trial of hypofractionated stereotactic radiotherapy for brain metastases: results and toxicity. *Radiother Oncol* 2006;81(1):18–24.
- [68] Ammirati M, Kshetry VR, Lamki T, Wei L, Grecula JC. A prospective phase II trial of fractionated stereotactic intensity modulated radiotherapy with or without surgery in the treatment of patients with 1 to 3 newly diagnosed symptomatic brain metastases. *Neurosurgery* 2014;74(6):586–594. discussion 594.
- [69] Wiggenraad R, Verbeek-de Kanter A, Mast M, et al. Local progression and pseudo progression after single fraction or fractionated stereotactic radiotherapy for large brain metastases. A single centre study. *Strahlenther Onkol* 2012;188(8):696–701.
- [70] Fahrig A, Ganslandt O, Lambrecht U, et al. Hypofractionated stereotactic radiotherapy for brain metastases – results from three different dose concepts. *Strahlenther Onkol* 2007;183(11):625–630.
- [71] Fokas E, Henzel M, Surber G, Kleinert G, Hamm K, Engenhart-Cabillic R. Stereotactic radiosurgery and fractionated stereotactic radiotherapy: comparison of efficacy and toxicity in 260 patients with brain metastases. *J Neurooncol* 2012;109(1):91–98.
- [72] Aoyama H, Shirato H, Onimaru R, et al. Hypofractionated stereotactic radiotherapy alone without whole-brain irradiation for patients with solitary and oligo brain metastasis using noninvasive fixation of the skull. *Int J Radiat Oncol Biol Phys* 2003;56(3):793–800.
- [73] Kim Y-J, Cho KH, Kim J-Y, et al. Single-dose versus fractionated stereotactic radiotherapy for brain metastases. *Int J Radiat Oncol Biol Phys* 2011;81(2):483–489.
- [74] Rajakesari S, Arvold ND, Jimenez RB, et al. Local control after fractionated stereotactic radiation therapy for brain metastases. *J Neurooncol* 2014;120(2):339–346.
- [75] Murai T, Ogino H, Manabe Y, et al. Fractionated stereotactic radiotherapy using CyberKnife for the treatment of large brain metastases: a dose escalation study. *Clin Oncol* 2014;26(3):151–158.
- [76] Oermann EK, Kress M-AS, Todd JV, et al. The impact of radiosurgery fractionation and tumor radiobiology on the local control of brain metastases. *J Neurosurg* 2013;119(5):1131–1138.
- [77] Sperduto PW, Wang M, Robins HI, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys* 2013;85(5):1312–1318.
- [78] Liebnner DA, Walston SA, Cavaliere R, et al. Radiation necrosis mimicking rapid intracranial progression of melanoma metastasis in two patients treated with vemurafenib. *Melanoma Res* 2014;24(2):172–176.
- [79] Barkhoudarian G, Deutsch G, Yost S, et al. Bm-05 ipilimumab therapy for melanoma brain metastases is associated with increased radiation necrosis. *Neuro-Oncology* 2014;16(Suppl. 5). v33.
- [80] Carlson JA, Nooruddin Z, Rusthoven C, et al. Trastuzumab emtansine and stereotactic radiosurgery: an unexpected increase in clinically significant brain edema. *Neuro-Oncology* 2014;16(7):1006–1009.
- [81] Du Four S, Wilgenhof S, Duerinckx J, et al. Radiation necrosis of the brain in melanoma patients successfully treated with ipilimumab, three case studies. *Eur J Cancer* 2012;48(16):3045–3051.
- [82] 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(17):1485–1489.
- [83] Brennan C, Yang TJ, Hilden P, et al. A phase 2 trial of stereotactic radiosurgery boost after surgical resection for brain metastases. *Int J Radiat Oncol Biol Phys* 2014;88(1):130–136.
- [84] Luther N, Kondziolka D, Kano H, et al. Predicting tumor control after resection bed radiosurgery of brain metastases. *Neurosurgery* 2013;73(6):1001–1006. discussion 1006.
- [85] Minniti G, Esposito V, Clarke E, et al. Multidose stereotactic radiosurgery (9 Gy × 3) of the postoperative resection cavity for treatment of large brain metastases. *Int J Radiat Oncol Biol Phys* 2013;86(4):623–629.
- [86] Ahmed KA, Freilich JM, Abuodeh Y, et al. Fractionated stereotactic radiotherapy to the post-operative cavity for radio-resistant and radiosensitive brain metastases. *J Neurooncol* 2014;118(1):179–186.
- [87] Jarvis LA, Simmons NE, Bellerive M, et al. Tumor bed dynamics after surgical resection of brain metastases: implications for postoperative radiosurgery. *Int J Radiat Oncol Biol Phys* 2012;84(4):943–948.
- [88] Ahmed S, Hamilton J, Colen R, et al. Change in postsurgical cavity size within the first 30 days correlates with extent of surrounding edema: consequences for postoperative radiosurgery. *J Comput Assist Tomogr* 2014;38(3):457–460.
- [89] Asher AL, Burri SH, Wiggins WF, et al. A new treatment paradigm: neoadjuvant radiosurgery before surgical resection of brain metastases with analysis of local tumor recurrence. *Int J Radiat Oncol Biol Phys* 2014;88(4):899–906.