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Review

Management of cerebral metastasis: Evidence-based approach for surgery, stereotactic radiosurgery and radiotherapy

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ABSTRACT

Brain metastases constitute a significant disease burden and have a major impact on morbidity and mortality. This review discusses the relative merits of open surgery, whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS), which have been used alone and in combination with varying degrees of success for the treatment of newly diagnosed brain metastasis. Treatment aims to provide disease control with a good quality of life, although prolonged survival may not always be achieved. Decision to treat is based on several prognostic factors including age, performance status and control of the primary cancer. The recently developed disease-specific graded prognostic assessment (DS-GPA) scales can aid in clinical decision making for individual patients. Whole brain radiotherapy remains the mainstay of treatment and provides effective palliation. Omission of WBRT results in worse local and distant control, though not survival. Local tumour control can be achieved by either resection of stereotactic radiosurgery (SRS). In long-term survivors WBRT may cause cognitive decline and SRS is being explored as an alternative method of disease control. Increasingly, quality of life and neuro-cognitive function are being used as end-points in clinical trials.

1. Introduction

Brain metastases arise in 10–40% of all cancer patients[1,2], and are the commonest intracranial tumour, accounting for an estimated 27,000 cases per year in the United Kingdom (UK) and up to 170,000 cases per year in the United States of America (USA).[3] The rising incidence is most likely to be related to several factors including improved neuro-imaging facilities, an ageing population and better systemic treatment for the primary disease.[4] Consequently, brain metastases cause significant mortality and morbidity, including significant cognitive impairment at the time of presentation.[5,6]

The management of patients with cerebral metastasis involves a multi-disciplinary team (MDT) with contribution from neurosurgeons, clinical/radiation oncologists, palliative care physicians, specialist nurses and neuro-radiologists. The recently published evidence-based clinical practice parameter guidelines developed by the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) have sought to provide a practical approach for treating clinicians through a systematic literature review.[7–9] This review focuses on the relative roles of surgery, stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT) in the treatment of newly diagnosed brain metastases.

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2. Prognosis of cerebral metastasis

Tumours with a high incidence in the general population are the most frequently encountered brain metastasis; lung and breast account for approximately two-thirds.[10] Some primary tumours are much more likely to metastasise to the central nervous system (CNS), e.g. small cell lung carcinoma, indeed, such is the propensity for brain metastasis that patients are often treated with prophylactic cranial irradiation.[11] Other tumours including gastric and prostate cancer are rarely associated with CNS spread.[12] Precocious (found before the primary tumour) and synchronous (found within 2 months of the primary tumour) brain metastasis account for approximately 20% of cases; the remaining 80% present with a known primary tumour. Newer systemic treatments are extending the disease-free interval for certain cancers, for example, HER-2 positive breast cancer is sensitive to the monoclonal antibody trastuzumab achieving prolonged control of the primary tumour, however, compared to historical controls, CNS progression occurs despite excellent systemic control.[13,14] The so called 'HER-2 paradigm' has re-focused efforts on developing and delivering more effective treatment for brain metastasis, which are a significant source of morbidity and mortality. Nevertheless, the prognosis for brain metastases remains poor; median survival is approximately 7 months.[15]

Performance status is a key factor for determining suitability for treatment and prognosis. Karnofsky performance status (KPS) forms a part of the recursive partitioning analysis (RPA) classification system, along with age, status of primary tumour and extent of extracranial disease.[16] The three prognostic classes (I, II and III) were determined from analysis of three randomised controlled trials (RCT) of approximately 1200 patients in the Radiation Therapy Oncology Group (RTOG) database who received whole brain radiotherapy (WBRT)[16], and has been subsequently validated in several population and treatment groups (Table 1). More recently a new prognostic index, the graded prognostic assessment (GPA) has been reported, which also takes into account the number of metastasis to give a score for each patient from 0 to 4.[17] The GPA remains to be validated in clinical trials, but appears to be as prognostic as the RPA system (Fig. 1). In addition, a prognostic index has been developed specifically for patients undergoing radiosurgery, namely the score index for radiosurgery (SIR), which takes into account factors used in the RPA system, as well as size, site and number of lesions, and whether WBRT was administered.[18] Whilst histopathology of the primary tumour was not a component of the prognostic grading scales[16–18], a recently published retrospective multi-institutional analysis of 4259 patients with brain metastases has led to the development of the disease-specific graded prognostic assessment (DS-GPA) scale that may provide a more accurate estimate of the prognosis.[15] In addition to age, KPS, extracranial disease and number of metastases, prognosis also depends on the primary tumour type.[15] This appears to show better accuracy in predicting prognosis, but has not been applied to clinical trials.

Table 1 – Components of recursive partitioning analysis (RPA) classification use to determine prognosis in cerebral metastasis[16].

Class	Clinical parameters	Median overall survival (OS) (months)
I	<65 years; Karnofsky performance status (KPS) ⩾ 70; controlled primary; no extracranial spread	7.1
II	⩾65 years; KPS ⩾ 70; uncontrolled primary; extracranial spread	4.2
III	KPS < 70	2.3

3. Current treatment strategies

Treatment strategies aim to improve locoregional control of cerebral metastases and utilise surgery, radiosurgery and whole brain radiotherapy in various combinations. The benefits of locoregional control as a means to potentially prolong overall survival must be balanced against patient quality of life and neurological function. The trial data supporting the following treatment paradigms are presented in Table 2 and discussed below.

3.1. *Resection + WBRT versus WBRT*

Whole brain radiotherapy has been the primary treatment for brain metastasis for several decades and can provide effective and rapid palliation. When used in combination with surgical resection improved quality of life and increased survival can be achieved. The seminal randomised controlled trial by Patchell et al. in 1990 compared surgical resection plus WBRT ($n = 25$) to WBRT alone ($n = 23$) for single brain metastases.[19] This demonstrated a significant overall survival advantage in the surgery + WBRT group (40 weeks) compared to the WBRT alone group (15 weeks). In addition, there was greater preservation of functional independence in the surgery + WBRT group (38 weeks versus 8 weeks; $P < 0.005$). These results have been validated in a second RCT of 63 patients with single brain metastasis where the overall survival was 10 months in those treated with surgery + WBRT compared to 6 months for WBRT alone.[20] A third larger trial failed to demonstrate a significant difference in overall survival between the two treatment arms[21], however, the patients in this trial had a lower performance status and death was more frequently due to systemic progression rather than neurological recurrence. Whilst the current evidence suggests that the addition of resection to WBRT rather than WBRT alone is beneficial for patients, this is derived from only three small, albeit randomised, trials.

3.2. *Resection versus resection + WBRT*

Several studies have addressed the benefit of adding WBRT to surgical resection for single brain metastasis with mixed results.[22–25] Only one randomised trial has been performed which, in the resection + WBRT group, demonstrated a significant decrease in tumour recurrence locally (10% versus 46%)

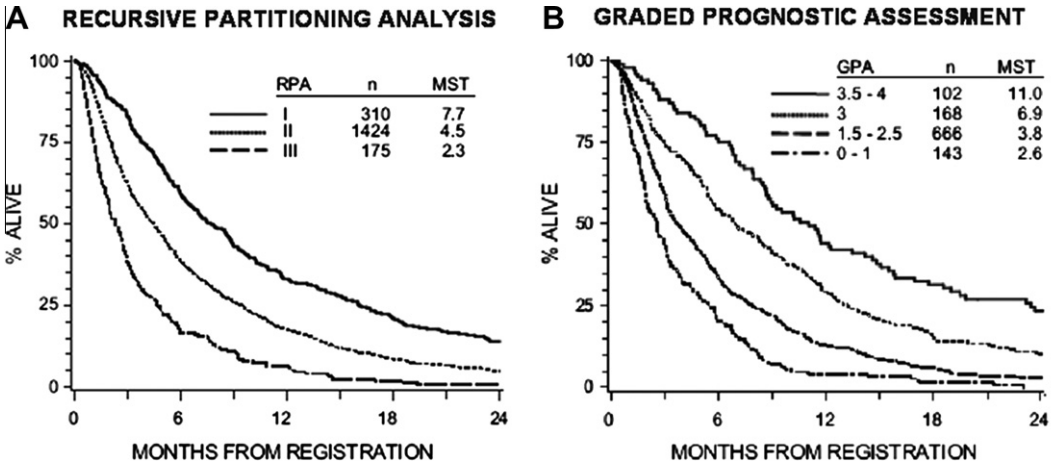

Fig. 1 – Kaplan-Meier overall survival (OS) curves for (A) recursive partitioning analysis (RPA) and (B) graded prognostic assessment (GPA) showing the number of patients in each class and median survival time (MST) (adapted with permission from Sperduto et al.[17]).

and elsewhere in the brain (18% versus 70%).[22] In those receiving WBRT, the rate of neurological death was lower (14% versus 44%), however, the trial was not powered to detect a survival difference and because of the high crossover rate to WBRT (61% at recurrence in the surgery only group), the median survival time for both groups was similar (10.8 versus 12.0 months). Nevertheless, this trial[22] in addition to several retrospective studies[23–25] has demonstrated the added benefit of WBRT. The recently closed EORTC 22952-26001 study, which investigated the role of adjuvant WBRT versus observation after local treatment (i.e. SRS or resection) for 1–3 metastases randomised 340 patients.[26] The preliminary results reported that whilst those receiving WBRT had reduced levels of intracranial relapse at 6 and 24 months (15.2% and 31.4% respectively) compared to the observation arm (39.7% and 54.0% respectively), the overall survival (10.9 months) was the same in both arms.[26] Whilst not the original intention of the study, subgroup analysis of the impact of either SRS or resection is awaited in the final publication. The current evidence suggests that resection + WBRT delivers better local and regional control compared to surgical resection alone.

3.3. *SRS versus resection + WBRT*

One RCT[27] and two retrospective studies[28,29] have compared these treatment options. The multi-centre German RCT was restricted to single operable metastasis and closed early due to poor patient accrual (only 64 of a planned 242 enrolled) – the study investigators had difficulty randomising patients.[27] Overall survival was the primary outcome measure and there was no significant difference between those receiving SRS (10.3 months) and those treated with resection + WBRT (9.5 months). Local control rates were similarly high in both groups, however, those who underwent resection + WBRT had longer progression free survival from distant brain metastasis.[27] Studies across two disciplines, that is, surgery and radiosurgery are difficult due to the different risk profiles of the treatment options. It is, therefore, unlikely that this clinical comparison will ever be completed as part of a randomised controlled trial. No definitive conclusions can be drawn, however, based on the current evidence these two treatment options may provide equivalent functional and overall survival outcomes, but the risk of distant failure is higher with SRS alone, therefore, vigilant imaging surveillance is required with the availability of salvage SRS or WBRT.

3.4. *WBRT versus SRS + WBRT*

Two randomised controlled trials have compared WBRT to SRS + WBRT for the treatment of up to four brain metastases.[30,31] The largest RCT randomised 331 patients with good performance status (KPS $\geqslant$ 70) and up to three metastases (the largest having a diameter not greater than 4 cm).[30] The groups were well matched and analysis was performed on an intention to treat basis, however, in the SRS + WBRT group (n = 164), 19% did not receive their planned SRS, and in the WBRT arm, 17% received salvage SRS. Therefore, there was a substantial crossover rate in both groups. In addition tumours up to 4 cm in diameter were treated, which are known to respond less favourably to SRS. Nevertheless, there were several important results from this study. In the SRS + WBRT group, only patients with single metastasis had significantly better survival (P = 0.01), better local control (P = 0.01) and better performance status. Unfortunately, the trial suffered from poor follow up data; post treatment imaging being available in only 57% of cases.[30] The second RCT was from a single institution treating 2–4 metastases with a mean tumour diameter $\leqslant$ 2.5 cm.[31] This very small study (n = 27) was prematurely stopped at the 60% accrual rate after the interim analysis demonstrated significantly better local control rates at 1 year (92% versus 0%) and progression free survival at the original tumour site (36 versus 6 months) in those receiving SRS + WBRT. The study was insufficiently powered to demonstrate statistical significant improvement in overall survival, despite a trend favouring SRS + WBRT (11 versus 7.5 months).[31] The large RCT[30] provides the best evidence that the addition of WBRT to SRS may afford improved local

Table 2 – Best available trial evidence for treatment of brain metastasis using a combination of surgical resection, whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS). Where median local and distant progression free survival was not reported in the original paper, the 1 year control rate is listed instead. OS = overall survival, PFS = progression free survival, NS = not significant, and RCT = randomised controlled trial.

	Study type	Intervention (# patients)	Median OS	Local control	Overall brain control
Resection + WBRT versus WBRT				*Median PFS*	*Control rate*
Patchell et al.[19]	RCT	WBRT (n = 23) Resection + WBRT (n = 25)	3.5 months 9.2 months (P < 0.01)	4.8 months >13.6 months (P < 0.0001)	87% 80% (P = NS)
Resection versus resection + WBRT				*Median PFS*	*Median PFS*
Patchell et al.[22]	RCT	Resection (n = 46) Resection + WBRT (n = 49)	10.8 months 12.0 months (P = NS)	6.7 months >11.5 months (P < 0.001)	6 months 51 months (P < 0.001)
SRS versus resection + WBRT				*1 year control rate*	*1 year control rate*
Muacevic et al.[27]	RCT	SRS (n = 31) Resection + WBRT (n = 33)	10.3 months 9.5 months (P = NS)	97% 82% (P = NS)	74% 97% (P < 0.05)
WBRT versus SRS + WBRT				*At original site*	*Overall in brain*
Andrews et al.[30]	RCT	WBRT (n = 167) SRS + WBRT (n = 164)	6.5 months 5.7 months (P = NS)	71% 82% (P = 0.01)	66% 72% (P = NS)
Resection + WBRT versus SRS + WBRT				*Median PFS*	*Median PFS*
Schoggl et al.[34]	Retrospective cohort	Resection + WBRT (n = 66) SRS + WBRT (n = 67)	9 months 12 months (P = NS)	3.9 months 4.9 months (P = NS)	3.7 months 4.4 months (P = NS)
SRS alone versus WBRT				*Median PFS*	*Median PFS*
Li et al.[36]	Prospective	SRS alone (n = 23) WBRT (n = 19)	9.3 months 5.7 months (P < 0.0001)	6.9 months 4.0 months (P < 0.001)	6.7 months 4.1 months (P < 0.0001)
SRS + WBRT versus SRS alone				*1 year control rate*	*1 year control rate*
Aoyama et al.[37]	RCT	SRS + WBRT (n = 65) SRS alone (n = 67)	8.0 months 7.5 months (P = NS)	53.2% 23.6% (P < 0.001)	58.5% 36.3% (P = 0.003)
Resection + WBRT versus resection + SRS				*1 year control rate*	*Median PFS*
Serizawa et al.[39]	Retrospective cohort	Resection + WBRT (n = 34) Resection + SRS (n = 62)	6.6 months 12.5 months (P = 0.0158)	Not reported 94.8%	17.9 months 14.1 months (P = NS)

disease control compared to WBRT alone in patients with good performance status.

3.5. *Resection + WBRT versus SRS + WBRT*

To date there are no prospective studies comparing these two strategies. A phase III Australian RCT (http://clinicaltrials.gov/ct2/show/NCT00124761) has recently closed prematurely due to poor patient accrual. Subgroup analysis of data from the EORTC 22952-22601 study may yield interesting new data in time.[26] The current literature evidence is, therefore, restricted to four retrospective studies and the results are conflicting.[32–35] Two studies reported longer overall survival in patients undergoing resection + WBRT[32,33], which was statistically significant in one report [resection + WBRT (16.4 months) compared to SRS + WBRT (7.5 months)], however, those receiving SRS + WBRT were medically less well.[32] In contrast the other two studies revealed a trend towards longer OS in those receiving SRS + WBRT, but this did not reach statistical significance.[34,35] These two treatment options, therefore, appear to

be equally effective for the management of suitable solid metastases less than 3 cm in diameter, however, the studies may be subject to selection bias when deciding whether to treat with open surgical resection or SRS.

3.6. SRS alone versus WBRT

There are no randomised trials comparing these two treatment modalities, however, one prospective three-armed trial of 60 patients compared WBRT versus SRS versus SRS + WBRT.[36] Both small cell and non-small cell cancer patients were included, Karnofsky performance status was $\geqslant$60 and metastases up to 4.5 cm in diameter were treated. All patients had single brain metastasis and in those patients treated with SRS alone the median survival time (9.3 months) was significantly longer than those treated with WBRT (5.7 months). In addition, time to progression was also significantly longer in the SRS group.[36] The poor evidence base means that no recommendation can be made about the role of these two treatment modalities being used as the only therapeutic intervention.

3.7. SRS + WBRT versus SRS alone

In a multi-centre RCT of up to four metastases patients were randomised to either SRS alone ($n = 67$) or SRS + WBRT ($n = 65$).[37] In those receiving WBRT the SRS dose was reduced by 30%. There was a considerable cross-over rate between the two trial arms, which may account for the lack of statistically significant difference in median OS (SRS + WBRT = 8.0 months; SRS alone 7.5 months). However, the local and overall brain control rate was significantly lower in those patients who received SRS alone.[37] In the prospective three-armed trial of Li et al. described previously[36], there was also no significant difference in median overall survival (10.6 months for SRS + WBRT versus 9.3 months for SRS alone). In contrast to the RCT data[37] omission of WBRT from the treatment protocol did not result in significantly worse local control rates or disease progression.[36] In a recently published RCT that was stopped early by the data monitoring committee, 58 patients were randomised to either SRS alone or SRS + WBRT of up to three metastases from a variety of primary tumours.[38] The primary study objective was assessment of neurocognitive function 4 months after completion of radiation treatment; overall survival and disease control were secondary outcome measures. Whilst median OS was higher in the SRS group (15.2 months) compared to the SRS + WBRT group (5.7 months), in the SRS group the 1-year local control rate was lower (67% versus 100%) along with the 1-year distant recurrence rate (45% versus 73%). Thirty-three percent of patients in the SRS group required salvage resection and WBRT for local failure, compared to 6% who underwent salvage SRS in the SRS + WBRT group.[38] Cognitive decline (specifically verbal memory tests) was significantly less in those treated with SRS alone. It is important to note that it took 6 years to recruit the 58 patients for this trial, and the clinical relevance of verbal memory decline at 4 months is questionable – other measure of quality of life may be more important to patients. Nevertheless, the evidence suggests that SRS may deliver a similar survival advantage to SRS + WBRT, although there appears to be a greater risk of distant recurrence requiring continued imaging surveillance.

3.8. Resection + WBRT versus resection + SRS

There are no prospective studies for this treatment comparison. The best evidence for this comes from a retrospective cohort study in patients with multiple metastases from non-small cell lung cancer.[39] Thirty four patients received resection + WBRT and 62 resection (if >3 cm) + SRS to lesions <3 cm. The patients receiving resection + SRS has significantly longer survival (12.5 versus 6.6 months), but the study is flawed as in the resection + WBRT arm not all of the multiple metastasis in each patient were resected. One additional option available with this treatment strategy is the application of SRS to the resection cavity post-operatively instead of WBRT. Aside from small cases series suggesting improved local control and[40,41], there are no prospective or randomised studies. Prospective clinical trials are required to assess these treatment modalities and there is currently insufficient evidence to make a recommendation.

4. Patient selection for aggressive local treatment paradigms

Given the poor prognosis for patients with brain metastases (median overall survival ~7 months)[15], careful selection of suitable patients for treatment of brain metastases is essential to avoid unnecessary risk to those unlikely to benefit from aggressive local treatment. Clinical and functional status, histology and primary disease control and imaging features all contribute to clinical decision making. Patients likely to benefit from more aggressive local treatment, i.e. resection or SRS, are those with good functional status and controlled primary and extracranial disease. In addition, the recently published DS-GPA scale identified that brain metastases had statistically significant different prognostic factors and similarly different prognoses depending on the primary tumour, e.g. breast cancer median survival was 11.93 months compared to 6.74 months for melanoma.[15] Surgery can be used for lesions of any size, whilst SRS is typically restricted to tumours $\leqslant$3 cm diameter, with no significant mass effect and no associated hydrocephalus. Surgery has the advantage of immediate relief of mass effect and lower corticosteroid requirement compared to SRS, but has higher complication and mortality rates often dictated by tumour location.[42] Increasingly the management of metastases in specific malignancies is being re-examined and clinical trials of brain metastasis in lung cancer and melanoma are ongoing or in development. As with breast cancer, the emphasis is shifting back towards achieving better intracranial disease control with preserved cognitive and functional status.

5. Conclusions

Despite the substantial number of publications on the treatment of brain metastasis, there is a relative paucity of good quality studies investigating the various management options. Based in the current literature evidence the following

recommendations can be applied to the management of newly diagnosed brain metastasis.

(1) WBRT plus surgical resection is better than surgery alone with respect to reduced risk of distant brain metastasis.
(2) WBRT plus surgical resection is superior to WBRT alone with respect to prolonged survival and preserved functional status in single metastasis.
(3) Local tumour control can be achieved with either surgical excision or SRS, but treatment choice may depend on tumour location radiosurgery availability.
(4) Local tumour control (surgery or SRS) in combination with WBRT improves survival in single brain metastasis.
(5) Omission of WBRT results in worse local and regional control but does not appear to affect survival.
(6) SRS alone can provide effective local control (imaging surveillance for distant recurrence is necessary) and is associated with less cognitive decline compared to WBRT treated patients.

Ultimately, the optimal management strategy for patients will be individually tailored according to clinical disease status and after appropriate discussion by the treating multi-disciplinary team. The rationale behind the available strategies is local control by resection or SRS, followed by management of the rest of the brain to address regional control. Historically this has been with whole brain radiotherapy, but more recently, focus has shifted towards investigation of the cognitive impact of WBRT and whether SRS can be used as an alternative.[38,43] Whilst the primary aim is disease control, this may come at the expense of cognitive function and several recent studies have demonstrated that omission of WBRT and treatment with SRS alone preserve neurocognition for longer.[38,43] These findings may represent the start of a paradigm shift away from whole brain radiotherapy in the treatment of brain metastasis and highlights the continuing need for clinical trials to assess not only traditional outcome measures of survival and disease control, but also cognitive function and quality of life.

Conflict of interest statement

None declared.

REFERENCES

1. Soffietti R, Ruda R, Mutani R. Management of brain metastases. *J Neurol* 2002;**249**(10):1357–69.
2. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. *J Neurooncol* 2005;**75**(1):5–14.
3. Brem S, Panattil JG. An era of rapid advancement: diagnosis and treatment of metastatic brain cancer. *Neurosurgery* 2005;**57**(Suppl. 5):S5–9 [discussion S1–4].
4. Soffietti R, Ruda R, Trevisan E. Brain metastases: current management and new developments. *Curr Opin Oncol* 2008;**20**(6):676–84.
5. Chang EL, Wefel JS, Maor MH, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. *Neurosurgery* 2007;**60**(2):277–83 [discussion 283–4].
6. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol* 2004;**22**(1):157–65.
7. Gaspar LE, Mehta MP, Patchell RA, et al. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;**96**(1):17–32.
8. Kalkanis SN, Kondziolka D, Gaspar LE, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;**96**(1): 33–43.
9. 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. *J Neurooncol* 2010;**96**(1):45–68.
10. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. *Cancer* 1996;**78**(8):1781–8.
11. Dowell JE. Small cell lung cancer: are we making progress? *Am J Med Sci* 2010;**339**(1):68–76.
12. Nguyen T, Deangelis LM. Treatment of brain metastases. *J Support Oncol* 2004;**2**(5):405–10 [discussion 411–6].
13. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer* 2003;**97**(12):2972–7.
14. Lin NU, Winer EP. Brain metastases: the HER2 paradigm. *Clin Cancer Res* 2007;**13**(6):1648–55.
15. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. *Int J Radiat Oncol Biol Phys* 2010;**77**(3):655–61.
16. 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.
17. 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):510–4.
18. 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):1155–61.
19. 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.
20. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993;**33**(6):583–90.
21. 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):1470–6.
22. 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):1485–9.

23. Armstrong JG, Wronski M, Galicich J, et al. Postoperative radiation for lung cancer metastatic to the brain. *J Clin Oncol* 1994;**12**(11):2340–4.
24. Hagen NA, Cirrincione C, Thaler HT, DeAngelis LM. The role of radiation therapy following resection of single brain metastasis from melanoma. *Neurology* 1990;**40**(1):158–60.
25. Skibber JM, Soong SJ, Austin L, Balch CM, Sawaya RE. Cranial irradiation after surgical excision of brain metastases in melanoma patients. *Ann Surg Oncol* 1996;**3**(2):118–23.
26. Mueller RP, Soffietti R, Abacioglu MU, et al. Adjuvant whole brain radiotherapy versus observation after radiosurgery or surgical resection of 1–3 cerebral metastasis – results of the EORTC 22952-26001 study. *J Clin Oncol* 2009;**27**(15S) [abstract number 2008].
27. Muacevic A, Wowra B, Siefert A, et al. 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.
28. Muacevic A, Kreth FW, Horstmann GA, et al. Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. *J Neurosurg* 1999;**91**(1):35–43.
29. Rades D, Bohlen G, Pluemer A, et al. Stereotactic radiosurgery alone versus resection plus whole-brain radiotherapy for 1 or 2 brain metastases in recursive partitioning analysis class 1 and 2 patients. *Cancer* 2007;**109**(12):2515–21.
30. 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):1665–72.
31. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys* 1999;**45**(2):427–34.
32. Bindal AK, Bindal RK, Hess KR, et al. Surgery versus radiosurgery in the treatment of brain metastasis. *J Neurosurg* 1996;**84**(5):748–54.
33. O'Neill BP, Iturria NJ, Link MJ, et al. A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases. *Int J Radiat Oncol Biol Phys* 2003;**55**(5):1169–76.
34. Schoggl A, Kitz K, Reddy M, et al. Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastases. *Acta Neurochir (Wien)* 2000;**142**(6):621–6.
35. Garell PC, Hitchon PW, Wen BC, Mellenberg DE, Tonrner J. Stereotactic radiosurgery versus microsurgical resection for the initial treatment of metastatic cancer to the brain. *J Radiosurgery* 1999;**2**(1):1–5.
36. Li B, Yu J, Suntharalingam M, et al. Comparison of three treatment options for single brain metastasis from lung cancer. *Int J Cancer* 2000;**90**(1):37–45.
37. 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):2483–91.
38. 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.
39. Serizawa T, Iuchi T, Ono J, et al. Gamma knife treatment for multiple metastatic brain tumors compared with whole-brain radiation therapy. *J Neurosurg* 2000;**93**(Suppl. 3):32–6.
40. Do L, Pezner R, Radany E, et al. Resection followed by stereotactic radiosurgery to resection cavity for intracranial metastases. *Int J Radiat Oncol Biol Phys* 2009;**73**(2):486–91.
41. Jagannathan J, Yen CP, Ray DK, et al. Gamma knife radiosurgery to the surgical cavity following resection of brain metastases. *J Neurosurg* 2009;**111**(3):431–8.
42. Al-Shamy G, Sawaya R. Management of brain metastases: the indispensable role of surgery. *J Neurooncol* 2009;**92**(3):275–82.
43. 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):1388–95.