

Integrated treatment of brain metastases

Nicola Rosenfelder *

Consultant Clinical Oncologist

Royal Marsden NHS Foundation Trust

Fulham Road

London SW3 6JJ

nicola.rosenfelder@rmh.nhs.uk

Michael Brada

Professor of Radiation Oncology

University of Liverpool & Clatterbridge Cancer Centre NHS Foundation Trust

Bebington

Wirral CH63 4JY

michael.brada@liverpool.ac.uk

* corresponding author

key words and phrases.

Surgery for brain metastases

Stereotactic radiosurgery for brain metastases

Systemic therapy for brain metastases

Abstract

Purpose of review:

Optimal treatment of brain metastases has been limited to local treatment with few systemic options. Increasing use of targeted therapies, chemotherapy and immunotherapy and combination of local and systemic treatments resulted in plethora of publications. We review the existing evidence for individual treatments and new evidence for the integration of systemic and combination of local treatments.

Recent findings:

Encouraging efficacy of systemic therapies supports combination of systemic and local treatment albeit without randomised trials. Efficacy particularly of targeted agents provides an opportunity to delay local treatments including radiosurgery and whole brain radiotherapy. Randomised trials testing the integration of surgery, radiotherapy and radiosurgery are reviewed with emphasis on patient relevant endpoints to guide the clinician in the choice and sequence of treatments and integrating systemic and local therapies.

Summary:

There is increasing tendency to use focused radiation for single and oligometastases with or without surgery and decline in whole brain radiotherapy which is limited to multiple metastases in tumours without effective systemic options. Systemic therapies have promising intracranial efficacy and the sequence and combination with localised radiation is awaiting trials. Changes in practice with a move to primary systemic treatment for brain metastases without radiation, should be undertaken with caution and close monitoring.

Introduction

The incidence of brain metastases and associated morbidity and mortality is rising most likely as a result of more frequent brain imaging and the use of more effective local and systemic therapies. Up to 30% of patients with tumours such as melanoma and lung adenocarcinoma have intracranial metastases at the time of diagnosis (1) and many more will develop intracranial disease during the course of their disease; up to 50% of patients with Her-2 positive breast cancer develop brain metastases (2).

Metastatic disease in the brain had been considered within a “sanctuary site” and treatment approaches have been directed specifically at the brain. With greater understanding of the natural history and response to treatment, management policies have become more complex and varied often combining treatment for brain and systemic disease, the use of surveillance in asymptomatic patients and the use of more localised treatment approaches with surgery and focused radiation. We discuss the current evidence which underpins the changing practice particularly focusing on the integration of the various treatments. With increasing interest in new approaches to tackle intracranial metastatic disease, treatments considered appropriate in 2020 may also become outdated. However any newly accepted treatment policies should be guided by high level evidence rather than enthusiasm for novelty and technological advances of uncertain clinical importance, and should be demonstrated to be of real benefit to patients in terms of survival and quality of life, avoiding intermediate and surrogate endpoints of little or no relevance to patients.

Changing role of whole brain radiotherapy (WBRT)

The role of WBRT, standard “fit all” treatment of previous decades, has been challenged by the QUARTZ trial which compared WBRT with “optimal supportive care” (OSC) including corticosteroids, in 538 patients with poor prognosis non-small cell lung cancer (NSCLC) and brain metastases. With an overall median survival of only 2 months (i.e. the worst prognosis patients) it showed no survival or quality of life benefit for WBRT. While it has been interpreted by some as showing that WBRT has no role in patients with NSCLC and brain metastases, a potential survival benefit was seen in younger patients and those with a more favourable prognostic profile (3).

WBRT therefore currently remains the treatment of choice in patients with NSCLC and other primary tumours with more favourable prognosis and disseminated malignancy not responsive to systemic treatment and not amenable to local therapies (radiosurgery or surgery). However, WBRT should be carefully considered

for each patient as achieving intracranial disease control may be associated with worse cognitive decline than seen in patients receiving local therapies (4, 5).

In patients with multiple lesions localised to specific parts of the brain partial brain irradiation (as fractionated conformal radiotherapy) to either palliative or radical doses dependent on the status of systemic disease provides an alternative to WBRT. Partial brain radiotherapy has not been subject to randomised studies although it carries a significant benefit in terms of avoiding radiation to large parts of apparently uninvolved normal brain avoiding possible functional consequences of irradiation. The use of Memantine to reduce the cognitive decline ascribed to WBRT failed to show a clinically significant improvement in a randomised study (6, 7).

Stereotactic radiosurgery (SRS)

SRS allows for highly focussed radiation to small targets. It can be delivered using a conventional linear accelerator, a small linear accelerator mounted on a robotic arm (Cyberknife™) or a multiheaded cobalt unit (Gamma Knife™). While there are technical differences in the detail of treatment planning and treatment delivery there are no known significant differences in the outcome of treatment using any of the equipment and treatment techniques. However the use of focal RT needs to be supported by a significant infrastructure and expertise in high precision treatment delivery.

The demonstration that SRS in addition to WBRT prolongs survival in patients with single brain metastases (8) has led to increasing use of SRS in patients with oligometastases and multiple brain metastases as an alternative to wide field irradiation. In patients with multiple brain metastases treated with radiation alone (i.e. without previous surgery) SRS alone has not been formally compared to WBRT. In patients with oligometastases neuro-cognitive function decline is greater following WBRT than SRS alone (9) though this is not yet demonstrated for a larger number of lesions where the temptation is to treat each lesion as an individual metastasis with SRS (10).

A technically simpler alternative to avoid WBRT is a technique of single isocentre volumetric modulated arc therapy (VMAT) using a linear accelerator. With either of the techniques, which are manpower and equipment use intensive, a significant dose is delivered to normal unaffected brain although lower than WBRT dose and the potential advantage in sparing cognitive function remains to be demonstrated. In the absence of a survival benefit for the more localised technique of radiation, the most important endpoint for patients with single or multiple brain metastases is improvement in symptoms and maintenance of quality of life (QoL) rather than endpoints such as local or distant failure potentially amenable to further treatment providing this is appropriate in the context of the overall disease. Randomised

studies focusing on QoL and functional endpoints in addition to survival are needed to help with the choice of treatment for individual patients.

Most randomised studies evaluating technology tend to include patients with a range of tumour types and are not generally single disease specific. Further studies in different tumours and molecular subtypes particularly in patients with favourable prognosis may define optimal use and timing of SRS. Such refinements are likely to be driven by the availability and efficacy of systemic treatments.

SRS is not without risk and can cause radiation necrosis, cognitive decline and vascular sequelae. The risk of radiation necrosis is in the region of 10-20%, is dose and volume dependent and is increased by previous cranial surgery and radiation. Due to the higher risk of radiation necrosis treating large lesions to high single doses the current trend is to use high dose fractionated/hypofractionated stereotactic radiotherapy with similar efficacy and lesser toxicity (11) although this has not been subject to randomised trials.

Surgery

With modern surgical techniques, resection is considered the treatment of choice for patients with large and cystic lesions with a significant mass effect who are likely to benefit from surgical debulking (12) where removal of a tumour mass is likely to provide rapid symptomatic relief. Surgical resection is considered suitable for up to 3 lesions, although surgery for multiple metastases has not been subject to randomised trials. Surgery in combination with WBRT is associated with survival benefit in patients with solitary metastases compared to WBRT alone (13) although this was not clearly demonstrated in larger randomised studies (14, 15). While not subject to head-to-head comparison in randomised trials, it is likely that both SRS and surgery are equivalent in achieving local disease control where surgery is preferred for accessible lesions with a significant mass effect.

Combination of surgery, radiosurgery and radiotherapy

Due to a significant risk of distant intracranial disease progression following treatment of solitary brain metastases with surgery or SRS the policy had been to offer adjuvant whole brain radiotherapy following local treatment. Three randomised trials of WBRT (16-18) while demonstrating improved intracranial disease control have shown no survival benefit, no prolongation of functional independence (measured as remaining with good performance status) (17) with detriment in terms of cognitive function. There is currently therefore no clear justification for the use of WBRT following surgery or radiosurgery for solitary or oligometastases.

Due to a risk of recurrence at the site of tumour resection, adjuvant SRS to the resection cavity following tumour excision was examined in randomised trials. Although local and distant brain control were worse with adjuvant SRS than WBRT (19), the overall survival was no different and WBRT was associated with worse cognitive decline. A single-centre randomised trial of SRS to the resection cavity following surgery compared with surgery alone (20) demonstrated high local control rates following SRS similar to those achieved following WBRT (19). However adjuvant SRS was not associated with a survival benefit and 4% of patients receiving SRS developed radiation necrosis. While SRS has lesser adverse effect than WBRT it is less effective in achieving disease control in the brain outside the treated site so that same proportion of SRS and surveillance patients require subsequent treatment with WBRT (19, 20). Post-operative radiotherapy was compared in a randomised trial to surveillance and salvage SRS (similar to a comparison of WBRT and SRS where only proportion of patients receive SRS). The study showed no survival difference and no difference in cognitive function measured with Mini-Mental Status Examination (MMSE) though this is a poorly discriminatory test (21). Following surveillance and salvage SRS proportion of surviving patients received WBRT within 6 months of surgery. The studies suggest that it is reasonable to defer adjuvant treatment and offer SRS or WBRT depending on the pattern of brain recurrence. As there is no survival advantage with either WBRT or SRS postoperatively, avoidance of toxicity is an important factor on which to decide to offer adjuvant treatment. The reduction of cognitive decline with SRS compared to WBRT is clinically important particularly for patients with high risk of progression following surgery.

SRS to the resection cavity is considered by some as the “standard of care” (22, 23) based on local control at the resection site and little risk of toxicity and therefore has been widely adopted, although the absolute advantage remains of uncertain relevance for the patient, and may ultimately vary with other factors such as systemic control and systemic treatment options as well as the risk of local and overall intracranial recurrence. Randomised-controlled, stratified studies comparing surveillance with post-operative SRS would help answer this question with relevant primary endpoints such as retaining functional status and independence, freedom from the need for further treatment and QoL.

Delivering SRS preoperatively may confer some advantages to post-operative treatment, including the ability to treat the actual rather than imagined site of disease with a potential lower risk of necrosis. SRS may also reduce the viability of residual tumour cells at the tumour margin and theoretically may reduce intraoperative tumour spillage and therefore the risk of leptomeningeal disease as suggested in retrospective studies (24). A randomised trial of preoperative versus postoperative SRS is currently underway as well as a further trial assessing molecular changes in resected tissue following SRS (25) (clinicaltrials.gov; NCT03398694). It is important that such studies focus on patient relevant endpoints rather than disease control.

The use of local therapies with an option for further treatment at the time of development of distant intracranial disease requires more intensive surveillance of intracranial disease although the frequency of imaging is not clearly defined. In addition, the development of metastatic disease in the brain, as in other systemic sites, has prognostic implications and not infrequently requires palliative care input.

Systemic therapy

Chemotherapy

Historically, systemic therapy was considered of limited value for brain metastases due to poor penetration of agents through the blood-brain barrier (BBB). However, enhancing brain metastases have impaired BBB and a range of chemotherapy agents have shown efficacy for intracranial disease. Primary systemic therapy has long been considered the primary treatment of choice for patients with brain metastases from chemosensitive tumours such as small cell lung cancer and lymphoma as well as for chemonaïve chemoresponsive tumours with a significant chance of achieving a meaningful tumour response. Newer targeted systemic therapies with small (and lipid soluble) molecules have demonstrated superior penetration of the BBB and in some instances may deal with microscopic as well as macroscopic intracranial disease (26).

Targeted therapy

Targeted agents are currently the treatment of choice in advanced and disseminated tumours with targetable mutations such as EGFR and ALK driven non-small cell lung cancer (NSCLC), HER2 positive breast cancer and melanoma with BRAFV600E as well as MEK mutation. Although there is evidence of varying sensitivity of brain metastases to different tyrosine kinase inhibitors (TKIs), the efficacy in terms of shrinkage of brain metastases parallels systemic response rate which means that newer EGFR inhibitors such as Osimertinib, effective against a second mutation (T790M) are also more effective for CNS disease. Response rates and the duration of CNS disease control is improved with newer TKIs in ALK mutated tumours such as Alectinib and Lorlatinib when compared with Crizotinib which also parallels systemic efficacy (26-30).

In general TKIs do not prevent the development of brain metastases in patients with microscopic (imaging undetectable) disease in the CNS with the exception of ALK mutated NSCLC where patients treated with second and third generation TKIs such as Alectinib or Lorlatinib, have lower incidence of brain metastases than following Crizotinib (26, 30-32).

With improved survival of patients with HER2+ breast cancer there has been a clear increase in the incidence of brain metastases, and antibody and small molecule

therapies such as trastuzumab, trastuzumab emtansine (T-DM1) and lapatinib, have demonstrated intracranial activity. Retrospective studies suggested prolonged survival with trastuzumab in patients with HER2+ disease with brain metastases (33). Retrospective subgroup analyses of larger trials suggest that second-line T-DM1 despite its large size, is active at the time of trastuzumab resistance as well as in untreated patients. Newer HER2 targeted therapies show promise in heavily pretreated patients with intracranial response rates up to 30-40% (34).

Immunotherapy

Immunotherapy either alone or in combination with chemotherapy has become standard of care in many tumour types with a particular focus on melanoma, epithelial tumours especially NSCLC and renal cell carcinoma. Initial trials defining the efficacy of single agent immune checkpoint inhibitors tended to exclude patients with brain metastases. The apparent reduction of efficacy of immunotherapy in combination with corticosteroids, used frequently as symptomatic treatment for brain metastases also led to relatively slow introduction into the treatment of CNS disease. Nevertheless, where reported, brain metastases had shown shrinkage in line with systemic response in melanoma (35) and NSCLC (36). The possible interaction of radiation and immunomodulatory agents has led to initial concerns but a suggestion of enhanced efficacy needs further exploration (37-39).

Combination of systemic therapy and radiation therapy/SRS

Despite the efficacy of systemic therapy in the control of brain metastases the disease almost invariably recurs with a risk independent of status of systemic disease. This has led to policies of adjuvant radiotherapy either in the form of WBRT/partial brain RT or SRS. Retrospective studies suggest improvement in long term disease control in the brain although survival benefit of adjuvant radiotherapy (WBRT) or SRS compared to delayed treatment at the time of progression remains unclear and is subject to current randomised studies. Similarly adjuvant SRS may be of value as an additional treatment of oligometastases with suggestion of improved intracranial disease control in patients with targetable EGFR/ALK mutated tumours (40) and this too is the subject of ongoing randomised trials. Early results of SRS in addition to chemotherapy in patients with cerebral oligometastases at presentation of NSCLC (in non-mutated tumours) did not demonstrate benefit of SRS in intracranial tumour control or survival (41).

The suggestion of increased efficacy of upfront combined cranial radiation with TKI compared to the use of TKI alone (42) is intriguing suggesting a potential future role for combined sequential or concomitant therapy and results of ongoing trials will help inform optimal sequencing (NCT03497767).

In patients with HER2+ breast cancer, lapatinib intracranial response rate and duration of tumour control is improved with the addition of SRS (43, 44). This is associated with a significant risk of radionecrosis particularly when SRS is combined with T-DM1 and until prospective studies are completed, this combination should be used with caution.

In HER2+ patients, prospective randomised trials are required for new targeted systemic therapies particularly when used alone. Until there is clear high-quality evidence to support substitution of treatments with proven efficacy, treatment with systemic targeted therapies without the use of radiation should be undertaken with caution and close monitoring.

In patients with brain metastases and HER2 negative tumours, there is limited data that would allow for a change in practice from the evidence-based treatments of radiation (WBRT or SRS) or surgery.

Molecular analysis of metastases at different sites including the brain suggests ongoing phylogenetic evolution with development of new mutations, particularly in breast cancer (45, 46). This may include the evolution of new targetable mutations as well as decline in existing targetable mutations. While the current standard is to offer treatment on the basis of molecular analysis of the primary tumour or accessible systemic metastases it may be appropriate that future strategies include molecular analyses of brain metastases with tissue obtained either by local sampling or through circulating tumour DNA (ctDNA). Whether this approach will lead to true widening of therapeutic options remains highly speculative.

Conclusion

Despite an ever-increasing number of management options for patients with brain metastases long term control remains a challenge and the choice of treatment has to be considered in the context of the overall disease and not as an isolated entity. Increasing use of more localised treatments in the form of surgery and stereotactic radiosurgery while more effective at achieving disease control at the treated site has limited impact on the overall intracranial disease control in patients with multiple brain metastases. Similarly the increasing use of systemic therapies for brain metastases, while effective in terms of tumour response rarely results in lasting intracranial disease control. The combination of local and systemic treatments holds promise though the combination requires robust evidence from tumour specific and ideally randomised prospective studies as combination of treatment also combines toxicities. The focus in assessing the effectiveness of new treatment approaches should shift to quality of life and survival likely to be dictated by overall disease control rather than intracranial tumour control alone. This also means that the current tendency to move the primary decision making to specialists in brain tumour management, be it surgeons or radiation oncologists, needs rethinking with primary

responsibility remaining under the control of tumour specific specialists, working closely with a neuro-oncology multidisciplinary team.

The appearance of brain metastases remains an expression of disease dissemination with life expectancy implications and early support and involvement of palliative care services should be an integral part of management for a significant majority of patients.

1. Cagney DN, Martin AM, Catalano PJ, Redig AJ, Lin NU, Lee EQ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro Oncol.* 2017 Oct 19;19(11):1511-21. PubMed PMID: 28444227. Pubmed Central PMCID: PMC5737512. Epub 2017/04/27.
2. Gori S, Rimondini S, De Angelis V, Colozza M, Bisagni G, Moretti G, et al. Central nervous system metastases in HER-2 positive metastatic breast cancer patients treated with trastuzumab: incidence, survival, and risk factors. *Oncologist.* 2007 Jul;12(7):766-73. PubMed PMID: 17673608. Epub 2007/08/04.
- *3. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet.* 2016 Oct 22;388(10055):2004-14. PubMed PMID: 27604504. Pubmed Central PMCID: PMC5082599. Epub 2016/10/30.
The lack of improvement in quality of life and survival with the addition of WBRT in patients with poor prognosis NSCLC has resulted in omission of WBRT, although it remains appropriate for patients with favourable prognosis.
4. Schneider JR, Chakraborty S, Boockvar JA. Effect of Whole Brain Radiation Therapy on Cognitive Function. *Neurosurgery.* 2017 Mar 1;80(3):N7-N16. PubMed PMID: 28362974. Epub 2017/04/01.
5. Wilke C, Grosshans D, Duman J, Brown P, Li J. Radiation-induced cognitive toxicity: pathophysiology and interventions to reduce toxicity in adults. *Neuro Oncol.* 2018 Apr 9;20(5):597-607. PubMed PMID: 29045710. Pubmed Central PMCID: PMC5892147. Epub 2017/10/19.
- *6. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol.* 2013 Oct;15(10):1429-37. PubMed PMID: 23956241. Pubmed Central PMCID: PMC3779047. Epub 2013/08/21.
The addition of memantine to WBRT did not results in a statistically significant benefit in terms of cognitive decline
7. Tsao MN, Xu W, Wong RK, Lloyd N, Laperriere N, Sahgal A, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev.* 2018 Jan 25;1:CD003869. PubMed PMID: 29365347. Pubmed Central PMCID: PMC6491334. Epub 2018/01/25.
8. 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 May 22;363(9422):1665-72. PubMed PMID: 15158627. Epub 2004/05/26.
9. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* 2009 Nov;10(11):1037-44. PubMed PMID: 19801201. Epub 2009/10/06.
10. Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol.* 2014 Apr;15(4):387-95. PubMed PMID: 24621620. Epub 2014/03/14.
- *11. Lehrer EJ, Peterson JL, Zaorsky NG, Brown PD, Sahgal A, Chiang VL, et al. Single versus Multifraction Stereotactic Radiosurgery for Large Brain Metastases: An International Meta-analysis

of 24 Trials. *Int J Radiat Oncol Biol Phys.* 2019 Mar 1;103(3):618-30. PubMed PMID: 30395902. Epub 2018/11/06.

The meta-analysis demonstrated non-inferiority in local control and radionecrosis for multifraction stereotactic radiotherapy versus single fraction SRS

*12. Soffietti R, Abacioglu U, Baumert B, Combs SE, Kinhult S, Kros JM, et al. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). *Neuro Oncol.* 2017 Feb 1;19(2):162-74. PubMed PMID: 28391295. Pubmed Central PMCID: PMC5620494. Epub 2017/04/10.

European guidelines summarise the current recommendations for the treatment of patients with brain metastases, based on evidence available up to 2017

13. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990 Feb 22;322(8):494-500. PubMed PMID: 2405271. Epub 1990/02/22.

14. Noordijk EM, Vecht CJ, Haaxma-Reiche H, Padberg GW, Voormolen JH, Hoekstra FH, 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 Jul 1;29(4):711-7. PubMed PMID: 8040016. Epub 1994/07/01.

15. Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer.* 1996 Oct 1;78(7):1470-6. PubMed PMID: 8839553. Epub 1996/10/01.

16. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA.* 2006 Jun 7;295(21):2483-91. PubMed PMID: 16757720. Epub 2006/06/08.

17. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, 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 Jan 10;29(2):134-41. PubMed PMID: 21041710. Pubmed Central PMCID: PMC3058272. Epub 2010/11/03.

*18. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. *JAMA.* 2016 Jul 26;316(4):401-9. PubMed PMID: 27458945. Pubmed Central PMCID: PMC5313044. Epub 2016/07/28.

The addition of WBRT to SRS has no effect on survival and is associated with worse cognitive decline that SRS alone suggesting that WBRT is not necessary after SRS.

*19. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol.* 2017 Aug;18(8):1049-60. PubMed PMID: 28687377. Pubmed Central PMCID: PMC5568757. Epub 2017/07/09.

Postoperative WBRT resulted in worse cognitive decline compared with SRS with no difference in survival despite improved intracranial disease control

*20. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol.* 2017 Aug;18(8):1040-8. PubMed PMID: 28687375. Pubmed Central PMCID: PMC5560102. Epub 2017/07/09.

Postoperative SRS to the tumour bed compared to observation alone reduced local recurrence at the treated site without survival benefit without improvement in overall intracranial disease control.

*21. Kayama T, Sato S, Sakurada K, Mizusawa J, Nishikawa R, Narita Y, et al. Effects of Surgery With Salvage Stereotactic Radiosurgery Versus Surgery With Whole-Brain Radiation Therapy in Patients With One to Four Brain Metastases (JCOG0504): A Phase III, Noninferiority, Randomized Controlled Trial. *J Clin Oncol*. 2018 Jun 20;JCO2018786186. PubMed PMID: 29924704. Epub 2018/06/21.

The non-inferiority of deferred SRS to post-operative adjuvant WBRT provides support for omission of adjuvant treatment; a proportion of initial surveillance patients were subsequently treated with WBRT

22. Ainsworth NL, McLean MA, McIntyre DJO, Honess DJ, Brown AM, Harden SV, et al. Quantitative and textural analysis of magnetization transfer and diffusion images in the early detection of brain metastases. *Magn Reson Med*. 2017 May;77(5):1987-95. PubMed PMID: 27279574. Pubmed Central PMCID: PMC5412685. Epub 2016/06/10.

23. Minniti G, Soltys SG, Halasz LM, Breneman JC, Chan M, Laack NN, et al. Stereotactic Radiosurgery for Resected Brain Metastases: New Evidence Supports a Practice Shift, but Questions Remain. *Int J Radiat Oncol Biol Phys*. 2018 Mar 1;100(3):535-8. PubMed PMID: 29413262. Epub 2018/02/08.

24. Prabhu RS, Miller KR, Asher AL, Heinzerling JH, Moeller BJ, Lankford SP, et al. Preoperative stereotactic radiosurgery before planned resection of brain metastases: updated analysis of efficacy and toxicity of a novel treatment paradigm. *J Neurosurg*. 2018 Dec 1:1-8. PubMed PMID: 30554174. Epub 2018/12/17.

25. Huff WX, Agrawal N, Shapiro S, Miller J, Kulwin C, Shah M, et al. Efficacy of pre-operative stereotactic radiosurgery followed by surgical resection and correlative radiobiological analysis for patients with 1-4 brain metastases: study protocol for a phase II trial. *Radiat Oncol*. 2018 Dec 20;13(1):252. PubMed PMID: 30572923. Pubmed Central PMCID: PMC6302493. Epub 2018/12/24.

*26. Gadgeel S, Peters S, Mok T, Shaw AT, Kim DW, Ou SI, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann Oncol*. 2018 Nov 1;29(11):2214-22. PubMed PMID: 30215676. Pubmed Central PMCID: PMC6290889. Epub 2018/09/15.

Patients with newly diagnosed ALK mutated NSCLC and CNS disease treated with alectinib had superior intracranial disease control compared to crizotinib

27. Gadgeel SM. Optimal front-line ALK (anaplastic lymphoma kinase) directed therapy. *Lung Cancer*. 2017 Jul;109:147-8. PubMed PMID: 28365051. Epub 2017/04/04.

*28. Gandhi L, Ou SI, Shaw AT, Barlesi F, Dingemans AC, Kim DW, et al. Efficacy of alectinib in central nervous system metastases in crizotinib-resistant ALK-positive non-small-cell lung cancer: Comparison of RECIST 1.1 and RANO-HGG criteria. *Eur J Cancer*. 2017 Sep;82:27-33. PubMed PMID: 28646771. Epub 2017/06/25.

Durable responses to alectinib were demonstrated in patients ALK mutated NSCLC who had progressed on crizotinib with efficacy in the brain, including in the second-line setting

29. Yang J, Gong W. Lorlatinib for the treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer. *Expert Rev Clin Pharmacol*. 2019 Mar;12(3):173-8. PubMed PMID: 30657349. Epub 2019/01/19.

*30. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017 Aug 31;377(9):829-38. PubMed PMID: 28586279. Epub 2017/06/07.

Alectinib in patients with ALK+ NSCLC demonstrated superior efficacy and reduced CNS progression compared to crizotinib

31. Nishio M, Nakagawa K, Mitsudomi T, Yamamoto N, Tanaka T, Kuriki H, et al. Analysis of central nervous system efficacy in the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. *Lung Cancer*. 2018 Jul;121:37-40. PubMed PMID: 29858024. Epub 2018/06/03.
32. Tomasini P, Egea J, Souquet-Bressand M, Greillier L, Barlesi F. Alectinib in the treatment of ALK-positive metastatic non-small cell lung cancer: clinical trial evidence and experience with a focus on brain metastases. *Ther Adv Respir Dis*. 2019 Jan-Dec;13:1753466619831906. PubMed PMID: 30786826. Pubmed Central PMCID: PMC6385324. Epub 2019/02/23.
33. Laakmann E, Muller V, Schmidt M, Witzel I. Systemic Treatment Options for HER2-Positive Breast Cancer Patients with Brain Metastases beyond Trastuzumab: A Literature Review. *Breast Care (Basel)*. 2017 Jul;12(3):168-71. PubMed PMID: 28785185. Pubmed Central PMCID: PMC5527181. Epub 2017/08/09.
34. Freedman RA, Gelman RS, Anders CK, Melisko ME, Parsons HA, Cropp AM, et al. TBCRC 022: A Phase II Trial of Neratinib and Capecitabine for Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases. *J Clin Oncol*. 2019 May 1;37(13):1081-9. PubMed PMID: 30860945. Pubmed Central PMCID: PMC6494354. Epub 2019/03/13.
- *35. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2016 Jul;17(7):976-83. PubMed PMID: 27267608. Pubmed Central PMCID: PMC5526047. Epub 2016/06/09.
- Pembrolizumab demonstrated activity in patients with NSCLC and melanoma brain metastases*
36. Protopapa M, Kouloulis V, Nikoloudi S, Papadimitriou C, Gogalis G, Zygogianni A. From Whole-Brain Radiotherapy to Immunotherapy: A Multidisciplinary Approach for Patients with Brain Metastases from NSCLC. *J Oncol*. 2019;2019:3267409. PubMed PMID: 30853981. Pubmed Central PMCID: PMC6378013. Epub 2019/03/12.
37. Singh C, Qian JM, Yu JB, Chiang VL. Local tumor response and survival outcomes after combined stereotactic radiosurgery and immunotherapy in non-small cell lung cancer with brain metastases. *J Neurosurg*. 2019 Feb 15:1-6. PubMed PMID: 30771783. Epub 2019/02/17.
38. Bhalla N, Brooker R, Brada M. Combining immunotherapy and radiotherapy in lung cancer. *J Thorac Dis*. 2018 May;10(Suppl 13):S1447-S60. PubMed PMID: 29951296. Pubmed Central PMCID: PMC5994496. Epub 2018/06/29.
39. Diao K, Bian SX, Routman DM, Yu C, Ye JC, Wagle NA, et al. Stereotactic radiosurgery and ipilimumab for patients with melanoma brain metastases: clinical outcomes and toxicity. *J Neurooncol*. 2018 Sep;139(2):421-9. PubMed PMID: 29696531. Epub 2018/04/27.
40. Lee JH, Chen HY, Hsu FM, Chen JS, Liao WY, Shih JY, et al. Cranial Irradiation for Patients with Epidermal Growth Factor Receptor (EGFR) Mutant Lung Cancer Who Have Brain Metastases in the Era of a New Generation of EGFR Inhibitors. *Oncologist*. 2019 May 24. PubMed PMID: 31127020. Epub 2019/05/28.
41. Lim SH, Lee JY, Lee MY, Kim HS, Lee J, Sun JM, et al. A randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligometastases in non-small-cell lung cancer. *Ann Oncol*. 2015 Apr;26(4):762-8. PubMed PMID: 25538174. Epub 2014/12/30.
42. Wang C, Lu X, Zhou Z, Wang J, Hui Z, Liang J, et al. The Efficacy of Upfront Intracranial Radiation with TKI Compared to TKI Alone in the NSCLC Patients Harboring EGFR Mutation and Brain Metastases. *J Cancer*. 2019;10(9):1985-90. PubMed PMID: 31205558. Pubmed Central PMCID: PMC6548172. Epub 2019/06/18.
43. Parsai S, Miller JA, Juloori A, Chao ST, Kotecha R, Mohammadi AM, et al. Stereotactic radiosurgery with concurrent lapatinib is associated with improved local control for HER2-positive breast cancer brain metastases. *J Neurosurg*. 2019 Feb 8:1-9. PubMed PMID: 30738402. Epub 2019/02/10.

44. Kim JM, Miller JA, Kotecha R, Chao ST, Ahluwalia MS, Peereboom DM, et al. Stereotactic radiosurgery with concurrent HER2-directed therapy is associated with improved objective response for breast cancer brain metastasis. *Neuro Oncol.* 2019 May 6;21(5):659-68. PubMed PMID: 30726965. Pubmed Central PMCID: PMC6502492. Epub 2019/02/07.
45. Brastianos PK, Carter SL, Santagata S, Cahill DP, Taylor-Weiner A, Jones RT, et al. Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets. *Cancer Discov.* 2015 Nov;5(11):1164-77. PubMed PMID: 26410082. Pubmed Central PMCID: PMC4916970. Epub 2015/09/28.
46. Berghoff AS, Preusser M. New developments in brain metastases. *Ther Adv Neurol Disord.* 2018;11:1756286418785502. PubMed PMID: 30034538. Pubmed Central PMCID: PMC6048670. Epub 2018/07/24.

key points

1. Review of the current evidence for treatment of brain metastases particularly focusing on combination of treatment approaches.
2. Surgical resection or SRS alone remain the current treatment of choice for patients with small volume limited intracranial disease, good performance status and treatable or absent extracranial disease.
3. New targeted systemic therapies and immunotherapy have intracranial efficacy and may allow reduction or deferral of surgery, SRS and WBRT. Randomised trial data are awaited to inform correct sequencing and integration of systemic and local targeted therapies.
4. Future trials should focus on patient relevant endpoints in the context of overall life expectancy and QoL.

Acknowledgements

We would like to thank Yi Wen Hon at The Royal Marsden for her assistance with the study.

Financial support and sponsorship

This work did not require any additional support or financial sponsorship.

Conflicts of interest

Authors have no conflicts of interest.