Integrated treatment of brain metastases

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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.

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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.

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Conflicts of interest
Authors have no conflicts of interest.