Brain metastases: a subtype-specific medical approach

Claire Phillips

Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia.
University of Melbourne, Victoria, Australia
Email: Claire.Phillips@petermac.org

Abstract
In the past, brain metastases were essentially all treated in the same way, and heralded a poor prognosis. Improvements in ways of delivering radiotherapy as well as in anaesthetic and neurosurgical techniques and in imaging mean that much more can be achieved. A knowledge of what subtype of breast cancer is being treated is now critical to take into account, especially in HER2 positive disease, where an expanding array of anti-HER2 drugs means that extra-cranial disease may be controlled for many years. Ideally, brain metastases should be managed in a multidisciplinary setting, so that imaging, radiation oncology and neurosurgery input can be combined.

Brain metastases (BM) are a common, and frequently challenging, clinical problem in the contemporary management of metastatic breast cancer. While the management of extracranial metastatic breast cancer is now strongly defined by tumour phenotype, this approach is not so well defined for BM. This review considers brain metastases in HER2 breast cancer and triple negative breast cancer (TNBC) cancer populations as BM are common in these phenotypes; estimated to occur in 30-55% of patients with metastatic HER2 positive breast cancer (HER2BC) and 25-46% of patients with metastatic hormone negative HER2 receptor negative, or ‘Triple negative’, breast cancer.1 BM from these phenotypes present contrasting clinical scenarios and management must be tailored accordingly.

Prognostic factors

The Radiation Therapy Oncology Group (RTOG) conducted many of the most significant BM trials, especially through the 1980s and 90s. Its large database of BM patients from these studies has provided critical information regarding prognostic factors for breast cancer BM, presented as the Breast Cancer Graded Prognostic Analysis (BrGPA), Table 1a.2 The BrGPA shows clearly that phenotype and performance status are the most important prognostic factors for breast cancer BM, whereas patient age has minor significance Table 1b. The total number of brain metastases was not found to an independent prognostic factor in the BrGPA but others have questioned this, finding lesion number to be of similar prognostic significance to age.3

Typical patterns of disease behaviour

HER2-positive disease (HER2BC)
HER2BC has a well-described propensity to metastasise to the central nervous system (CNS).1 This is thought to be due to several factors; tropism of HER2BC cells for the CNS, the striking success of targeted-HER2 therapies in treating extracranial metastatic disease (ECD) and the relatively poor efficacy of these systemic agents against disease within the brain (and neuraxis more generally). The natural history of HER2BC has been changed by the targeted-HER2 agents, which prevent early death from visceral metastases and so ‘allow time’ for more patients to develop BM while living with metastatic breast cancer.

There has been a dramatic shift in the median survival of patients with HER2BC BM. The population in the RTOG database was mostly treated before the availability of HER2-targeted therapies (and newer agents for hormone positive breast cancer). For this population the median survival of the best prognosis patients with ER negative HER2BC was 17.9 months and ER positive HER2BC 22.9 months.2 In a recent unselected series from Memorial Sloan Kettering Cancer Centre the median survival for ER negative HER2BC was 41 months and for ER positive HER2BC 63 months.4
Although BM develop as the first site of metastatic disease in about 2% of patients with metastatic HER2BC, it is more common for BM to arise while a patient is receiving HER2-targeted therapy for ECD. BM may arise (or progress) while ECD is well controlled. If ECD progression occurs with new or progressive BM, the ECD may well be controlled with another line of HER2-targeted whereas the BM cannot be expected to respond with such confidence. Therefore, the challenge in HER2BC is to maintain control of BM over many months to several years, and not simply to offer palliation of symptomatic BM in a dying patient.

**Triple-negative breast cancer (TNBC)**

TNBC also has a particular propensity to metastasize to the brain and the interval from early-stage disease to BM diagnosis is the shortest of all breast cancer phenotypes. In the RTOG database, this was 27.5 months (compared 35.8 months for ER negative HER2BC and 47.4 months for ER positive HER2BC and 54.4 months for ER/PR positive HER2 negative BC). BM as a first site of metastatic disease is more common in TNBC than the other phenotypes. BM from TNBC typically occur in the setting of chemoresistance; that is, the response of intra and extracranial disease to chemotherapy is often poor or of short duration. Because of this there is a substantial competing risk of death from progressive extracranial disease. New agents such as the poly ADP ribose polymerase inhibitors and the immune therapy agents have not altered this devastating pattern in a meaningful way.

The median survival of all patients with TNBC BM is approximately six months, 3-4 months for poor performance status and 6-9 months for good performance status patients. In some recent series median survival is as high as 12 months for the best performance status patients. TNBC BM often respond well to radiotherapy (of any type) but the duration of response is shorter than for other phenotypes. Similarly, local failure after surgical excision can be rapid. It is common for patients to succumb quickly to progressive extracranial disease, early recurrence of BM after therapy, or both. For the majority of patients, the development of TNBC BM represents an immediate threat to quality and duration of life and management is truly palliative in nature.

**Treatment**

The mainstays of first-line therapy for BM are whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) and neurosurgery. SRS and neurosurgery are local therapies that only treat the known BM (gross disease). They have complimentary but overlapping clinical roles. WBRT is regional, treating known BM and any subclinical disease (occult disease). Systemic agents have much less predictable efficacy and are reserved for progressive disease, usually when there is no local therapy option.

**Whole brain radiotherapy**

WBRT delivers a moderate dose of radiotherapy to all of the brain tissue. It is palliative in nature and does not deliver enough radiation dose to effect ‘cure’ of gross disease. WBRT can reduce recurrence in the brain at sites other than the known BM (distant brain failure) by treating occult disease present in the brain at time of WBRT, however the risk of occult breast cancer BM relative to number of known BM and by phenotype is unknown. In prior phase III BM studies of local therapy with or without WBRT, a 50% reduction in distant brain BM was observed after WBRT and this persisted for up to 12 months. Thereafter the rate of distant BM was the same, whether WBRT was given or not. These studies included tumours from any disease site but most commonly non-small cell lung cancer (60%). A retrospective review of breast cancer cases treated with radiosurgery but no WBRT found that the 12-month rate of distant brain failure was highest in TNBC (79%), intermediate for HR+breast cancer (~47%) and least for HER2BC (36%). The rate of failure by lesion number, extracranial disease status and use of systemic therapies was not reported.

Short-term side effects of WBRT include fatigue, total alopecia, headache, nausea, vomiting and transient memory impairment (especially in the elderly). The main long-term side effect is reduced short-term memory. While this can be detected if measured carefully, global cognitive impairment that affects social function is uncommon, particularly in the breast cancer population that does not smoke or have other risk factors for cerebrovascular disease to the same extent as the lung cancer population. WBRT can be given for a second time (ideally at least 12 months after the first course) but is not given repeatedly because with each repeat course the risk of serious neuro-cognitive impairment and frank brain parenchyma necrosis goes up substantially.
Hippocampal-avoidance WBRT (HA-WBRT) is a complex, resource-intensive, intensity-modulated form of WBRT in which the total dose to the bilateral hippocampi is kept as low as possible, ideally less than 10 Gy. The intention of this therapy is to reduce the cognitive toxicity of WBRT, in particular effects on memory. An RTOG phase II study was designed to assess cognition for up to two years after WBRT, but the median survival of the study population was only 6.8 months. The investigators reported cognitive outcomes at four months after WBRT. Cognitive outcomes were better after HA-WBRT compared to an historic control population. Disease response in the brain was not reported.

BM recurrence in the hippocampus was 4.5%. This is weak evidence for the proof of principle that a reduced dose to the hippocampus may protect patients from the transient memory impairment that is known to occur 2–4 months after WBRT. Cognitive outcomes 12 or 24 months after HA-WBRT are not yet known. A cost-benefit analysis, using standardised United States Medicare costs adjusted for Chicago found that HA-WBRT became cost-effective for patients with a median survival of at least 12 months. This model assumed that hippocampal-avoidance WBRT removes all risk of cognitive impairment.

WBRT plays an important palliative role in treatment of multiple symptomatic brain metastases which are not amenable to SRS and/or neurosurgery or when extensive leptomeningeal disease is present.

**Stereotactic radiosurgery**

SRS is a specialised radiation technique in which sophisticated technology is used to deliver 1-5 large radiation doses to small targets, typically up to 3.0cm but potentially up to 4.0cm in size. The high radiation dose delivered with SRS achieves better local control of the treated BM than WBRT but in trials to date, survival is only improved for patients with a solitary BM (compared with use of WBRT alone).

SRS has typically been reserved for treatment of 1 to 3 or maybe four BM, but in recent years there has been a shift towards use of SRS for treatment of multiple lesions, as many as 10 lesions or more. This shift has been facilitated by improvements in SRS technology, however there are no clinical trial data to guide practice with regard to which patients benefit from this approach. Consequently practice varies widely depending on access to SRS technology and the philosophy of the treating medical team. Patient choice can also be a driving factor.

Early toxicities of SRS are headache, nausea and transient worsening of any neurologic deficit due to post-treatment oedema (days to weeks). These are uncommon. There is no hair loss. The main long-term toxicity is radiation necrosis (months to years). This is asymptomatic in 20–30% of cases and symptomatic in 5-10%.

**Neurosurgery**

Neurosurgery is generally reserved for solitary or larger and symptomatic lesions. Modern neurosurgery typically involves a short hospital stay and has low morbidity but not all lesions are amenable to safe resection. Removal of a BM usually leads to prompt resolution of any associated oedema and achieves rapid palliation of headache and any neurologic deficits.

Side effects include neurologic deficit, infection, wound problems and anaesthetic misadventure. The risk of these primarily depends on tumour location, patient age and medical comorbidities.

**Systemic agents**

Historically, clinical trials of systemic therapies have excluded patients with BM. Consequently prospective data on the use of systemic agents for BM that might guide treatment are limited. A few small phase II studies and post hoc analyses of large phase III trials have demonstrated that many systemic agents have activity in the brain. These agents include cytotoxic agents such as capecitabine, platinum agents, microtubule inhibitors, temozolomide, and methotrexate. Targeted therapies with potential CNS activity include lapatinib in combination with capecitabine, TDM-1 in HER2BC, and anecdotally, some novel immune checkpoint inhibitors. There is considerable interest in systemic agents for breast cancer BM but no specific systemic agent is yet approved specifically for this indication. Radiosensitising agents have been combined with WBRT and SRS in an attempt to optimise CNS control but results have been disappointing.
Management

For HER2BC, the need to integrate available therapies over several years is complex. Ideally a multidisciplinary team made up of breast medical and radiation oncologists, neuro-radiation oncologist, neurosurgeon and neuroradiologist would consider any new case of oligometastatic BM and any case of progressive BM. Apart from large BM that need an urgent neurosurgical opinion, there is always time to refer such cases to a larger centre for a multidisciplinary opinion where such a service is not available in the treating centre. Radiology picture archiving and communication systems and email have made this especially feasible.

For poor performance status and TNBC patients, the early input of a palliative care multidisciplinary team is important.

Poor performance status patients

When performance status is poor (Karnofsky < 70), the influence of tumour phenotype on prognosis is less marked and the emphasis of management is to palliate. In this setting asymptomatic BM should be observed. Where performance status is poor because of a large ECD disease burden survival will likely be determined by response of that ECD to any systemic therapy. In this case consideration of best supportive care over any treatment for symptomatic BM is important. Where it is deemed appropriate to offer palliative treatment, available evidence supports the use of WBRT over SRS (whatever the lesion number) as WBRT is quick and simple to instigate at any radiotherapy department, addresses the likely higher rate of occult BM with uncontrolled extracranial disease, and is cost effective.\(^{19,24}\) Chemotherapy is not usually recommended in this setting, given the low chance of disease response and high chance of acute toxicity.

If poor performance status is of short duration and very likely due to a large BM, neurosurgery should be considered as excision is very likely to restore pre-morbid function. Most neurosurgeons would not operate if the predicted survival is in the order of three months or less.

Good performance status HER2BC

Given the long median survival with HER2BM, avoidance of early WBRT is ideal however the ‘correct’ number of BM for which WBRT is best withheld is not known. It is important to acknowledge that WBRT plays an important role treating multiple small lesions (‘miliary’ disease) and when leptomeningeal disease is present. When WBRT is truly indicated, the wish is to give ‘full dose’ WBRT rather than the ‘gentle’ version that is typically used for repeat WBRT, reinforcing the importance of not giving WBRT unless it is truly necessary.

In many cases SRS and/or neurosurgery can be used to treat gross BM over years. These therapies should always be considered before WBRT is given to a well patient. Similarly, it is not always necessary to treat small asymptomatic BM immediately. Surveillance MRI (usually every three months) will demonstrate if the lesions are growing or stable, the former requiring consideration for treatment whereas continued observation is appropriate for the latter. It must be emphasised that this approach pertains to patients who are receiving a targeted HER2 agent or for whom another line of HER2 therapy is available. Good control of ECD is correlated with better CNS disease control (either because of reduced CNS seeding or due to activity of the systemic agent in the CNS or both – the former seems to be the dominant reason for most patients). The best integration of neurosurgery, radiation and systemic therapy for management of de novo BM is unknown and is an important area for future clinical study.

Multiple progressive HER2BM after WBRT can pose a substantial risk to the patient’s life and/or cognition, which can justify use of repeat WBRT. However, a change of HER2-targeted systemic therapy may offer an effective alternative in HER2BC and should be considered prior to repeat WBRT.

Good performance status TNBC

The poor overall prognosis and high probability of early failure in the brain and at distant sites mean that WBRT should provide the basis of treatment. Neurosurgery should be used as necessary for large symptomatic lesions. SRS may be used to try to improve local control of individual lesions but in at least one series, local control of TNBC with SRS was disappointing.\(^{23}\) SRS alone with delay of WBRT is not recommended for this phenotype because of high rates of distant brain failure. The exception may be in the case of one or two de novo BM, absence of any ECD and a long interval
since diagnosis and treatment of the primary breast cancer (a rare scenario in TNBC). Systemic therapy is rarely effective and is not recommended as an alternative to radiation and neurosurgery.

**Conclusion**
Performance status and breast cancer phenotype strongly influence the outcome after the diagnosis of BM and this must be taken into account when making management decisions. A multidisciplinary approach to BM management is encouraged, such that radiological, radiation oncology and neurosurgical input can be combined. There is a pressing need for prospective clinical trials that are breast cancer phenotype-specific. The goal is to better understand how the various treatment modalities may be best sequenced and integrated in order to improve the outcomes of BCBM therapy.
Table 1a* Prognosis scores indicated by the Radiation Therapy Oncology Group (RTOG) Breast Cancer Graded Prognostic Analysis and the MD Anderson Cancer Centre (MDACC) modification

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RTOG = Radiation Therapy Oncology Group; KPS = Karnofsky performance status; MDACC = MD Anderson Cancer Centre, HER2HN = HER2-positive, hormone-negative; HER2HP = HER2-positive, hormone-positive

Table 1b* Radiation Therapy Oncology Group (RTOG) Breast Cancer Graded Prognostic Analysis and MD Anderson Cancer Centre (MDACC) modification scores and overall survival

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* Adapted from references 3 and 13
References


