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Review

Management of breast cancer brain metastases: A practical review

Claire Phillips [a, *], Rosalind Jeffree [b], Mustafa Khasraw [c]

[a] Division of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia
[b] Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, Queensland, Australia
[c] NHMRC Clinical Trials Centre, University of Sydney, NSW, Australia

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ABSTRACT

Brain metastases 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 brain metastases. We review available evidence regarding management of brain metastases, including the limited breast-cancer-specific data. A framework for management according to breast cancer phenotype is proposed.

1. Introduction

Brain metastases (BM) occur in a significant number of cancer patients and are detrimental to quality of life and survival. In the United States alone, the incidence of BM is at least 200 000 cases per year, of which 10–15% occur in breast cancer (BC) patients The incidence of BC BM is increasing when compared with historic series. Improved efficacy of systemic therapy and increased use of magnetic resonance imaging (MRI) screening contribute to this increase [1]. BM are estimated to occur in 25–46% of patients with metastatic hormone negative HER2 receptor negative or 'triple negative' breast cancer (TNBC), 30–55% with metastatic HER2 positive BC (HER2BC) and approximately 10% with metastatic hormone receptor positive HER2 negative BC (HR + BC). Survival by phenotype, without consideration of performance status, is in the order of 6, 20 and 10 months respectively [1–3].

The management of extracranial metastatic breast cancer is now strongly defined by tumour phenotype however this approach is not so well defined for brain metastases, for which there is a paucity of breast cancer-specific evidence. This review seeks to provide a practical approach to this problem.

2. Prognostic factors

Performance status (PS) and tumour phenotype are the dominant prognostic factors. The Radiation Therapy Oncology Group (RTOG) Breast Cancer Graded Prognostic Analysis (BrGPA) [4] is arguably the best recognised prognostic tool. In this tool, age has a relatively small effect on the total score and lesion number is not prognostic. Using their large institution database, investigators at the MD Anderson Cancer Centre (MDACC) published a modification of the BrGPA in which lesion number was found to be a significant prognostic factor, having an effect similar to age [5]. (Tables 1a and 1b) Overall, it can be said that phenotype and PS have a much greater influence on prognosis than lesion number but the true prognostic significance of lesion number remains controversial and the its effect according to phenotype is unknown. The information regarding lesion number in the RTOG and MDACC databases is relatively limited. Cases were scored to have 1 or 1–3 or >3 BM. There is little information regarding the prognostic significance or otherwise of a much larger number of BM.

2.1. Brain metastasis size and location

The effect of lesion size and location on prognosis has not been studied in much detail. When treated with radiation, local control is poorer for larger lesions compared with smaller lesions but the effect on survival has not been studied directly. The brainstem is a special case because of high eloquence of the anatomic site

* Corresponding author. Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC, 3000, Australia.
E-mail address: claire.phillips@petermac.org (C. Phillips).

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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*.

	Score				
	0	0.5	1.0	1.5	2.0
RTOG Breast Graded Prognostic Assessment					
KPS	≤50	60	70–80	90–100	–
Phenotype	TNBC	–	HR + BC	HER2HN	HER2HP
Age (years)	≥60	<60	–	–	–
MDACC revalidation of RTOG Graded Prognostic Analysis					
KPS	≤50	60	70–80	90–100	
Phenotype	TNBC	HR + BC	HER2HN	HER2HP	–
Age (years)	>50	≤50	–	–	–
Number	>3	1–3	–	–	–

RTOG = Radiation Therapy Oncology Group; KPS = Karnofsky performance status; MDACC = MD Anderson Cancer Centre, HER2HN = HER2-positive, hormone-negative; HER2HP = HER2-positive, hormone-positive.
* Adapted from Refs. [4,5].

CNS [1–3]. In addition, the striking success of targeted-HER2 therapies has altered the natural history of the disease by preventing early death from visceral metastases. This 'allows time' for the development of CNS disease in a population that would otherwise already have succumbed such that the median survival after a diagnosis of HER2BC is now remarkably long [14]. In the RTOG population the median survival of the best prognosis patients with ER negative HER2BC was 17.9 months and ER positive HER2BC 22.9 months [4]. In a recent unselected series from Memorial Sloan Kettering Cancer Centre the median survival for ER negative HER2 BC was 41 months and for ER positive HER2BC 63 months [15].

HER2BC BM manifest later than triple-negative BC BM and earlier than HR + BC BM [7]. Hormone-negative HER2BC may develop BM earlier than hormone-positive HER2BC [1]. BM develop as the first site of metastatic disease in about 2% of patients with metastatic HER2BC [16]. More commonly, BM arise whilst the patient is receiving HER2-targeted therapy for ECD. Now that several lines of HER2-targeted therapy are available, BM often arise or progress whilst ECD is well controlled or when its progression may be controlled with another line of HER2-targeted therapy. At least one retrospective series suggests that neurologic death, defined as death from uncontrolled metastatic intracranial disease rather than from systemic disease, may be more common in HER2BC than the other phenotypes [17]. Although evidence has not been published, HER2BC appears tropic to the posterior fossa, often with development of multiple small lesions and often associated with leptomeningeal spread. Over the long median survival of patients with good PS, the disease can be tenacious at this site.

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

RTOG score	Overall survival (months)	MDACC score	Overall survival (months)
0–1.0	3.4	0–1.0	2.6
1.5–2.0	7.7	1.5–2.0	9.2
2.5–3.0	15.1	2.5–3.0	29.9
3.5–4.0	25.3	3.5–4.0	28.8

* Adapted from Refs. [4,5].

precludes surgery and limits radiation dose. A matched-pair cohort analysis by Trifiletti at al [6] found that prognosis was poorer for patients with any brainstem lesion compared with no brainstem lesion, despite equal rates of local tumour control in the brainstem compared with non-brainstem sites (all solid tumour types).

3. Typical disease pattern by phenotype

The probability of developing BM and the likely time along the disease course at which BM will occur, varies according to the tumour phenotype [7]. For the purposes of this discussion the phenotypes are simplified into three broad groups: triple-negative BC (TNBC), HER2BC, and hormone receptor positive, HER2 negative BC (HR + BC).

3.1. Triple-negative breast cancer (TNBC)

TNBC has a particular propensity to metastasize to the brain [3,8,9]. The interval from early-stage disease to BM diagnosis is short, and de novo brain disease is more common than for the other phenotypes. BM from triple-negative BC typically occur in the setting of chemoresistance so the effect of further systemic therapy on extracranial disease (ECD) is often poor or of short duration [10]. It is common for patients to succumb quickly to progressive ECD, early recurrence of BM after radiation therapy, or both. The median survival of all comers with TNBC BM is approximately 6 months, 3–4 months for poor PS and around 9 months for good PS patients. In recent series median survival is as high as 12 months for the best PS patients [4,5,11]. New drugs, such the Poly ADP Ribose Polymerase inhibitors (PARPi) yet to alter this devastating pattern in a meaningful way [11–14].

3.2. HER2-positive disease (HER2BC)

HER2BC has a well-described propensity to metastasize to the

3.3. Hormone-positive, HER2-negative disease (HR + BC)

HR + BC has the least well-defined clinical pattern. BM tend to occur late in the natural history of this phenotype, some time after extracranial metastatic disease has been treated with one or several lines of endocrine therapy. De novo BM are not common. The relatively slow natural history of the HR + BC phenotype is such that rapid death from CNS disease is unusual. The median survival of patients with HR + BC and good PS is 15–17 months [4,10]. It is not known how the array of new systemic agents that are now available for this phenotype may affect median survival in the coming decade.

4. Risk of micrometastatic BM

The risk of occult BM relative to lesion number and by phenotype is unknown. A retrospective review of cases treated with radiosurgery without WBRT in one institution found that the 12-month rate of failure in the brain (distant from sites of radiosurgery) was highest in TNBC (79%), intermediate for HR + BC (~47%) and least for HER2BC (36%). The rate of failure by lesion number, extracranial disease status and use of systemic therapies was not reported [17].