CNS metastases in women with secondary breast cancer

Recommendations for the management of central nervous system (CNS) metastases in women with secondary breast cancer

May 2014 | Incorporates published evidence to February 2013

A CLINICAL PRACTICE GUIDELINE DEVELOPED BY CANCER AUSTRALIA

This document supplements information contained in the Clinical practice guidelines for the management of advanced breast cancer, 2001[1]

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Purpose

This guideline includes statements and recommendations based on available, high-level evidence about the management of metastases in the central nervous system (CNS) in women with secondary breast cancer. The guideline provides health professionals with information designed to assist in making management recommendations for improved patient outcomes.

Endorsed by:

Background

Metastatic breast cancer, also known as secondary breast cancer or advanced breast cancer is defined as invasive breast cancer that has spread from the breast to other parts of the body.

Treatment for women with metastatic breast cancer includes the use of supportive drug treatments to reduce disease-related symptoms and slow the progression of disease, thereby extending and enhancing the woman's quality of life.

Breast cancer is a common cancer associated with central nervous system (CNS) metastases.[2,3] Approximately 10-15% of women living with metastatic breast cancer will be diagnosed with CNS metastases.[2,3] Improvements in the systemic treatment of breast cancer have resulted in an increased incidence of CNS metastases[4] as patients survive long enough to experience progression in the brain.[5] Advances in technology and increasing availability of imaging modalities such as MRI, allow detection of small metastases at follow-up screening examinations.[6] CNS metastases are less common than bone, liver or lung metastases. In most cases, involvement of lungs, liver or bone precedes diagnosis of CNS metastases.[3]

Women with HER2-positive or triple negative breast cancer have been reported to have an increased risk of developing CNS metastases.[5] Other risk factors associated with an increased likelihood of developing CNS metastases include young age (<40 years), pulmonary metastases, BRCA1 mutation carriers and ER-negative tumours.[3]

A systematic review[7] on the management of CNS metastases in women with metastatic breast cancer was undertaken to support the development of this clinical practice guideline. For details on the literature search including research questions, see Evidence from trial or study results.

Clinical practice recommendations and practice points

The recommendations are based on the statements of evidence for the management of central nervous system (CNS) metastases in women with metastatic breast cancer. Practice points and supporting information are also provided to help guide clinical decisions for the management of CNS metastases in women with metastatic breast cancer. Practice points are based on expert opinion when the evidence to make a recommendation is insufficient or where the evidence is outside the scope of the systematic review.

All recommendations have been graded using the National Health and Medical Research Council (NHMRC) evidence grading system.[8] The FORM framework consists of five components (evidence base, consistency, clinical impact, generalisability and applicability) which are used by guideline developers to structure their decisions on how to convey the strength of a recommendation through wording and grading via a considered judgment form. The NHMRC grades (A-D) assigned to the recommendation given are intended to indicate the strength of the body of evidence underpinning the recommendation (refer to Table 1). Appendix 1 provides further detail of the NHMRC FORM grading methodology and the process undertaken in the grading of all recommendations contained in this guideline. See also Appendix 2 for Evidence Statements for Grading the Recommendations.

Table 1: Definition of NHMRC grades of recommendations[8,9]

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Recommendations and practice points should be considered in the context of clinical judgement for each patient.

Considerations should include the absolute benefits and harms of treatments, other treatments used, patient's preferences and quality of life issues. These factors should be discussed with the woman and her family and carer(s), tailored to their preferences for information and decision-making involvement.

The recommendations for the management of central nervous system (CNS) metastases in women with metastatic breast cancer should be considered within a multidisciplinary team setting.

Multidisciplinary care is the best practice approach to providing evidence-based cancer care. Multidisciplinary care (MDC) is an integrated team-based approach to cancer care where medical and allied health care professionals consider all relevant treatment options and collaboratively develop an individual treatment and care plan for each patient.[10] A multidisciplinary team approach to care should be considered for all patients

with advanced breast cancer. The multidisciplinary team for advanced disease should reflect clinical and psychosocial aspects of care.[11]

RECOMMENDATIONS – SURGERY		Grade	References
1	In patients with a single metastasis or limited number of brain metastases, the multidisciplinary team should consider initial surgery or radiosurgery(RS)# (see rec #3) for selected patients*. * Patients with good performance status with a single (or small number of metastases) accessible lesion(s), inactive/well-controlled extra-cranial disease and limited co-morbidities, and patients with raised intracranial pressure or other uncontrolled symptoms.	B	Hart 2011[12] Andrews 2004[13] Aoyama 2006[14] Akyurek 2007[15]
2	In patients who have had local therapy (surgery or RS) for all metastases and have no measurable CNS disease, give consideration to observation alone with an appropriate salvage technique (surgery, RS or WBRT) used on brain progression. Further treatment should be based on individual patterns of relapse.	B	EORTC 22952-26001 (Kocher 2011 and Soffieti 2013)[16,17]
PRACTICE POINTS – SURGERY			**References**
a	Following surgical resection or radiosurgery to brain metastases, monitor the patient with imaging every three months to identify lesions early to maximise management options.		EORTC 22952-26001 (Kocher 2011 and Soffieti 2013)[16,17]
b	For selected patients* with multiple brain metastases, surgical resection of a symptomatic lesion(s) may be considered. * Patients with good performance status with an accessible lesion(s), inactive/well-controlled extra-cranial disease and limited co-morbidities, and patients with raised intracranial pressure or other uncontrolled symptoms, and/or HER2-positive.		
c	Ensure pathological review of surgically resected specimens to confirm histology and hormone and HER2 receptor status, which may differ from the primary tumour.		
d	Anticonvulsant medication is indicated only if a patient has had a seizure.		Mikkelson et al (2010)[18] Quality Standards Subcommittee of the American Academy of Neurology (2000)[19]
e	The minimum effective dose of steroids (dexamethasone) should be used when indicated for the relief of neurological symptoms. Consider avoiding a night-time dose of steroids to minimise the toxicity profile.		Vecht 1994[20]

RECOMMENDATIONS – SURGERY		Grade	References
f	Driving is not recommended for patients with newly diagnosed CNS metastases. Return to driving may be considered based on seizure control, neurological deficit, tumour control and response to therapy. Refer to the local licensing authority for up-to-date information about driving and returning to driving, and any testing that may be required http://www.austroads.com.au/drivers-vehicles/assessing-fitness-to-drive Consider referral to social work services for local transport assistance options.		Austroads 2012[21] Beran 2013[22]
g	Following surgery, radiotherapy or chemotherapy, consider assessment by allied health and/or rehabilitation services to optimise function and quality of life.		
h	The multidisciplinary team should consider use of the Breast-GPA as a tool to assess prognosis and to aid treatment decisions. The Breast-GPA is a prognostic index for breast cancer patients with brain metastases. The GPA was developed following the Radiation Therapy Oncology Group's (RTOG) Recursive Partitioning Analysis as an updated index for patients with brain metastases.		Sperduto 2012[23,24]

Abbreviations: GPA – Graded Prognostic Assessment

[#]Note: the term radiosurgery in these guidelines applies to the use of a single dose (or limited number of doses) of ablative radiotherapy to brain metastases using highly precise immobilisation, dosimetric planning, delivery and verification system and can include (but is not limited to) stereotactic radiosurgery, gamma knife radiosurgery, Cyber knife radiosurgery or radiosurgery delivered using Tomotherapy or IMRT/VMAT.

RECOMMENDATIONS – RADIOTHERAPY		Grade	References
3	On diagnosis of brain metastases, the multidisciplinary team should consider local therapies (radiosurgery or surgery, refer to rec #1) in selected patients*. * Patients with good performance status (KPS score above 70), small number and small size of metastases suitable for localised therapies, adequate haematological reserve and well-controlled primary disease.	B	Hart 2011[12] Andrews 2004[13] Aoyama 2006[14] Akyurek 2007[15]
4	Consider WBRT for patients* who are not eligible for surgery or radiosurgery. * Patients with multiple metastases, uncontrolled extra-cranial	C	Harwood 1977[25] Kurtz 1981[26] Andrews 2004[20]

RECOMMENDATIONS – RADIOTHERAPY		Grade	References
	disease, limited prognosis, or not expected to benefit from radiosurgery or surgery.		
2	In patients who have had local therapy (surgery or RS) for all metastases and have no measurable CNS disease, give consideration to observation alone with an appropriate salvage technique (surgery, RS or WBRT) used on brain progression. Further treatment should be based on individual patterns of relapse.	B	EORTC 22952-26001 (Kocher 2011 and Soffieti 2013)[16,17]
PRACTICE POINTS – RADIOTHERAPY			**References**
i	If adjuvant WBRT is delayed following local therapy of limited brain metastases, monitor the patient with imaging every three months.		EORTC 22952-26001 (Kocher 2011 and Soffieti 2013)[16,17]
j	Patients with poor performance status who are considered unlikely to benefit from local therapies or WBRT should be referred to specialist palliative care services, based on a determination of their prognosis and complexity of needs.		NICE guidelines[27]
e	The minimum effective dose of steroids (dexamethasone) should be used when indicated for the relief of neurological symptoms. Consider avoiding a night-time dose of steroids to minimise the toxicity profile.		Vecht 1994[20]
f	Driving is not recommended for patients with newly diagnosed CNS metastases. Return to driving may be considered based on seizure control, neurological deficit, tumour control and response to therapy. Refer to the local licensing authority for up-to-date information about driving and returning to driving, and any testing that may be required http://www.austroads.com.au/drivers-vehicles/assessing-fitness-to-drive Consider referral to social work services for local transport assistance options.		Austroads 2012[21] Beran 2013[22]
g	Following surgery, radiotherapy or chemotherapy, consider assessment by allied health and/or rehabilitation services to optimise function and quality of life.		
h	The multidisciplinary team should consider use of the Breast-GPA as a tool to assess prognosis and to aid treatment decisions. The Breast-GPA is a prognostic index for breast cancer patients with brain metastases. The GPA was developed following the Radiation Therapy Oncology Group's (RTOG) Recursive Partitioning Analysis as an updated index for patients with brain metastases.		Sperduto 2012[23], [24]

Abbreviations: CNS – central nervous system; GPA – Graded Prognostic Assessment; MRI – magnetic resonance imaging; RS –radiosurgery*; WBRT – whole brain radiotherapy; KPS – Karnofsky Performance Status.

*Note: the term radiosurgery (RS) in these guidelines applies to the use of a single dose (or limited number of doses) of ablative radiotherapy to brain metastases using highly precise immobilisation, dosimetric planning, delivery and verification system and can include (but is not limited to) stereotactic radiosurgery, gamma knife radiosurgery, Cyber knife radiosurgery or radiosurgery delivered using Tomotherapy or IMRT/VMAT.

RECOMMENDATIONS – SYSTEMIC THERAPIES		Grade	References
5	Avoid routine use of chemotherapy with WBRT in patients with newly diagnosed brain metastases.	C	Mehta 2010[28]
6	To achieve optimal control of extra-cranial disease, HER2-targeted therapies (such as trastuzumab) should be started or continued in HER2-positive patients after the diagnosis of brain metastases.	C	Pestalozzi 2013[29] Bartsch 2007[30] Church 2008[31] Dawood 2008[32] Park 2009[33] Le Scodan 2011[34] HERA 2013[29]
7	HER2-positive patients with progressive or residual disease following local therapy and trastuzumab may be offered lapatinib in combination with capecitabine.	C	Lin 2009[35]
PRACTICE POINTS – SYSTEMIC THERAPIES			**References**
k	Consider lapatinib and capecitabine for initial treatment for HER2-positive patients who develop brain metastases without mass effect. Close observation of response is appropriate, and radiotherapy or surgery may be offered on progression.		Bachelot 2013[36]
l	For patients with progressive brain metastases who are fit for further chemotherapy, platinum-based agents **or** high dose methotrexate may be considered.		
m	Only start anticonvulsant medication if a patient has had a seizure.		Mikkelson et al (2010)[18] Quality Standards Subcommittee of the American Academy of Neurology (2000)[19]

RECOMMENDATIONS – SYSTEMIC THERAPIES		Grade	References
e	The minimum effective dose of steroids (dexamethasone) should be used when indicated for the relief of neurological symptoms. Consider avoiding a night-time dose of steroids to minimise the toxicity profile.		Vecht 1994[20]
f	Driving is not recommended for patients with newly diagnosed CNS metastases. Return to driving may be considered based on seizure control, neurological deficit, tumour control and response to therapy. Refer to the local licensing authority for up-to-date information about driving and returning to driving, and any testing that may be required (include link) Consider referral to social work services for local transport assistance options.		Austroads 2012[21] Beran 2013[22]
g	Following surgery, radiotherapy or chemotherapy, consider assessment by allied health and/or rehabilitation services to optimise function and quality of life.		
h	The multidisciplinary team should consider use of the Breast-GPA as a tool to assess prognosis and to aid treatment decisions. The Breast-GPA is a prognostic index for breast cancer patients with brain metastases. The GPA was developed following the Radiation Therapy Oncology Group's (RTOG) Recursive Partitioning Analysis as an updated index for patients with brain metastases.		Sperduto 2012[23], [24]

Abbreviations: GPA – Graded Prognostic Assessment; HER2 – human epidermal growth factor receptor 2; WBRT – whole brain radiotherapy

RECOMMENDATIONS – SPINAL CORD COMPRESSION		Grade	References
8	In patients* with symptomatic spinal cord compression caused by metastatic disease, circumferential surgical decompression should be performed (within 24 hours), with or without fusion, followed by radiotherapy. *Patients who are acceptable surgical candidates and have expected survival of at least three months.	B	Patchell 2005[40]
9	Start external beam radiotherapy as soon as possible for patients considered unsuitable for surgery.	B	Loblaw 2005[41]
PRACTICE POINTS – SPINAL CORD COMPRESSION			**References**
n	Dexamethasone should be started on suspicion of spinal cord compression and while awaiting assessment. Monitor closely for side effects and taper		Vecht 1989[37]

RECOMMENDATIONS – SPINAL CORD COMPRESSION		Grade	References
	after radiotherapy.		Sorensen 1994[38] Heimdal 1992[39]
o	Spinal cord compression is a medical emergency and urgent multidisciplinary management is advisable.		Loblaw 2005[41]
p	Consider use of whole spine MRI to investigate suspected spinal cord compression.		Loblaw 2005[41]
g	Following surgery or radiotherapy consider assessment by allied health and/or rehabilitation services to optimise function and quality of life.		
q	Patients considered unsuitable for disease-specific treatment, or with progression of neurological deficit after treatment, require input from specialist palliative care services based on a determination of their long-term survival and complexity of needs. Consider seeking advice from a spinal injuries unit for appropriate care needs of patients with spinal cord compression.		NICE guidelines[27]

Abbreviations: MRI – magnetic resonance imaging

Statements of evidence

The statements of evidence are based on evidence identified in the Cancer Australia systematic review[7] as well as primary studies included in the identified Cochrane reviews. Further details are available in the Cancer Australia systematic review and the Evidence from trial or study results section. The systematic review focused on evidence for the management of CNS metastases in women with metastatic breast cancer, however some studies were included that had patient populations with various primary tumours.

No.	STATEMENTS OF EVIDENCE – SURGERY	Reference	Level of evidence[8]
	Overall survival		
1	Pooled data from three RCTs including patients with multiple cancer primaries, showed no significant difference in overall survival among patients having surgery and WBRT compared to patients having WBRT alone.	Hart 2011[12]	I
2	Mortality at 30 days was not significantly different in patients who had surgery and WBRT compared to patients who had WBRT alone in three RCTs (I^2=0%).	Mintz 1996[42]	II
	Functionally independent survival / neurological death		
3	In one RCT, compared to WBRT alone, surgery and WBRT was found to increase the duration of Functionally Independent Survival and may reduce the risk of death due to neurological cause.	Patchell 1990[43]	II
	Adverse effects		
4	The risk of adverse effects was not significantly different among patients who had surgical resection and WBRT compared to patients who had WBRT alone.	Vecht 1993[44] Mintz 1996[42]	II

Abbreviations: RCT – randomised controlled trial; WBRT – whole brain radiotherapy

No.	STATEMENTS OF EVIDENCE – RADIOTHERAPY	Reference	Level of evidence
Radiosurgery*			
	Overall survival		
1	Among patients with 1-4 brain metastases from various primary tumours, no significant survival benefit was demonstrated for WBRT plus stereotactic radiosurgery boost versus WBRT alone.	Tsao 2012[45]	I
2	Among patients with a single, un-resectable brain metastasis, improved survival was observed for WBRT plus SRS (6.5 months)	Andrews 2004[13]	II

No.	STATEMENTS OF EVIDENCE – RADIOTHERAPY	Reference	Level of evidence
	compared to WBRT alone (4.9 months).		
	Recurrence		
3	WBRT plus radiosurgery boost may improve local disease control in selected patients, compared to WBRT alone.	Andrews 2004[13] Kondziolka 1999[46]	II
4	One year local control rates were 79% for patients receiving SRS as initial treatment, and 77% for patients receiving salvage SRS after WBRT treatment. Rates of distant brain metastases-free survival were not statistically different between patients receiving SRS alone as initial treatment (64%) compared to SRS as salvage treatment after initial WBRT (57%) at one year.	Akyurek 2007[15]	IV
WBRT			
	Overall survival		
5	Among patients who have had prior radiosurgery or surgery, similar rates of survival are found following WBRT or observation.	Kocher 2011(EORTC 22952-2600)[16]	II
6	Among patients with 1-4 brain metastases, no significant difference between radiosurgery alone and radiosurgery plus WBRT was observed.	Tsao 2012[45]	I
7	Among patients treated with WBRT, improved survival rates were associated with KPS ≥70, age less than 65 years, controlled primary disease, and no extra-cranial metastases. Shorter median survival rates were associated with KPS <70.	Gaspar1997[47]	IV
8	Analysis of breast cancer patients treated with different WBRT regimens as the primary therapy for brain metastases identified that improved survival was significantly associated with KPS score ≥70, lower RPA class, lower number of brain metastases (1-3) and no extra-cranial metastases on multivariate analyses.	Rades 2011[48] Rades 2007[49]	IV
	Recurrence		
9	Compared to observation alone, WBRT reduced the probability of intra-cranial progression at initial sites and new sites in the brain following surgery or radiosurgery. WBRT also reduced the need for salvage treatment.	Kocher (EORTC [16]	II

No.	STATEMENTS OF EVIDENCE – RADIOTHERAPY	Reference	Level of evidence
10	Radiosurgery plus WBRT conferred a significant benefit in local control (p=<0.0001) and distant brain control (p=<0.00001) compared to radiosurgery alone in three RCTs. Retrospective analysis of breast cancer patients with brain metastases observed no significant difference between SRS alone and SRS plus WBRT.	Tsao 2012[45] Aoyama 2006[14] Chang 2009[50] Kocher 2011[16]	II
11	WBRT plus SRS was significantly associated with improved brain tumour control (p=0.002) and less frequent need for salvage treatment compared to SRS alone.	Aoyama 2006[14]	II
12	Among patients with a single brain metastasis, compared with surgical resection alone, WBRT following surgery confers significant reduction in recurrence in the brain (18% vs. 70%, p=<0.001). Recurrence was less frequent at the original site and at distant sites within the brain (p=0.001). The time to any recurrence was significantly longer among the group who had post-operative WBRT.	Patchell 1998[51]	II
13	Retrospective analysis comparing SRS as initial treatment to SRS as salvage treatment following WBRT observed similar rates of distant brain metastases-free survival (64% and 57% at one year). Of the 34 patients treated with initial SRS alone, ten (29%) later received WBRT. The one-year freedom from WBRT was 62%.	Akyurek 2007[15]	IV
	Quality of life		
14	Palliative WBRT is associated with significant improvements in intracranial pressure (p=<0.01), headache (p=<0.001) and sensory dysfunction (p=<0.01). Improvements (though not significant) were also observed for motor function and convulsions.	Yaneva 2006[52]	III
15	One prospective trial observed a significant improvement in global health-related quality of life scores at 9 months among patients who had observation only following local therapy (surgery or SRS) compared to patients who had adjuvant WBRT (p=0.0148). Included patients had 1-3 brain metastases from various primary tumours. Improved mean scores were reported for physical, role and cognitive functioning using the EORTC-C30 scale. No differences were found at any other time points.	Soffietti (EORTC [17]	II
Altered fractionation WBRT			
	Overall survival		
16	No survival benefit was shown in altered fractionation WBRT compared to the control dose (30 Gy in 10 daily fractions), although	Tsao 2012[45]	I

No.	STATEMENTS OF EVIDENCE – RADIOTHERAPY	Reference	Level of evidence
	one RCT (with 19% of included patients have brain metastases from breast cancer) found a significant difference favouring the control dose, compared to 12 Gy in two fractions.	Rades 2007[49] Rades and Lohrynska 2007[53] Rades 2011[48] Priestman 1996[54]	
	Neurological function		
17	Significant improvement in neurological function is associated with the standard WBRT regimen (30 Gy in 10 fractions) compared to a lower dose (p=0.03). There was no significant difference in neurological function for those treated with a higher dose compared to the standard dose.	Tsao 2012[45] Borgelt 1980[55] Borgelt 1981[56] Kurtz 1981[26]	I
	Recurrence		
18	Similar rates of progression of intra-cerebral disease were observed among patients receiving a WBRT regimen of 5 fractions of 4 Gy (12%) and patients receiving higher doses (9%).	Rades & Lohrynska 2007[53]	IV
	Adverse events		
19	Similar rates of adverse events (including grade three toxicity) were observed in patients receiving a standard WBRT regimen of 30 Gy in 10 fractions compared to higher doses (45 Gy in 15 fractions and 40 Gy in 20 fractions) or shorter schedules (20 Gy in 5 fractions).	Rades 2007[49]; Rades & Lohrynska 2007[53]	IV
WBRT plus radiosensitisers			
20	The addition of radiosensitisers to WBRT compared to WBRT alone did not confer any benefit in rates of survival or brain tumour response.	Tsao 2012[45]	I
Subgroups			
21	Following WBRT, HER2-positive status is significantly associated with improved survival compared to HER2-negative status, hormone receptor-positive or triple receptor-negative disease.	Wolstenholme 2008[57] Dawood 2010[58]	IV

Abbreviations: EORTC – European Organisation for Research and Treatment of Cancer; HER2 – human epidermal growth factor receptor 2; KPS – Karnofsky Performance Status; SRS – stereotactic radiosurgery; WBRT – whole brain radiotherapy

No.	STATEMENTS OF EVIDENCE – SYSTEMIC THERAPIES	Reference	Level of evidence
Chemotherapy			
	Overall survival		
1	Among patients with newly diagnosed brain metastases from various primary tumours, the addition of chemotherapy to WBRT added no benefit for overall survival or neurologic progression compared to WBRT alone.	Mehta 2010[28]	I
2	Two studies investigating the use of methotrexate alone or in combination with other chemotherapies in patients with brain metastases from breast cancer observed median overall survival of 6.5 months and 6.9 months.	Bazan 2011[59] Jacot 2010[60]	IV
	Progression free survival / time to progression		
3	In a systematic review, six studies investigated temozolomide alone or in combination with other chemotherapies in patients with recurrent/progressive metastatic brain disease from various primary tumours. A median time to recurrence or progression after re-treatment of 2–4 months was observed. Some patients had an objective radiographic response and/or improvement in functional status after chemotherapy treatment.	Ammirati 2010[61]	II
	Adverse events		
4	Commonly reported adverse events of various chemotherapies include thrombocytopenia, nausea, vomiting, headache, fatigue, leukopenia, anaemia and neutropenia.	Bazan 2011[59] Christodoulou 2005[62] Freedman 2011[63] Melisko 2009[64] Murphy 2009[65] Rivera 2006[66] Siena 2010[67]	III

No.	STATEMENTS OF EVIDENCE – SYSTEMIC THERAPIES	Reference	Level of evidence
Trastuzumab			
	Overall survival		
5	For women with HER2-positive breast cancer, increased survival was reported among those treated with trastuzumab or who continued trastuzumab after diagnosis of CNS metastases.	Bartsch 2007[30] Church 2008[31] Dawood 2008[32] Park 2009[33] Le Scodan 2011[34]	IV
6	In hormone receptor-negative, HER2-positive patients, the median survival after a brain metastases diagnosis was significantly longer in patients given trastuzumab after brain metastases compared with no trastuzumab treatment after brain metastases diagnosis.	Park 2009[33]	IV
7	Survival was significantly longer among HER2-positive patients receiving trastuzumab compared with HER2-negative patients (p=0.027).	Church 2008[31]	IV
	Incidence of CNS metastases as first relapse site		
8	Compared to no treatment, one year of trastuzumab for patients with HER2-positive early breast cancer significantly reduces the cumulative incidence of non-CNS relapses as the first recurrent event (p=<0.0001), however the frequency of CNS relapse did not differ.	HERA trial[29]	IV
	Time to progression		
9	Among HER2-positive breast cancer patients, trastuzumab was significantly associated with longer time to progression than no trastuzumab treatment.	Park 2009[33]	IV
Lapatinib and capecitabine: previously untreated CNS metastases^			
	Overall survival		
10	Among HER2-positive patients treated with lapatinib and capecitabine, a median overall survival of 17 months was observed, with 90.9% overall survival at six months.	Bachelot 2013[36] (LANDSCAPE)	III
	Response rate		
11	Of HER2-positive patients taking lapatinib and capecitabine, 65.9%	Bachelot	III

No.	STATEMENTS OF EVIDENCE – SYSTEMIC THERAPIES	Reference	Level of evidence
	had an objective CNS response (n=29, all partial responses).	2013[36] (LANDSCAPE)	
12	The rates of objective CNS responses following lapatinib and capecitabine were similar among patients previously treated with trastuzumab compared to no previous trastuzumab treatment.	Bachelot 2013[36] (LANDSCAPE)	III
	Volumetric reduction		
13	A CNS volumetric reduction of 80% or greater was observed in nine HER2-positive patients (20%) taking lapatinib and capecitabine. 84% of patients (n=37) had a reduction in tumour volume from baseline measurements.	Bachelot 2013[36] (LANDSCAPE)	III
	Time to progression		
14	Median time to progression for HER2-positive patients treated with lapatinib and capecitabine was 5.5 months. The median time to radiotherapy was 8.3 months. The reported sites of first progression were: • CNS alone in 78% (n=32) • Extra-CNS alone in 5% (n=2) • Both CNS and extra-CNS in 12% (n=5).	Bachelot 2013[36] (LANDSCAPE)	III
	Adverse events		
15	Of HER2-positive patients treated with lapatinib and capecitabine, approximately half experienced at least one grade 3 or grade 4 adverse event, most commonly diarrhoea and hand-foot syndrome.	Bachelot 2013[36] (LANDSCAPE)	III
Lapatinib and capecitabine: previously treated CNS metastases^			
	Overall survival		
16	Treatment with lapatinib and capecitabine is significantly associated with improved median survival after brain progression compared to trastuzumab-based therapy alone (27.9 months vs. 16.7 months, p=0.01). At a median of 26 months follow-up, overall survival was not reached for the 6 patients who received lapatinib and capecitabine as the first systemic therapy after diagnosis of brain metastases.	Metro 2011[68]	IV
	Response rate		
17	Among HER2-positive patients previously treated with WBRT and chemotherapy plus trastuzumab, lapatinib in combination with capecitabine was shown to have higher response rates than lapatinib alone. No objective responses were observed in patients who received lapatinib with topotecan.	Lin 2009[35] Lin 2011[69]	III

No.	STATEMENTS OF EVIDENCE – SYSTEMIC THERAPIES	Reference	Level of evidence
	Adverse events		
18	Among HER2-positive breast cancer patients receiving lapatinib the most commonly reported adverse events as diarrhoea, fatigue, rash, headache and vomiting.	Lin 2008[70] Lin 2009[35]	III
19	Among HER2-positive breast cancer patients receiving lapatinib in combination with capecitabine, the most commonly reported adverse events were diarrhoea, palmar-plantar erythrodysesthesia, nausea and fatigue.	Lin 2009[35] Lin 2011[69]	III
20	A prospective study comparing lapatinib and capecitabine to lapatinib and topotecan closed accrual of patients to the lapatinib and topotecan arm due to tolerability issues in combination with a lack of early efficacy.	Lin 2011[69]	III

Abbreviations: CNS – central nervous system; CDDP - cis-diamminedichloroplatinum (Cisplatin); HER2 – human epidermal growth factor receptor 2; KPS – Karnofsky Performance Status; SRS – stereotactic radiosurgery; WBRT – whole brain radiotherapy

No.	STATEMENTS OF EVIDENCE – SPINAL CORD COMPRESSION	Reference	Level of evidence
	Symptoms of spinal cord compression		
1	Frequently observed symptoms of spinal cord compression include back pain, motor weakness, sensory changes and bladder dysfunction.	Loblaw 2005[41]	II
	Investigation of suspected spinal cord compression		
2	Three case series and a retrospective review on the accuracy of MRI, reported sensitivity from 0.44 to 0.93 and specificity from 0.90 to 0.98.	Husband 2001[71] Hagenau 1987[72] Carmody 1989[73] Li 1988[74]	IV
	Use of corticosteroids		
3	In an RCT comparing a 100mg to 10mg initial dose of dexamethasone, there were no significant differences in pain, ambulation or bladder function. All patients were treated with	Vecht 1989[37]	II

No.	STATEMENTS OF EVIDENCE – SPINAL CORD COMPRESSION	Reference	Level of evidence
	radiotherapy and maintenance dexamethasone of 16mg/d orally after the initial treatment.		
4	In one RCT comparing high-dose dexamethasone with no dexamethasone as adjunct to radiotherapy a successful treatment result, defined as gait function after treatment, was achieved in 81% of patients treated with dexamethasone compared with 63% of patients not receiving dexamethasone. In a subgroup analysis of breast cancer patients a successful treatment result was achieved in 94% of dexamethasone patients compared with 69% of patients without dexamethasone, although difference was not significant.	Sorensen 1994[38]	II
5	Life table analysis demonstrated a higher percentage of patients receiving dexamethasone surviving with gait function during 1 year compared with those not receiving dexamethasone (p=0.046).	Sorensen 1994[38]	II
	Surgery for spinal cord compression		
6	One RCT comparing surgery followed by radiotherapy (n=50) to radiotherapy alone (n=51) found significantly more patients in the surgical arm were able to walk after treatment compared to those receiving radiotherapy (84% vs. 57%, odds ratio 6.2, p=0.001). Patients treated with surgery maintained the ability to walk significantly longer than those treated with radiotherapy alone (median 122 days vs. 13 days, p=0.003).	Patchell 2005[40]	II
7	Thirty-day mortality rates were 6% in the surgical arm compared to 14% in the radiotherapy arm (p=0.32). The median hospital stay was 10 days for patients in both treatment arms (p=0.86).	Patchell 2005[40]	II
8	The RCT found surgical treatment was significantly associated with the maintenance of continence, muscle strength, functional ability and increased survival times.	Patchell 2005[40]	II
	Radiotherapy		
9	Various doses of radiotherapy to treat spinal cord compression were investigated in eight studies. No regimens demonstrated higher rates of ambulation compared with another.	Maranzano 1995[75]; Maranzano 1996[76] Helweg-Larsen 1996[77]	III-2 - IV

No.	STATEMENTS OF EVIDENCE – SPINAL CORD COMPRESSION	Reference	Level of evidence
		Maranzano 1998[78] Greenberg 1980[79] Kovner 1999[80] Ampil 1995[81] Rades 2002[82]	

* Note: the term radiosurgery in these guidelines applies to the use of a single dose (or limited number of doses) of ablative radiotherapy to brain metastases using highly precise immobilisation, dosimetric planning, delivery and verification system and can include (but is not limited to) stereotactic radiosurgery, gamma knife radiosurgery, Cyber knife radiosurgery or radiosurgery delivered using Tomotherapy or IMRT/VMAT.

^ Based on a trial population not treated with WBRT or SRS

^ Based on trial populations who may have been treated with WBRT or SRS

Evidence from trial or study results

A Cancer Australia systematic review[7] on the management of CNS metastases in women with metastatic breast cancer was undertaken, with available evidence published between January 2001 and April 2012.

A systematic literature search was conducted in Medline, Embase and Pubmed to identify relevant studies which addressed the inclusion criteria. A search of conference websites was also conducted, including the American Society of Clinical Oncology and San Antonio Breast Cancer Symposium. The search undertaken for the systematic review identified a conference abstract on the LANDSCAPE study; a full paper for this study was published in February 2013[36] and was included in the systematic review and is referred to in these guidelines.

The systematic review focused on evidence for the management of CNS metastases in women with metastatic breast cancer not CNS metastases from various primary tumours. However, some studies included in the systematic review had patient populations with mixed primary tumours and where available, the results specific to the breast cancer populations of these studies were reported. The systematic review included evidence reported for metastases in the brain and in the spinal cord (including metastatic spinal cord compression), and for both parenchymal and meningeal (leptomeningeal) metastases.

A total of 1315 citations were identified. Following application of the exclusion criteria, a total of 108 citations and one abstract were identified as eligible for the current review.

Fifty-seven citations addressed the primary research questions:

1. What is the effectiveness of surgery in the management of CNS metastases from breast cancer?
2. What is the effectiveness of radiotherapy in the management of CNS metastases from breast cancer?
3. What is the effectiveness of systemic therapies in the management of CNS metastases from breast cancer?
4. What is the effectiveness of combinations of the above treatments in the management of CNS metastases from breast cancer?
5. Are there specific requirements for the management of the sub-group of patients diagnosed with asymptomatic CNS metastases?

In addition, 51 citations addressed other issues:

- The incidence/prevalence of CNS metastases in breast cancer patients, specifically those with HER2-positive and triple negative breast cancer.
- The course, nature and extent of neurocognitive and psychological impairments in CNS metastases in metastatic breast cancer, and how these impairments are assessed.
- The impacts of these impairments on everyday functioning and quality of life of women with CNS metastases from breast cancer including restrictions on driving, seizures.
- The identification of effective strategies for providing supportive and palliative care to women with CNS metastases from breast cancer.
- Multidisciplinary care including involvement of allied health such as physiotherapy and rehabilitation,

psychology, care coordinators, social work, speech pathology.

- Measurements of Quality of Life (QoL).
- Meningeal metastases in women with metastatic breast cancer.
- Use of other medications including steroids and anticonvulsants.

There were few large prospective trials identified that investigated the use of surgery, radiotherapy, systemic therapies or multimodal treatment for the management of CNS metastases in women with metastatic breast cancer, specifically from breast cancer. Most of the relevant trial data were limited to small breast cancer patient cohorts or retrospective studies.

The systematic review identified seven systematic reviews, including two Cochrane reviews. These systematic reviews included evidence for management for CNS metastases in populations of mixed primary cancers. While they were not specific to the management of CNS metastases from breast cancer**,** the Cochrane reviews and included primary studies have been used as primary references in the recommendations and statements of evidence of this clinical practice guideline due to the limited high quality evidence identified for the management of CNS metastases from breast cancer. Details of the Cochrane reviews and the included primary studies are outlined in Evidence from trial or study results.

Refer to the Cancer Australia systematic review[7] for detailed evidence from studies on the management of CNS metastases in patients with metastatic breast cancer.

Evidence from trial or study results: surgery

A Cochrane review by Hart et al 2011[12] assessed if resection of single brain metastasis followed by WBRT holds any clinical advantage over WBRT alone. Three RCTs were identified that included a total of 195 patients. Of note, the three RCTs by Mintz et al 1996,[42] Patchell et al 1990[43] and Vetch et al 1993,[44] included in the Cochrane review were published before 2001. All studies included populations with mixed primary tumours, including one study (Patchell 1990) with less than ten breast cancer patients. No results were reported by Hart et al for breast cancer patients separately.

Two retrospective studies on surgery among breast cancer patients were identified.

Patient selection

The surgical trials identified in the Hart et al Cochrane review were limited to patients with good performance status, with a single or limited number (1-3) of accessible lesions, inactive or well-controlled primary disease and limited co-morbidities, and patients with raised intracranial pressure or other uncontrolled symptoms. Generally, patients were considered unsuitable for surgery when there were multiple lesions, when the lesion was surgically inaccessible, or patients with active primary disease or significant comorbidities.[12]

Overall survival

The Hart et al Cochrane review found no significant difference in survival (HR 0.72, 95% CI 0.34 to 1.55, random effects, p = 0.40) although there was heterogeneity between trials (I^2 = 83%).[12] There was some indication that surgery and WBRT might reduce the risk of deaths due to neurological cause. The Hart et al Cochrane review reported that those treated with surgery and WBRT were less likely to die from neurological causes although this did not reach statistical significance (RR 0.68, 95% CI 0.43 to 1.09, p=0.11; three trials).[12] Mortality at 30 days was similar in both arms of each trial.

Although no statistically significant difference between surgery plus WBRT and WBRT alone was observed, the Patchell 1990[43] and Vecht 1993[44] trials were in favour of surgery while the Mintz 1996[42] trial was in favour of WBRT alone. The Patchell 1990 trial included a majority of patients with non-small cell lung cancer, which is highly radio-resistant and would not be expected to respond well to WBRT. There may have been selection bias in this trial also, as patients were selected for surgery by a single neurosurgeon. The Mintz 1996 trial included patients with a poorer KPS, and a larger proportion of patients had extra-cranial metastases.[42]

Functionally independent survival

One trial in the Hart et al Cochrane review (Patchell 1990) reported results on functional independent survival.[43] The trial found that patients treated by surgery and WBRT maintained their functional independence for longer than those treated by WBRT alone (HR 0.42, 95% CI 0.22 to 0.82, p=0.01).[43]

Adverse events

The results of each trial identified in the Hart et al Cochrane review found that neither surgery in combination with WBRT or WBRT alone was more likely to cause adverse effects (RR 1.27, 95% CI 0.77 to 2.09, p=0.35).[12] It is noted that the reporting of the trials did not allow for clustering of adverse effects within patients. Commonly reported adverse events for patients in the surgical arms of the trials included respiratory problems, haematoma and infections.

Evidence from trial or study results: radiotherapy

RADIOSURGERY±

A Cochrane review by Tsao et al (2012) assessed the effectiveness of whole brain radiotherapy (WBRT) either alone or in combination with other therapies in adult participants with newly diagnosed multiple brain metastases.[45] The review updated a previous 2006 Cochrane review. Nine new RCTs involving 1420 participants were added to the updated review. The updated review included a total of 39 trials involving 10,835 participants with mixed primary tumours. Results are presented under stereotactic radiosurgery (SRS), WBRT, altered fractionations and radiosensitizers.[45]

The Tsao et al 2012 Cochrane review compared WBRT plus radiosurgery versus WBRT.[45] Three trials (Andrews 2004,[13] Chougule 2000, Kondziolka 1999[46]) examining the use of WBRT with or without radiosurgery boost for up to four brain metastases (469 participants in total) were included. Two trials were fully published (Andrews 2004,[13] Kondziolka 1999[46]) and included populations of mixed primary tumours. In addition, five retrospective analyses reporting results of radiosurgery in patients with central nervous (CNS) metastases were identified; three are discussed here.[14,15,83]

Overall survival

Pooled results of two randomised controlled trials comparing WBRT plus radiosurgery and WBRT alone (Andrews 2004[19] and Kondziolka 1999[46] showed no difference in six-month survival (p=0.24).[45] The Andrews trial reported improved survival (p=0.0393) for a subset of patients with a single, surgically un-resectable brain metastasis treated with WBRT and radiosurgery (6.5 months) compared to WBRT alone (4.9 months).

Kased et al 2009 retrospectively reviewed 176 patients who underwent gamma knife stereotactic radiosurgery (SRS) for brain metastases from breast cancer.[83] Among the 95 patients with newly diagnosed brain metastases, median survival time was 16 months. Among the 81 patients treated for recurrent brain metastases, median survival time was 11.7 months. In patients treated with SRS alone initially, survival was 17.1 months compared to 15.9 months for patients treated with SRS and upfront WBRT (p=0.20). Factors associated with longer survival included age less than 50 years, primary tumour control, ER positivity, and HER2-positive disease.[83]

Akyurek 2007 retrospectively reviewed 49 breast cancer patients who underwent SRS for brain metastases; 34 patients as primary treatment, and 15 as salvage treatment following prior WBRT.[15] The median overall survival for patients receiving SRS as primary treatment was 25 months and 14 months for patients receiving SRS as salvage treatment.

Recurrence

The Tsao et al 2012 Cochrane review pooled data for local brain control at one year from two studies (Andrews 2004 and Kondziolka 1999).[13,46] A statistically significant improvement in local brain control favouring WBRT and radiosurgery boost compared to WBRT alone was observed (RR 1.20, p=0.003).

The Kondziolka 1999 trial also reported median time to local brain failure of 6 months for patients receiving WBRT alone in comparison to 36 months after WBRT and radiosurgery.[46] The Andrews trial found no statistically significant difference (p=0.1278) regarding overall time to intracranial tumour progression.[13]

A retrospective analysis of breast cancer patients (Akyurek 2007) reported on local brain tumour control.[15] One year local control rates were 79% for patients receiving SRS as initial treatment, and 77% for patients receiving salvage SRS after WBRT treatment. Two-year local control rates were 49% for the group receiving SRS alone and 46% for the SRS salvage treatment group. The difference was not statistically significant (p=0.99).[15] Akyurek 2007 also reported distant brain metastases-free survival; at one year, the survival rate was 69% in the 49 patients receiving either initial SRS alone or salvage SRS.[15] The one-year distant brain metastases-free survival rate was 64% among the group receiving initial SRS compared to 57% for the group receiving SRS salvage treatment. The difference was not statistically significant (p=0.62).

Kased et al 2009 reported on 176 patients who underwent SRS for brain metastases from brain cancer.[83] No significant difference was observed in freedom from progression between SRS alone and SRS with WBRT in the newly diagnosed patients. The median freedom from new brain metastases was 14.8 months for patients treated with SRS alone, compared to 11.3 months for patients in the SRS and WBRT arm (p=0.83).[83]

Neurologic function

Andrews 2004 reported that KPS was improved at six months in 13% of patients treated with WBRT and radiosurgery, compared to 4% of patients treated with WBRT alone (p=0.0331).[13] Mental status as measured using a mini-mental status examination did not show a significant difference.

Adverse effects

Tsao 2009 and the updated review in 2012 reported adverse effects identified in the Andrews 2004 trial.[84] In this trial, early and late toxic effects did not differ greatly for patients receiving WBRT alone compared to WBRT plus radiosurgery. More patients in the WBRT plus radiosurgery arm experienced acute grade three and four toxicity (4 of 160 patients), compared to those receiving WBRT alone (0 of 166 patients). More patients in the WBRT plus radiosurgery arm experienced late grade three and four toxicity (6 of 160 patients) compared to those receiving WBRT alone (3 of 166 patients).[13]

WHOLE BRAIN RADIOTHERAPY (WBRT)

The Cochrane review by Tsao et al (2012) identified three RCTs comparing radiosurgery alone to radiosurgery plus WBRT.[45] The trials (Aoyama 2006,[14] Chang 2009,[50] Kocher 2011[16]) included patients with up to three or four brain metastases from mixed primary tumours.

The systematic review by Kalkanis et al 2010[85] identified one RCT (Patchell et al 1998)[51] and three retrospective cohort studies that addressed the question of surgery alone versus surgery plus WBRT for the initial management of a single brain metastasis. The RCT by Patchell et al (1998) randomised patients to postoperative WBRT (50.4 Gy over 5 ½ weeks (n=49) or no further treatment (observation, n=46). The study included patients with various primary tumours including nine (9%) breast cancer patients.[51]

Gaspar 1997 was not identified in the systematic review as it was published prior to the search period of 2001 to 2012, but was included for additional background information on WBRT.[47] A prospective study was identified (Yaneva) that assessed the effect of palliative radiotherapy on quality of life in 65 patients with brain metastases from various primary tumours (33 breast cancer, 50.8%).[52]

Overall survival

Pooled data from two trials identified in the Tsao et al Cochrane review, found no difference in overall survival (Aoyama 2006 and Chang 2009), (HR 0.98, 95% CI 0.71 to 1.35, P = 0.88).[45]

Aoyama et al 2006 undertook a randomised controlled trial comparing WBRT plus SRS with SRS alone for the treatment of 132 patients with one to four brain metastases from various primary tumours (7% breast cancer patients).[14] Median survival time in the WBRT plus SRS group was 7.5 months compared to 8.0 months for the SRS alone group (p=0.42). Death was attributed to neurologic causes in 13 patients in the WBRT plus SRS group, and in 12 patients in the SRS alone group (p=0.64).[14]

Patients with one to three brain metastases from various solid tumours (12% breast cancer patients) treated with SRS or surgery were randomised to WBRT or observation in the European Organisation for Research and Treatment of Cancer (EORTC) 22952-26001 study.[16]

Tsao 2012 reported that for the Kocher 2011 trial, overall survival for the radiosurgery alone arm versus WBRT and radiosurgery boost could not be isolated.[45] Kocher et al 2011 reported that overall survival did not differ between the two arms, with a median survival of 10.9 months for patients who had observation only (surgery alone or radiosurgery alone), compared to 10.7 months for patients treated with WBRT (surgery and WBRT or radiosurgery and WBRT) (p=0.89). Malignant disease was the dominant cause of death in both arms.[16] The Patchell et al 1998 study included patients who had undergone complete surgical resection for a single brain metastasis, comparing patients randomly assigned to post-operative WBRT or no further treatment.[51] Overall survival rates did not differ significantly. Among the 49 patients who received WBRT, median length of survival was 48 weeks, compared to 43 weeks for the 46 patients who did not have further treatment (p=0.39). Patients who had WBRT were more likely to die of systemic disease rather than neurologic progression (p=<0.001).[51]

Rades et al 2007 retrospectively investigated whether SRS alone improved outcomes compared with WBRT for patients with one to three brain metastases.[86] Only patients in recursive partitioning analysis (RPA) classes 1 and 2 were included in the study. Median survival was 7 months for patients receiving WBRT compared to 13 months for patients receiving SRS.

Gaspar 1997 reviewed prognostic factors of patients with brain metastases in three RTOG trials conducted between 1979 and 1993, testing dose fractionation and radiation sensitisers.[47] The majority of included patients had a lung primary tumour (61%) with patients with a breast cancer primary comprising 12% of the population. Improved survival was associated with age less than 65 years, a Karnofsky Performance Status (KPS) of at least 70, and controlled primary tumour with the brain the only site of metastases. Shorter survival was observed among patients with a KPS of less than 70.

Recurrence

Pooled data in three trials (Aoyama 2006; Chang 2009; Kocher 2011) identified in the Tsao 2012 Cochrane

review found the addition of WBRT to radiosurgery significantly improves locally treated brain metastases control (HR 2.61, 95% CI 1.68 to 4.06, P < 0.0001) and distant brain control (HR 2.15, 95% CI 1.55 to 2.99, P < 0.00001).[45]

In Aoyama et al 2006 comparison of WBRT plus SRS with SRS alone, multivariate analysis shows that WBRT plus SRS was associated with a reduced risk of recurrence (p=<0.001).[14] Twenty-three patients in the WBRT plus SRS group experienced either distant or local brain tumour recurrence, compared to 40 in the SRS alone group. The 12 month brain tumour recurrence rate was 46.8% in the WBRT plus SRS group and 76.4% in the SRS alone group (p=<0.001). Twenty-one patients in the WBRT plus SRS group had new brain metastases at distant sites compared with 34 in the SRS alone group. The 12-month actuarial rate of developing new brain metastases was 41.5% in the WBRT plus SRS group and 63.7% in the SRS-alone group (P=0.003). Salvage treatment for progression of brain metastases was required significantly more frequently in patients receiving SRS alone compared to the group receiving SRS plus WBRT (29 patients vs. 10 patients respectively, p=<0.001).[14] Salvage WBRT was used for 11 of the patients who had SRS alone, but not used for any patient in the WBRT plus SRS group. Salvage SRS was used for 19 patients in the SRS alone group, and for 9 patients in the WBRT plus SRS.

Recurrence outcomes from the EORTC 22952-26001 study comparing WBRT to observation were reported in Kocher et al 2011.[16] Median progression-free survival was slightly longer in patients receiving WBRT (4.6 months) compared to patients in the observation arm (3.4 months) (p=0.20). Extra-cranial progression was reported at similar rates; in 64% of patients in the observation arm and 66% of patients in the WBRT arm. Progression at intracranial sites occurred significantly more frequently in patients in the observation arm compared to patients in the WBRT arm (p=<0.001). After surgery and SRS, WBRT reduced the probability of relapse at initial sites and at new sites. Salvage therapies for intracranial relapse were used more frequently in patients following observation (51%) compared to patients treated with WBRT (16%).[16] Thirty-one per cent of patients in the observation arm required salvage WBRT, compared to 3% in the WBRT arm.

In the Patchell et al 1998 study, patients who had WBRT after surgical resection to a single brain metastasis had significantly lower rates of tumour recurrence anywhere in the brain, compared to patients who had no further treatment after surgery (18% vs. 70%, p=<0.001).[51] The time to any brain recurrence was also significantly longer (p=<0.001). Multivariate analysis showed only post-operative radiotherapy lessened the risk of brain recurrence (p=<0.001).

Neurological function

Aoyama et al 2006 reported systemic functional preservation rates at 12 months were 33.9% in the WBRT plus SRS group, and 26.9% in the SRS alone group (p=0.53).[14]

Chang et al 2009 reported on patients with one to three brain metastases from various primary tumours, assigned to SRS plus WBRT or SRS alone. The trial was halted early based on the probability of decline in neurological function among patients in the SRS plus WBRT group compared to the SRS alone group.[50]

Quality of life

Patients with one to three brain metastases from various solid tumours treated with SRS or surgery were randomised to WBRT or observation in the EORTC 22952-26001 study.[17] Soffietti et al 2013 reported on quality

of life findings, using the Health-related Quality of Life (HRQOL) scale. A statistically significant and clinically meaningful difference in global HRQOL mean scores was detected at 9 months follow-up, in favour of patients who had observation alone (p=0.0148). No differences were found at any other time points. Patients in the observation only group had better mean scores in physical, role and cognitive functioning.[17]

Yaneva et al 2006 evaluated the influence of WBRT on quality of life and neurologic symptoms.[52] Patients with various primary tumours were included, including 50.8% breast cancer patients. All patients had a KPS above 70. After radiotherapy, all patients showed improvement in their clinical status and functioning including physical, role, emotional, cognitive and social functioning. Fatigue, pain, nausea, insomnia and appetite loss also improved significantly after WBRT.[52]

Adverse events

Aoyama et al 2006 reported that symptomatic acute neurological toxicity was observed in four of the 65 patients in the WBRT plus SRS arm, and in eight of the 67 patients in the SRS alone arm (p=0.36). Symptomatic late neurologic radiation toxic effects were observed in seven patients in the WBRT plus SRS group, and in three patients in the SRS alone group (p=0.20). Toxic effects were experienced for a median of 15.6 months in the WBRT plus SRS group and 6.2 months in the SRS alone group.[14]

The EORTC 22952-26001 study reported sixteen serious adverse events; 13 among patients in the WBRT arm compared to three in patients who underwent observation. Acute toxicity of WBRT was reported as mild.[16]

ALTERED FRACTIONATION WBRT

The Cochrane review by Tsao et al (2012) addressed altered WBRT schedules.[45] A total of nine published reports involved participants randomised to altered WBRT dose-fractionation schedules compared to standard 30 Gy in 10 daily fractions (Borgelt 1980,[56] Borgelt 1981,[56] Chatani 1985,[87] Chatani 1994,[88] Haie-Meder 1993, Harwood 1977,[25] Kurtz 1981,[26] Murray 1997,[89] Priestman 1996[54]). One study (Haie-Meder 1993) was excluded because the trial design did not include a standard WBRT dose-fractionation arm (30 Gy in 10 fractions or 20 Gy in five fractions). Eight studies therefore met the inclusion criteria for the review (3645 participants with mixed primary tumours).

Overall survival and recurrence

The Tsao et al 2012 Cochrane review identified six trials reporting on overall survival. Three trials (Chatani 1994[88]; Harwood 1977[25]; Priestman 1996[54]) compared a standard dose of 30 Gy in 10 fractions to a lower dose fractionation (20 Gy in 5 fractions, 10 Gy in a single fraction or 12 Gy in 2 fractions). Meta-analysis found a significant difference favouring the control dose of 30 Gy in 10 fractions (p=0.01). Of note, Chatani 1994 and Harwood 1977 reported no statistically significant difference, however Priestman 1996 did.

Four trials (Chatani 1985[87]; Chatani 1994[88]; Kurtz 1981[26]; Murray 1997[89]) compared a standard dose of 30 Gy in 10 fractions to a higher dose (50 Gy in 20 fractions, 54 Gy in 34 fractions). No statistically significant difference was observed in overall survival (p=0.65).[45]

Three retrospective studies were identified in the Cancer Australia systematic review[7] that compared various

radiotherapy regimens in patients with CNS metastases; two comparing shorter course WBRT with longer course and the third investigated the potential benefit of dose escalation beyond the standard 30 Gy treatment.

Rades et al (2007) investigated the potential benefit of dose escalation beyond the standard 30 Gy treatment in patients with ≥2 brain metastases from breast (26% of patients), lung and other primaries.[49] Two hundred and fifty seven patients who received 30 Gy in 10 fractions (10 fractions of 3 Gy each, with an overall treatment time of 2 weeks) were compared with 159 patients who received higher doses such as 45 Gy in 15 fractions (57 patients) and 40 Gy in 20 fractions (102 patients).[49] Rades et al found dose escalation beyond 30 Gy in 10 fractions did not improve survival (p=0.86) or local control (p=0.61).[49] Univariate and multivariate analyses of recurrence of brain metastases showed a significant association between breast cancer as the primary tumour and improved local control (p=<0.001 and p=0.012, respectively).

Rades and Lohrynska et al (2007) retrospectively compared survival and local control for short-course WBRT compared with longer programs in breast cancer patients.[53] Sixty-nine patients received short course WBRT with 20 Gy in 5 fractions. Long course WBRT with either 30 Gy in 10 fractions or 40 Gy in 20 fractions was given to 138 patients.[53] The WBRT schedule was not found to be associated with survival (p=0.254) or local control (p=0.397).

In another retrospective study by Rades et al (2011) shorter course and longer course WBRT were compared for elderly patients (≥ 65 years) treated between 2001 and 2010 for brain metastases.[48] The analysis compared 162 patients (23 breast cancer patients, 14%) who received 20 Gy in 5 fractions and 293 patients (53 breast cancer patients, 18%) who received 30 Gy in 10 fractions.[48] On univariate analysis, the WBRT regimen of 20 Gy in 5 fractions was significantly associated with improved overall survival (vs. 30 Gy in 10 fractions, p=0.020), however this was not maintained on multivariate analysis (p=0.13). The WBRT regimen was not significantly associated with improved local control (p=0.32). Breast cancer as the primary tumour (vs. lung cancer or other tumours) almost reached statistical significance for improved local control (p=0.054).[48]

Neurological function

The Tsao 2012 systematic review identified three studies (Borgelt 1980[55]; Borgelt 1981[56]; Kurtz 1981[26]) reporting on neurological function for patients with a baseline neurological function of grade two or three.[45] Among these patients there was a statistically significant difference in neurological function improvement favouring those treated with the control dose (30Gy in 10 fractions) compared to a lower dose (OR 1.74, p=0.03). There was no statistically significant difference in rates of neurological function improvement for those treated with higher doses compared to the control dose (OR 1.14, p=0.23).[45]

Adverse events

The Rades et al 2007[49] and Rades and Lohrynska et al 2007[53] retrospective reviews reported no significant differences in grade three toxicity among patients receiving a control dose of 30 Gy in 10 fractions compared to patients on other WBRT regimens.

Rades et al 2007 reported similar rates of grade 3 acute toxicity among patients receiving 30 Gy (5.8%) and higher doses (5%, p=0.92).[49] Neurocognitive dysfunction was noted in six patients treated with 30 Gy in 10 fractions (2.3%) compared to eight patients (5%) treated with higher doses (p=0.24).

Rades and Lohrynska et al 2007 reported that 9% of patients treated with 20 Gy in 5 fractions experienced grade three acute toxicity, compared with 4% of patients receiving 30 Gy in 10 fractions.[53] The rates of ≥ grade three late toxicity were less than 5% in each treatment group.

WBRT PLUS RADIOSENSITIZERS

The Cochrane review by Tsao et al (2012)[45] identified six published trials (DeAngelis 1989,[90] Eyre 1984,[91] Komarnicky 1991,[92] Mehta 2003,[93] Phillips 1995,[94] Suh 2006[95]) examining the use of radiosensitizers in addition to WBRT (2016 participants with mixed primary tumours). The radiosensitizers used were lonidamide (DeAngelis 1989[90]), metronidazole (Eyre 1984[91]), misonidazole (Komarnicky 1991[92]), bromodeoxyuridine (BrdU) (Phillips 1995[94]), motexafin gadolinium (Mehta 2003[93]) and efaproxiral (Suh 2006[95]).

The Cochrane review reported that the addition of radiosensitizers in the identified RCTs did not confer additional benefit to WBRT in either the overall survival times (HR 1.08, 95% CI 0.98 to 1.18, P = 0.11) or brain tumour response rates (HR 0.87, 95% CI 0.60 to 1.26, P = 0.46).[45]

HER2 STATUS AND RADIOTHERAPY

Three retrospective studies were identified examining the influence of HER2 status on outcomes in breast cancer patients following WBRT for brain metastases.[57,58,96]

A retrospective study, Wolstenholme et al (2008) assessed whether HER2 status had an effect on outcomes after WBRT.[57] A total of 181 patients with known HER2 status were included in the study (88 HER2-positive and 93 HER2-negative).

Dawood et al 2010 retrospectively reviewed the effect of receptor status in 223 women with breast cancer and brain metastases.[58] Sixty-seven patients had hormone receptor-positive/HER2-negative disease, 101 had HER2-positive disease, and 54 had triple-negative disease.

Significantly longer survival for HER2-positive compared to HER2-negative patients was reported in these two retrospective studies following WBRT.[57,58] Dawood et al 2010 found that the risk of death among women with triple-negative disease was not significantly different from women with hormone receptor-positive/HER2-negative disease (p=0.54).[58]

Matsunaga et al 2010 reviewed prognostic factors for women undergoing Gamma Knife surgery for brain metastases from breast cancer between 1992 and 2008.[96] Of the 101 included patients, 28 had HER2-positive disease, 37 had luminal A or B disease*, 36 had triple-negative disease. Median overall survival for women with HER2-positive disease (25 months) was significantly longer than survival with luminal (12 months) or triple-negative disease (5 months) on univariate and multivariate analyses (p=0.001). The difference in overall survival between patients with luminal disease and triple-negative disease was not statistically significant (p=0.569). There was no statistically significant differences between the three breast cancer subtypes for the incidence of new brain metastases following initial Gamma Knife surgery.[96]

± Note: the term radiosurgery in these guidelines applies to the use of a single dose (or limited number of doses) of ablative radiotherapy to brain metastases using highly precise immobilisation, dosimetric planning,

delivery and verification system and can include (but is not limited to) stereotactic radiosurgery, gamma knife radiosurgery, Cyber knife radiosurgery or radiosurgery delivered using Tomotherapy or IMRT/VMAT.

* Luminal A – hormone receptor-positive/HER2-negative disease; Luminal B – hormone receptor-positive/HER2-positive disease

Evidence from trial or study results: systemic therapies

CHEMOTHERAPIES

Two systematic reviews addressed the effectiveness of systemic therapies in the management of central nervous system (CNS) metastases from various primary tumours, including breast cancer.[28,61]

The systematic review by Mehta et al (2010) addressed the role of chemotherapy in the management of newly diagnosed brain metastases.[28] The use of chemotherapy for brain metastases was investigated in four questions, however, only the comparison of chemotherapy plus WBRT vs. WBRT alone was relevant as the other questions included studies of only lung cancer patients.

Five studies met the inclusion criteria for the question chemotherapy plus WBRT vs. WBRT alone: two phase III RCT's, two phase II RCT's and one retrospective cohort study.[28] In each RCT, patients were randomised to receive WBRT or WBRT plus carboplatin, chloroethylnitrosoureas or temozolomide.

The systematic review by Ammirati et al (2010) addressed the treatment of patients who develop recurrent/progressive brain metastases after initial therapy.[61] The review identified ten studies evaluating the role of chemotherapy in patients with recurrent/progressive metastatic brain disease. Of these, five are prospective single arm phase II studies, and five are case series. The chemotherapy agents assessed include cisplatin, temozolomide, vinorelbine, or fotemustine.

Six prospective studies were identified investigating different chemotherapies including temozolomide, sagopilone and patupilone.[62-67] All were phase I or phase II single arm studies, including small patient populations. These chemotherapies are not considered appropriate for use in breast cancer or funded through the Pharmaceutical Benefits Scheme; off-label use is not recommended. Four studies were in populations with CNS metastases from breast cancer only[63-66] and two studies were in populations with CNS metastases from various primary cancers including breast cancer.[62,67] Four studies investigated the use of temozolomide either alone or in combination with other chemotherapies; one study investigated sagopilone, and one study investigated patupilone.[62-67]

Overall survival

The systematic review by Mehta 2010 did not pool the results of the five identified studies. In the four RCTs, there was no significant survival difference between the control or intervention arms.[28]

The systematic review by Ammirati et al (2010) reported that median survival ranged from 3.5 months to 6.6 months in patients with recurrent or progressive brain metastases from various primary tumours.[61]

Among the prospective studies investigating temozolomide, sagopilone or patupilone, median survival ranged from 5.3 months to 6.9 months.[62-67]

Progression free survival

The ten studies identified in the systematic review by Ammirati et al (2010) indicated that some patients with recurrent or progressive brain metastases will have an objective radiographic response and/or improvement in functional status following treatment with chemotherapy.[61] Median time to recurrence after retreatment with various chemotherapy regimens ranged from 2 to 4 months. Of the three studies investigating chemotherapy regimens (temozolomide with cisplatin or vinorelbine), two studies reported a median time to recurrence ranging from 1.9 to 2.9 months.[61] Christodoulou 2005 investigated temozolomide and cisplatin; of the 32 patients assessed, complete response was observed for one patient, partial response was observed in nine patients, and five patients had stable disease.[62] The two studies investigating temozolomide and vinorelbine (Iwamoto 2008[97] and Omuro 2006[98]) observed complete responses for one patient each. Patients experienced progressive disease at a rate of 76% (Iwamoto 2008[97]) and 56% (Omuro 2006[98]).[61]

HER2-DIRECTED THERAPIES: Trastuzumab

Six retrospective studies were identified in the Cancer Australia systematic review that evaluated the use of trastuzumab in patients with brain metastases from HER2-positive breast cancer.[30-34,99]

Overall survival

Five studies reported on overall survival, see Table 2 below for results.[30-34] Patients with HER2-positive disease who received trastuzumab treatment, experienced longer median survival times compared to HER2-positive patients who did not receive trastuzumab and compared to HER2-negative patients.

Table 2: Overall median survival outcomes by HER2 status and trastuzumab treatment

Study	HER2-positive receiving trastuzumab	HER2-positive not receiving trastuzumab	HER2-negative	P value
Bartsch 2007[30]	21 months	Chemotherapy, no T: 9 months No further systemic therapy: 3 months	NR	<0.001
Church 2008[31]	11.9 months	3.0 months	3.8 months	0.05
Dawood 2008[32]	11.6 months	6.1 months	6.3 months	0.03
Park 2009[33]	T before BM: 4.0 months T after BM: 13.6 months	5.5 months	NR	<0.001
Le Scodan 2011[34]	19.53 months	5.6 months	5.9 months	NR

Abbreviations: BM – brain metastases; HER2 - human epidermal growth factor receptor 2, NR – not reported, T

– trastuzumab

Two studies (Park 2009; and Park, Park et al 2009) reported on overall survival for HER2-positive patients only,[33,99] (see Table 3 below for results). Both studies found significantly improved survival associated with trastuzumab treatment.

Table 3: Overall median survival outcomes among HER2-positive patients

Study	HER2-positive patients receiving trastuzumab after brain metastases	HER2-positive patients receiving trastuzumab before brain metastases	HER2-positive patients never receiving trastuzumab	P value
Park 2009[33]	13.6 months	4.0 months	5.5 months	<0.001
Park, Park et al 2009[99]	14.9 months		4.0 months	0.0005

Abbreviations: HER2 - human epidermal growth factor receptor 2.

Time to diagnosis of brain metastases

Three studies reported on the association between trastuzumab treatment and time to diagnosis of brain metastases.[30,33,99] Each study found that brain metastases were delayed in HER2-positive patients on trastuzumab compared to HER2-positive patients not taking trastuzumab or HER2-negative patients.

Park 2009 reported patients receiving trastuzumab had a median time to diagnosis of brain metastases of 19 months, compared to 8 months for patients who did not receive trastuzumab, or had trastuzumab treatment after brain metastases were diagnosed (p=<0.001).[33] Similar results were identified in the Park, Park et al 2009 study: 15 months for patients with prior trastuzumab treatment compared to 10 months among patients never receiving trastuzumab (p=0.035).[99]

The Dawood 2008 analysis found the median time to diagnosis of brain metastases among the whole cohort was 11.3 months.[32] Among HER2-negative patients, time to diagnosis was 8.9 months; 2.1 months for HER2-positive patients who did not receive trastuzumab, and 13.1 months for HER2-positive patients who did receive trastuzumab for first line treatment of first site of metastases.

Time to progression

Park 2009 investigated median time to progression of intracranial tumours, finding that progression was prolonged in patients treated with trastuzumab after diagnosis of brain metastases (7.8 months) compared to patients who never received trastuzumab (3.9 months) or who had trastuzumab after diagnosis of brain metastases (2.9 months) (p=0.006).[33]

Incidence of CNS metastases as first relapse site

The HERA trial (Pestalozzi et al 2013) investigated use of trastuzumab compared to observation in patients

with HER2-positive early breast cancer.[29] The incidence of CNS relapse as the first disease-free survival event did not differ between patients (p=0.55), however one year of trastuzumab was significantly associated with reduced incidence of non-CNS relapse (p=<0.0001).

HER2-DIRECTED THERAPIES: Lapatinib in previously untreated CNS metastases

The Cancer Australia systematic review[7] identified one study (LANDSCAPE), a single arm phase II study[36], which investigated the use of lapatinib in combination with capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer. Exclusion criteria included single brain metastases amenable to surgical resection, previous WBRT or SRS, current radiation therapy or current systemic treatment for breast cancer.

Overall survival

Overall survival at six months was 90.9%. Median overall survival was 17 months.[36]

Response to treatment

An objective CNS response (all partial responses) was observed in 29 (65.9%) patients. A CNS volumetric reduction of 80% or greater was observed in nine patients (20%), and overall, 37 patients (84%) had some reduction in tumour volume. Forty-two of 44 patients were available for assessment of best CNS response according to Response Evaluation Criteria In Solid Tumors (RECIST); two patients (5%) had a complete response, 22 patients (52%) had a partial response; thus 24 patients (57%) had an objective CNS response.[36]

Among the 30 patients who had prior trastuzumab treatment, 20 (67%) experienced an objective CNS response. Of the 14 patients who had not had prior trastuzumab, nine (64%) had an objective CNS response.[36]

Progression

Among 41 patients with available data, the site of first progression was CNS alone for 32 patients (78%); extra-CNS alone in two patients (5%) and, for five patients (12%) progression was observed in both the CNS and extra-cranially. Median time to progression was 5.5 months, and median time to radiotherapy was 8.3 months.[36]

Adverse events

Twenty-two of 45 patients experienced at least one grade 3 or grade 4 adverse event, and 14 (31%) experienced at least one serious adverse event.[36] The most commonly reported adverse events were diarrhoea and hand-foot syndrome. Sixteen patients required a reduction to their dose of lapatinib; 11 of which were during the first two cycles of treatment. Twenty-six patients required a dose reduction for capecitabine, most frequently in the second, third or fourth cycles.

Treatment discontinuation due to adverse events occurred in four patients (9%).[36]

HER2-DIRECTED THERAPIES: Lapatinib in previously treated CNS metastases

Eight studies were identified in the Cancer Australia systematic review[7] that examined the use of lapatinib for the treatment of CNS metastases in HER2-positive metastatic breast cancer patients previously treated.

Lin et al conducted two prospective phase II trials of lapatinib in patients with brain metastases from HER2 positive breast cancer, previously treated with trastuzumab and radiotherapy.[35,70] In Lin 2009 a subset of patients who progressed on lapatinib went on to receive lapatinib and capecitabine.[35] A subsequent randomised phase II trial comparing lapatinib in combination with capecitabine or topotecan was undertaken.[69] While these are small studies, they are some of the few high level evidence studies.

Three additional studies examined the combination of lapatinib and capecitabine, (including a conference abstract report[100]), however none included a control arm of capecitabine alone.[68,100,101]

Two further phase I studies (conference abstract reports) reported outcomes for use of lapatinib with temozolomide and lapatinib with WBRT.[102,103]

Overall survival

Two studies investigating the use of lapatinib reported on overall survival.[35,68] Metro 2011 found that patients treated with lapatinib and capecitabine (n=30) had a median overall survival of 27.9 months, significantly longer than patients treated only with trastuzumab-based therapies (n=23, 16.7 months; p=0.01).[68] Among the patients (n=6) who received lapatinib and capecitabine as the first systemic option after development of brain metastases, median overall survival was not reached. Among the 24 patients who received lapatinib and capecitabine after at least one trastuzumab-based therapy following development of brain metastases, overall survival was 27.1 months.[68]

Lin 2009 reported on outcomes for 242 patients treated with lapatinib, following prior trastuzumab treatment and local therapies. Median overall survival was 6.4 months.[35]

Response rate

Five studies investigating lapatinib use reported on response rates.[35,68-70,101] Lin 2008 assessed 39 patients receiving lapatinib after prior treatment with trastuzumab and other systemic and local therapies.[70] One patient achieved a partial CNS response, and four patients achieved partial responses in non-CNS sites. Three patients achieved at least 30% volumetric reductions in CNS lesions, and an additional seven patients achieved reductions of 10% to 30%. A trend towards a longer time to progression was found for patients with at least 30% volumetric reduction compared to other patients.[70]

Lin 2009 investigated the use of lapatinib among 242 patients, with 50 patients opting to enter a subsequent phase of treatment with lapatinib and capecitabine.[35] Among the 242 patients treated with lapatinib, an objective CNS response rate of 6% was observed. No complete responses were seen; 15 partial responses occurred. Assessment of volumetric changes to CNS lesions were available for 200 patients. Nineteen patients (8%) experienced a volumetric reduction of ≥50%, and a total of 50 patients (21%) experienced a ≥20%

reduction to their CNS lesions. A lower risk of disease progression compared to the rest of the study population was observed among patients who had at least a ≥20% volumetric reduction to their CNS lesions. Of the fifty patients who opted to enter the lapatinib and capecitabine extension phase, ten (20%) experienced an objective CNS response; all were classified as partial responses.[35]

Lin 2011 compared lapatinib and capecitabine with lapatinib and topotecan.[69] Of the 13 patients treated with lapatinib and capecitabine, five patients experienced a partial response. No objective responses were observed among the nine patients treated with lapatinib and topotecan.

Time to progression

Sutherland 2010 investigated lapatinib and capecitabine and reported on time to progression.[101] Median time to progression for the 34 patients with CNS metastases was 22 weeks. Among those previously treated with capecitabine, median time to progression was 17 weeks, compared to 30 weeks for patients who are capecitabine-naïve (p=0.06).

Progression free survival

Two studies reported on progression free survival.[35,68] On review of 237 patients treated with lapatinib in Lin 2009, the median progression free survival was 2.4 months.[35] Among the 50 patients opting to have a lapatinib and capecitabine extension phase of treatment, the median progression free survival was 3.65 months.

Metro 2011 assessed 30 patients for progression free survival from the start of lapatinib and capecitabine.[68] The median progression free survival was 5.1 months, with a median brain-progression free survival of 5.6 months.

Adverse events

Three studies reported on adverse events associated with lapatinib.[35,69,70] The most commonly reported adverse events include diarrhoea, rash, nausea and vomiting. The most commonly reported adverse events associated with lapatinib and capecitabine were palmar-plantar erythrodysesthesia, diarrhoea and nausea.

Among patients treated with lapatinib and topotecan, commonly reported adverse events include diarrhoea, nausea, fatigue and thrombocytopenia. The Lin 2011 study closed accrual of patients to the lapatinib and topotecan arm due to tolerability issues, in combination with a lack of early efficacy.[69]

TRIPLE NEGATIVE PATIENTS

One retrospective analysis of patients with metastatic triple-negative breast cancer was identified.[104] Lin and Claus et al 2008 retrospectively reviewed 116 patients with triple-negative breast cancer. Sixteen patients (14%) were diagnosed with CNS metastases at the initial metastatic diagnosis, 53 (46%) had a CNS metastasis at some point.[104]

Overall survival

Among the 53 patients with CNS metastases, the median survival from time of diagnosis of any metastasis was 11.6 months, and 4.9 months from time of diagnosis of first CNS metastasis. [104]

Response rate

Of the 53 assessed patients, 3 were judged to have stable or responsive systemic disease. [104]

Evidence from trial or study results: multimodal treatment

Five studies reported on various combinations of treatments in patients with central nervous system (CNS) metastases from breast cancer.[105-109]

Two non-comparative phase II trials investigated the combination of radiotherapy and chemotherapy.[105,106] Objective response rates were 58% and 76%, and complete response rates were observed in 7.4% and 12% of patients with breast cancer primary tumours in the Addeo 2008 and Cassier 2008 trials respectively. In the two studies, median overall survival was 8.8 months and 6.5 months, and 1 year survival was 18.5% and 28% in the Addeo 2008 and Cassier 2008 trials respectively. Median progression free survival was 6 months and 5.2 months in the Addeo 2008 and Cassier 2008 trials respectively.

One retrospective study reported significantly longer survival for surgery and radiotherapy compared to radiotherapy alone (p=0.001) as well as longer survival in patients who receive systemic chemotherapy after radiotherapy (p=0.015).[108] Treatment modality, KPS and administration of systemic chemotherapy were significant prognostic factors for overall survival on multivariate analysis.

One retrospective study that included 15% patients with breast cancer as the primary tumour reported that surgery and SRS was associated with longer survival compared with SRS alone (p=0.020) and that the survival of SRS alone patients was statistically superior to the survival of patients who received WBRT alone (p=<0.001).[107]

A third retrospective study that included 17% patients with breast cancer primary tumour found significant improvement in local control (p=0.002) with the addition of a boost to WBRT and surgery.[109]

Evidence from trial or study results: asymptomatic patients

One prospective study (Niwinska 2010) assessed outcomes in HER2-positive breast cancer patients with occult brain metastases compared with patients with symptomatic brain metastases.[110] Occult brain metastases were detected in 36% of the screening group. The median time between recurrence (distant and/or locoregional) and the diagnosis of occult brain metastases was 9 months.[110] Twenty-six patients were given WBRT, with 24 patients available for assessment of radiological response. At three months follow-up, MRI found that 29% of patients were in complete remission, 63% were in partial remission, and there was no change in the brain for 8%. At the time of analysis, complete remission was maintained for two of the five survivors.[110]

Evidence from trial or study results: spinal cord compression

This section is based on the 2001 Clinical practice guidelines for the management of advanced breast cancer[1] and updated to include results from a randomised trial on decompressive surgery[40] and a systematic review by Loblaw et al.[41] Results from a retrospective analysis of breast cancer patients by Tancioni et al included in the systematic review are also noted below.[111]

Symptoms of spinal cord compression

Patients who are known to have bony metastatic disease and their carers should be warned about the possibility of, and educated regarding the early symptoms of spinal cord compression. Patients should be encouraged to notify their doctor of such symptoms as soon as possible. Primary medical carers should also be aware of the risks of spinal cord compression and paraplegia and the importance of prompt action. Symptoms suspicious of spinal cord compression should be investigated in the absence of signs.[1]

The systematic review by Loblaw et al (2005) identified twelve studies investigating the clinical symptoms of metastatic spinal cord compression from various primary tumours.[41] Frequently observed symptoms include back pain, motor weakness, sensory changes and bladder dysfunction.

A retrospective review was included in the Loblaw 2005 systematic review(Talcott et al 1999) which identified six predictive factors for spinal cord compression, including the inability to walk, increased deep tendon reflexes, compression fractures on radiographs of the spine, bone metastases present, bone metastases diagnosed more than one year prior, and age less than 60 years.[112]

A prospective cohort study (Husband 1998) found that approximately 70% of patients with spinal cord compression experienced loss of neurologic function between the onset of symptoms and the start of treatment.[113] The majority of delays were attributed to lack of symptom recognition by the patient and diagnostic delay at the general practitioner or hospital level.

Investigation of suspected spinal cord compression

If spinal cord compression is suspected, whether on symptomatic or clinical grounds, the investigation of choice is MRI scan.[114] This is non-invasive and the precise level or levels of cord compression can be ascertained. If this is not available, then CT scan should be used.[115] The Loblaw 2005 systematic review identified four studies investigating the accuracy of MRI, reporting sensitivity ranging from 0.44-0.93 and specificity ranging from 0.90-0.98.

Use of corticosteroids

Dexamethasone should be started on suspicion of spinal cord compression and while awaiting assessment.[40,116]

One small RCT identified in the Loblaw 2005 systematic review (Vecht et al 1989) compared high (100mg) to moderate (10mg) initial dose of dexamethasone in patients with complex myelographic obstruction.[37] All patients were treated with radiotherapy and maintenance dexamethasone of 16mg/d orally after the initial treatment. At one week, no significant differences were reported between the high and moderate dose groups in pain, ambulation or bladder function.

A second RCT by Sorensen et al (1994) included in the Loblaw 2005 systematic review compared high-dose dexamethasone therapy as an adjunct to radiotherapy (n=27) with no dexamethasone (n=30).[38] Immediately after myelography or MRI, patients randomised to dexamethasone treatment received an intravenous bolus of 96mg. The patients were then maintained on a dose of 96mg dexamethasone for 3 days (given orally when possible in four divided doses), and the treatment was then tapered in 10 days. Successful treatment, defined as preservation of gait in ambulatory patients or restoration of gait within 3 months in non-ambulatory patients, was obtained in 81% of the patients treated with dexamethasone compared to 63% of the patients without dexamethasone treatment. In a subgroup analysis of breast cancer patients, a successful treatment result was achieved in 94% of dexamethasone patients compared with 69% of patients without dexamethasone, although difference was not significant.[38]

Life table analysis demonstrated a higher percentage of patients receiving dexamethasone surviving with gait function during 1 year compared with those not receiving dexamethasone (p=0.046).[38] Six months after treatment, 59% of the patients in the dexamethasone group were still ambulatory compared to 33% in the no dexamethasone group (p=0.05). Median survival was 6 months in the two treatment groups. Significant side-effects were reported in three (11%) of the patients receiving glucocorticoids, two of whom discontinued the treatment.[38]

A case-control study (Heimdel et al 1992) compared high and moderate doses of maintenance corticosteroids in patients treated with radiotherapy for spinal cord compression.[39] A statistically significant increase in the number of serious side effects was observed among patients receiving the high dose (4 of 28 patients, 14%), compared with no reports of serious side effects in the moderate dose group (p=0.0284). Serious adverse effects included ulcers with haemorrhage, rectal bleeding and gastrointestinal perforations. The total incidence of side effects was also significantly higher in the high dose group compared with the normal dose group; 8/28 vs. 3/38 respectively, p=0.0429.

Surgery

Patients presenting with suspected spinal cord compression should be reviewed as early as possible by a spinal surgeon or neurosurgeon with an interest and expertise in spinal problems in consultation with a multidisciplinary team as appropriate.[1]

A randomised trial assigned patients with spinal cord compression caused by metastatic cancer to either surgery followed by radiotherapy (n=50, breast cancer patients=7) or radiotherapy alone (n=51, breast cancer patients=6).[40] Radiotherapy for both groups was given as 30 Gy in 10 fractions. Patients with a displaced spinal cord by an epidural mass, restricted to a single area were eligible for inclusion. Patients were excluded if they had multiple compressive lesions, certain radiosensitive tumours (such as lymphoma) or pre-existing or concomitant neurological problems. Patients were required to have a good general medical status to be acceptable surgical candidates, with an expected survival of at least three months.[40] The primary endpoint of the trial was the ability to walk. Secondary endpoints were urinary continence, muscle strength and functional

status, the need for corticosteroids and opioid analgesics, and survival time.

Because of demonstrated superiority of surgical treatment, the trial was stopped early by the data safety and monitoring committee.

Significantly more patients in the surgery group (84%) than in the radiotherapy group (57%) were able to walk after treatment (odds ratio 6.2, p=0.001).[40] Patients treated with surgery also retained the ability to walk significantly longer than did those with radiotherapy alone (median 122 days vs. 13 days, p=0.003).

Among the subgroup of patients who could walk at study entry, 94% (32 of 34 patients) in the surgery group continued to walk after treatment, compared with 74% (26 of 35 patients) in the radiation group (p=0.024). Patients receiving surgery maintained the ability to walk significantly longer than patients receiving radiotherapy (median 153 days compared to median 54 days, odds ratio 1.82, p=0.024). Among the 16 patients in each group unable to walk at study entry, ten patients (62%) in the surgery group regained the ability to walk, compared with three patients (19%) receiving radiotherapy (p=0.012).

Surgical treatment was significantly associated with maintenance of continence, muscle strength, functional ability and increased survival times. The need for corticosteroids and opioid analgesics was significantly reduced among patients in the surgical group.[40]

Thirty-day mortality rates were 6% in the surgical arm compared to 14% in the radiation arm (p=0.32). The median hospital stay was 10 days for patients in the surgical and radiotherapy arms (p=0.86).

The authors concluded that decompressive surgery plus postoperative radiotherapy is superior to treatment with radiotherapy alone for patients with spinal cord compression caused by metastatic cancer.[40] The surgical approach should be dictated by the position of the tumour within the vertebra. When surgery is not considered appropriate, radiotherapy should be started immediately.

A retrospective analysis of breast cancer patients with metastatic epidural spinal cord compression identified 23 patients who underwent either minimal resection (n=5), curettage leaving microscopic residual tumour (n=18) or total resection (n=3) followed by radiotherapy within 30 days. Median survival of 36 months was reported. The median duration of clinical remission was 26 months. Complete or partial clinical remission of pain was obtained in all cases, and all 17 patients presenting with neurologic deficit experienced compete recovery.[111]

Radiotherapy

Three prospective studies, two case-control studies, one case series and three retrospective reviews were identified in the Loblaw 2005 systematic review comparing various doses of radiotherapy to treat metastatic spinal cord compression.[41] Doses included:

- 30 Gy in 10 fractions
- 37.5 Gy in 15 fractions
- 40 Gy in 20 fractions
- 28 Gy in 7 fractions
- 15 Gy in 3 fractions / 15 Gy in 5 fractions

- 8 Gy twice

No regimens demonstrated higher rates of ambulation compared with another.

As noted in the Surgery section above, a randomised controlled trial (Patchell 2005) comparing surgery followed by radiotherapy with radiotherapy alone was stopped early due to proven superiority of the surgical treatment. Ten patients in the radiation group (20%) experienced substantial decline in motor strength during radiotherapy and crossed over to receive surgery. None of these patients could walk at the time of surgery; three (30%) regained the ability to walk.

Supporting information for practice points

This section provides additional information relating to the practice points. This information was not sourced through a systematic review of the literature; relevant articles were identified by the Working Group and by Cancer Australia.

Multidisciplinary care

Multidisciplinary care is the best practice approach to providing evidence-based cancer care. Multidisciplinary care is an integrated team approach to health care, in which medical and allied health care professionals consider all relevant treatment options and collaboratively develop an individual treatment care plan for each patient.

The Multidisciplinary care principles for advanced disease[11] developed by Cancer Australia reflect the role of multidisciplinary care teams in the advanced cancer setting. These principles emphasise the importance of continuity of care, care coordination, and the involvement of the patient and their carer as appropriate, in the treatment and care planning process.

Membership of a multidisciplinary team for advanced cancer should reflect both clinical and psychosocial aspects of care. As patients with advanced cancer may have specific needs and issues relating to psychosocial impact of diagnosis and prognosis, the management of physical symptoms, quality of life and practical issues

Further information on the Multidisciplinary care principles for advanced disease is available at:
http://canceraustralia.gov.au/clinical-best-practice/multidisciplinary-care

Supportive and palliative care

Patients with brain metastases have complex care needs; optimal management should not only focus on physical symptoms, but should also take into account the psychosocial burden of the disease on the patients and their carer.

A United Kingdom Taskforce on metastatic breast cancer care recommended that all patients with metastatic breast cancer have access to a specialist nurse with a skill set appropriate to the secondary cancer setting.[117] A demonstration project on a specialist breast care nurse role in the Australian setting found strong support from health professionals and patients for the expansion of this role.[118]

The National Institute for Health and Clinical Excellence (NICE) guidelines for Improving supportive and palliative care for adults with cancer[27] identifies that all patients should have access to specialist palliative care services, including in-patient and community services. Rehabilitation services are important to the maintenance of physical function, promoting independence and supporting adaptation of the patient to their condition.

The NICE guidelines also identify that psychological distress is common among people affected by cancer, and that all patients should have access to appropriate psychological support, in addition to systematic

assessment at key points.

The involvement of rehabilitation and palliative care services and specialist nursing services within the multidisciplinary team supports the patient and their caregivers as treatment goals transition from curative to palliative and maximises functional status for as long as possible.[119]

Supporting information for practice points: surgery

Treatment of brain metastases should be determined in the context of a patient's systemic disease status; the views of medical and radiation oncology should be sought. Note that surgery may be urgent if the patient has a reduced conscious state or there is midline shift or extensive mass effect.

Potential benefits and risks of surgical resection

Surgical resection provides its main benefits through direct removal of the targeted lesion. Resection may help to maintain quality of life, prevent death directly from the metastasis and prolong survival.[12] Potential benefits of surgery include:

- Relief of symptoms, including focal neurological deficit, seizures, and headache from raised intracranial pressure.
- Reduced steroid requirements.
- Histological diagnosis and verification of receptor status of metastases.
- Local control if extra-cranial disease is controlled.
- In cerebellar and periventricular metastases, to prevent risk of hydrocephalus.
- In posterior fossa metastases, to prevent brainstem compression from tumour growth or swelling post irradiation.

The potential benefits of surgical resection must be balanced with the risks of post-operative morbidity and mortality.

Surgical resection of brain metastases is associated with a range of risks and side-effects. Focal neurological deficit is a potential complication of surgery. The tumour may recur after surgery at local site or elsewhere in the brain.

General complications include haemorrhage, infection and seizures.

Anti-convulsant medication

A systematic review by Mikkelson et al (2010) assessed if prophylactic anti-convulsants decrease the risk of seizures in patients with metastatic brain tumours compared with no treatment.[18] Only a single, underpowered randomised controlled trial (RCT) of melanoma patients with brain metastases was identified. The study did not detect a difference in seizure occurrence. The review concluded that there is a lack of clear and robust benefit from the routine prophylactic use of anti-convulsants.[18]

The Quality Standards Subcommittee of the American Academy of Neurology published a practice parameter on the use of prophylactic anti-convulsants in patients with primary and metastatic brain tumours (2000).[19] The recommendations in the practice parameter were based on a systematic review and meta-analysis. The practice parameter concluded that in 12 studies (four RCTs and eight cohort studies) examining the use of prophylactic anti-convulsants to prevent first seizures in patients with brain metastases, none have demonstrated efficacy. A meta-analysis of the four RCTs reported no evidence of an effect on the frequency of

first seizure in patients receiving anti-convulsant prophylaxis.

Specimen review

The choice of systemic therapy is usually based on the tissue characteristics of the primary tumour. A number of studies have shown that the immunophenotype of the distant breast cancer metastases may be different from that of the primary tumour. The most frequent finding was that compared to primary tumours, oestrogen and progesterone receptors are more frequently negative in distant metastases, whereas HER2 (human epidermal growth factor receptor 2) is more often positive.[120]

A pooled analysis of individual patient data from two large prospective trials undertaken included 289 patients with breast cancer primary tumour. The most frequent distant sites of metastases included in the studies were skin/soft tissue, bone or bone marrow and liver. Discordance in oestrogen, progesterone and HER2-receptors between the confirmed primary and recurrent breast cancer was 12.6%, 31.2% and 5.5% (all $p<0.001$).[121]

A retrospective analysis of 233 breast cancer patients reported receptor conversion rates for oestrogen (10.3%), progesterone (30%) and HER2 (5.2%) receptors. Of the 44 women with brain metastases, receptor conversion was noted at rates of 13.7% for oestrogen, 36.3% for progesterone and 2.3% for HER2. By comparison to other metastatic sites, receptor conversion was more frequent in brain, liver and gastro-intestinal metastases.[120]

Steroid use

Steroids frequently cause a resolution or improvement of symptoms but side effects can be problematic and without further treatment neurological symptoms will recur.[122] Steroids may be useful to manage symptoms and reduce cerebral oedema, particularly in the perioperative period.

A systematic review by Ryken et al 2010 addressed whether steroids improve neurologic symptoms in patients with metastatic brain tumours.[123] Of the two included studies, one provided evidence that the administration of steroids provides relief of symptoms in patients with symptomatic brain metastatic disease; however, recognising that there is no control group only the lowest grade of recommendation was made.[123]

A randomised double-blind study, performed in two phases, was undertaken to compare dexamethasone doses of 4mg, 8mg and 16mg per day for the treatment of brain tumour oedema.[20] The first series compared 8mg dexamethasone per day to 16mg per day. The second series, compared 4mg day versus 16mg day. The study found that the administration of 4mg dexamethasone per day results in the same degree of improvement as administration of 16mg per day after one week of treatment in patients with no sign of impending herniation. Toxic effects were found to be dose-dependent and during a four-week period occurred more frequently in patients using 16mg per day.[20]

A Cochrane review by Tsao et al (2012) assessed the effectiveness of steroids alone versus WBRT and steroids.[45] The review identified one RCT examining the use of WBRT and prednisone vs. prednisone alone and produced inconclusive results.[45]

Driving

A person's driving ability can be impaired by brain tumours, seizures and the associated treatment and medications used such as anti-convulsants. These impairments include affected vision, mobility, coordination, perception and judgement.[124]

The national medical standards for licensing published by the national transport commission, Assessing fitness to drive: for commercial and private vehicle drivers, (Austroads 2012), have established criteria to assess a patient's fitness to drive, which are based on the clinical management guidelines.[21]

The standards outline roles and responsibilities for patients, health professionals and the licensing authorities. Patients have a responsibility to report to their local licensing authority any long-term injury or illness that may affect their ability to drive; to respond honestly to questions about their health and its likely impact on their driving ability; and to comply with the requirements of a conditional license. Health professionals should assess a patient's suitability to hold a license; provide information to patients on fitness to drive, the impact of their medical condition, and the patient's responsibility to self-report new or recurring symptoms. Responsibility for all decisions regarding the licensing of drivers sits with the licensing authority.[21]

Patients may feel hostile towards the health professional when there is possibility of restrictions to their driving license, as it offers an important means of independence. In such circumstances, or situations where a health professional feels they cannot act objectively in assessing a patient's fitness to drive, a health professional may choose to refer a patient to another practitioner or directly to the local licensing authority.

Health professionals may refer patients to social work services to discuss local transport support services available.

For more information on driving after brain injuries, or for access to current driving guidelines refer to: here.

Confidentiality, privacy and reporting

The duty to protect confidentiality applies to driver licensing authorities, however with respect to assessing and reporting fitness to drive, the duty to maintain confidentiality is legally qualified in certain circumstances in order to protect public safety. The health professional should consider reporting directly to the licensing authority in situations where the patient is either:

- Unable to appreciate the impact of their condition;
- Unable to take notice of the health professional's recommendations due to cognitive impairment; or
- Continues to drive despite appropriate advice and is likely to endanger the public.[21]

Cerebellar/periventricular/posterior fossa metastases

Metastases to the cerebellum are generally not tolerated well, and carry a poorer prognosis compared to supratentorial metastases. Lesions in the posterior fossa can lead to hydrocephalus, herniation, brainstem compression, and death.[125] Metastatic disease within the periventricular brain tissue may obstruct the flow of cerebrospinal fluid produced in the ventricles to the subarachnoid space and may lead to an obstructive or

non-communication hydrocephalus.[126] Surgical management of patients with these metastases may be required.

Graded Prognostic Assessment (GPA)

The Breast-GPA is a prognostic index for breast cancer patients with brain metastases. The GPA was developed following the Radiation Therapy Oncology Group's (RTOG) Recursive Partitioning Analysis as an updated index for patients with brain metastases. The GPA was developed following the Radiation Therapy Oncology Group's (RTOG) Recursive Partitioning Analysis as an updated index for patients with brain metastases.[23,24]

The Breast-GPA was developed through retrospective analysis of 400 breast cancer patients treated for newly diagnosed brain metastases between 1993 and 2010, for prognostic factors for survival. Survival time was measured from the time of first treatment for brain metastases to the date of death or last follow-up. Prognostic factors were analysed by multivariate Cox regression and recursive partitioning analysis (RPA).[23,24]

The median overall survival for all patients was 13.8 months. At the time of data collection, 95 (24%) of the 400 patients were alive, with a median follow-up time of 17.1 months. Seventy-seven per cent of HER2-positive patients received trastuzumab, and 82% of ER/PR-positive patients received hormonal therapies. Eighty-three per cent of patients (n=332) were treated with radiotherapy (WBRT alone, SRS alone or WBRT plus SRS); 16.8% of patients (n=67) were treated with surgery plus radiotherapy (WBRT and/or SRS). One patient underwent observation. Data for chemotherapy treatment was not available.[24]

Multivariate Cox regression analysis identified the significant prognostic factors as KPS ($p<0.0001$), ER/PR status ($p=0.0002$), HER2 status ($p<0.0001$), and the interaction of ER/PR and HER2 ($p=0.027$).[24] Relative to patients with triple-negative breast cancer, the risk of death was 0.50 for Luminal A subtype; 0.38 for the HER2-positive subtype; and 0.35 for the Luminal B subtype. The prognostic factors identified as significant in the RPA analysis were consistent with the multivariate Cox regression analysis, with the addition of age for patients with KPS 60-80.[24] The number of brain metastases and whether extra-cranial metastases were present or absent were not significant prognostic factors.[24]

Table 4 shows the Breast-GPA index for women with breast cancer and brain metastases. The sum of the relevant values for each prognostic factor is the GPA for the individual patient. A score of 4.0 correlates with the best prognosis and 0.0 the poorest.[23,24]

Table 4: GPA index for women with breast cancer and brain metastases[23,24]

Value / Factor	0.0	0.5	1.0	1.5	2.0
KPS	≤50	60	70-80	90-100	-
Genetic subtype	Basal	-	Luminal A	HER2	Luminal B
Age	≥60	<60			

Abbreviations: KPS – Karnofsky Performance Status; Basal – triple negative disease; HER2 – HER2-positive and

Factor \ Value	0.0	0.5	1.0	1.5	2.0

ER/PR-negative; Luminal A – ER/PR-positive and HER2-negative; Luminal B – triple positive disease

The median survival times by GPA score were also estimated in the analysis. For GPA 0.0-1.0 median survival was 3.4 months (2.4-4.9). GPA score 1.5-2.0 had median survival of 7.7 months (4.8-9.7). Median survival for GPA score 2.5-3.0 was 15.1 months (10.8-17.9). GPA score 3.5-4.0 had median survival of 25.3 months (20.4-30.4).[23,24]

Treatment is not a factor in the Breast-GPA, as it is intended to be useful in making treatment choices rather than evaluating outcomes after treatment. It was noted that when treatment was added to the final multivariate Cox regression analysis, no significant change to the direction or magnitude of the estimated hazard ratio was found.[23,24]

Strengths and weakness of the evidence

Limited high quality evidence was available for the five primary research questions.

There were few large prospective trials identified that investigated the use of surgery, radiotherapy, systemic therapies or multimodal treatment for the management of CNS metastases in women with metastatic breast cancer, specifically from breast cancer. Most of the relevant trial data were limited to small breast cancer patient cohorts or retrospective studies.

The following studies were identified for women with CNS metastases from metastatic breast cancer:

- one randomised controlled trial
- one randomised phase II study
- one cohort study
- one non-comparative prospective study
- 18 single arm prospective phase I and II studies
- 26 retrospective studies.

Seven previously published systematic reviews, including two Cochrane reviews, were also used as primary references. These systematic reviews included evidence from studies with mixed primary tumours

Unanswered questions

Important unanswered questions about the management of CNS metastases in women with metastatic breast cancer are outlined below. Some of these questions may be addressed in ongoing trials.

- The optimal timing of whole brain radiotherapy (WBRT) and local therapies, with outcomes relating to quality of life and overall survival.
- The efficacy of surgery alone compared to radiosurgery alone.
- The safety and effectiveness of hippocampal sparing techniques.
- The role of systemic therapies after radiotherapy in patients with triple negative breast cancer.
- Differences between isolated CNS metastases and wider/systemic metastases.
- The impact of brain metastases on quality of life, including changes in appearance, and the impact on carers.
- The efficacy of 'active' treatments compared to supportive and/or palliative care alone.
- Supportive care, including rehabilitation requirements, and palliative care needs for women with CNS metastases from breast cancer.
- Differences in approach to treatment based on subtype of breast cancer.

International guidelines

The Cancer Australia systematic review[7] identified six international guidelines that addressed central nervous system (CNS) metastases from breast cancer in their recommendations. The specific recommendations are detailed in the systematic review.

1. **National Comprehensive Cancer Network (NCCN)**[127]
   Central nervous system cancers guidelines cover metastatic disease with separate recommendations for limited (1-3) metastatic lesions, multiple (>3) metastatic lesions, leptomeningeal metastases, and metastatic spine tumours (2012). These recommendations were made based on consensus of an international panel.

2. **National Institute for Health and Clinical Excellence (NICE)**[128]
   Advanced breast cancer: diagnosis and treatment (2009). These recommendations were based on a systematic review.

3. **European Society of Medical Oncology**[129]
   Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. These recommendations were made based on consensus of a Working Group.

4. **European Federation of Neurological Societies (EFNS)**[130]
   Brain metastases: EFNS guidelines on brain metastases (2011). These recommendations were based on a systematic review.

5. **Central European Cooperative Oncology Group**[131]
   Third consensus on medical treatment of metastatic breast cancer. These recommendations were based on a literature review.

6. **German Society of Radiation Oncology (DEGRO)**[132]
   DEGRO Practical Guidelines for palliative radiotherapy of breast cancer patients: brain metastases and leptomeningeal carcinomatosis (2010). These recommendations were based on a systematic review.

Ongoing and additional trials

Clinical trials registries were searched to identify any additional studies investigating central nervous system (CNS) metastases in metastatic breast cancer, and are noted in the Cancer Australia systematic review.[7] Areas of ongoing research in this population include:

- A phase II randomised controlled trial in Korea (NCT01622868) among patients with HER2-positive breast cancer, comparing patients taking lapatinib ditosylate and undergoing WBRT, with patients undergoing WBRT alone.[133]
- A French phase II randomised controlled trial (NCT00875355) on temozolomide use among patients having WBRT.[134]
- A phase II open-label study in the US (NCT00397501) comparing blood-brain barrier disruption followed by methotrexate and carboplatin, with or without trastuzumab.[135]
- A phase II randomised open-label study in France (NCT00977379) comparing capecitabine and WBRT with WBRT alone.[136]
- A US-based phase II open-label study (NCT01480583) comparing GRN1005 in combination with trastuzumab for HER2-positive patients with GRN1005 alone in HER2-negative patients.[137]
- A phase II, interventional open-label study in the US (NCT01494662) comparing 240mg daily of HKI-272/Neratinib to 40mg daily plus surgical resection.[138]
- A French phase III randomised controlled trial investigating the addition of concurrent prophylactic cranial radiotherapy to taxane/trastuzumab therapy.[139]
- A randomised phase III trial in the US (NCT01372774) comparing post-surgical SRS with post-surgical WBRT.[140]
- A phase II US-based trial (RTOG 0933) investigating hippocampal avoidance in WBRT.[141]
- A phase I randomised study on stereotactic radiosurgery to the cavity following surgical resection of brain metastases[142]

Information for women and their families and carers

The information in this guideline provides health professionals with current evidence to inform treatment planning. Information for women with metastatic breast cancer and their families and carers is available from these sources:

- Cancer Australia is the lead national cancer control agency. The Cancer Australia website provides evidence-based information about a range of cancers including metastatic breast cancer: www.canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/about-breast-cancer/types-breast-cancer/secondary-breast-cancer
- Breast Cancer Network Australia is a national organisation offering support to women through the provision of information and providing a network for women to share their experiences. The Hope & Hurdles kit is a free resource for women with metastatic breast cancer, which includes information on brain metastases as an optional item. To order Hope & Hurdles, visit www.bcna.org.au or call 1800 500 258.
- Cancer Councils in each state and territory offer a free, confidential telephone information and support service. Trained staff are available to answer questions about cancer and offer emotional or practical support. Call the Cancer Council Helpline on 13 11 20. Information is available on Cancer Council Australia's website: www.cancer.org.au.

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Guideline development process

Priority topic areas for guideline development are determined in consultation with key stakeholders including experts in relevant disciplines and consumer representatives. A specific multidisciplinary Working Group, including consumers, is established for each topic identified and is involved in all aspects of guideline development. A systematic evidence review is undertaken for each guideline. All members are asked to declare any conflicts of interest and these declarations are recorded. The content of the guideline is not influenced by any external funding body. The guideline is reviewed externally by key stakeholders and the wider community and endorsement is sought from relevant professional colleges and groups in Australia.

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Appendix 1: grading the recommendations

Grading Methodology

To accurately assess the strength of evidence available, the NHMRC methodology (FORM) was used in this clinical practice guideline to formulate and grade recommendations. The aim of this approach by NHMRC is to assist clinical practice guideline developers with a structured process for evaluating the evidence base corresponding to a particular key clinical question, in the context of the setting in which it is to be applied.[9]

The grading methodology allows for both the quality of the evidence and the strength of recommendations to be determined. Where insufficient evidence exists to formulate a grade, a practice point may be assigned instead. The NHMRC grading framework allows for these practice points to be included when developers consider it is important to provide non-evidence-based guidance.[9]

The NHMRC Evidence Statement Form sets out the basis for rating five key components of the 'body of evidence' for each recommendation. These components are:

1. The evidence base, in terms of the number of studies, level of evidence and quality of studies (risk of bias).
2. The consistency of the study results
3. The potential clinical impact of the proposed recommendation
4. The generalisability of the body of evidence to the target population for the guideline
5. The applicability of the body of evidence to the Australian healthcare context[8].

The first two components describe the internal validity of the study data in support of efficacy (for an intervention), accuracy (for a diagnostic test), or strength of association (for a prognosis or aetiological question). As suggested, the third component gives the likely clinical impact of the proposed recommendation. The final two components assess external factors that may influence the effectiveness of the proposed recommendation in practice, in terms of generalisability of study results to the intended target population for the Guideline and setting of the proposed recommendation, and applicability to the Australian (or other local) health care system.[8]

These described components should be rated according to the body of evidence matrix (refer to Table 5). The matrix system is used to summarise the rating of the five key components which allows each recommendation to be assigned an overall NHMRC Grade of Recommendation (A-D).[9]

Table 5: NHMRC Body of evidence matrix[8]

Component	A	B	C	D
Description	Excellent	Good	Satisfactory	Poor

Component	A	B	C	D
Evidence base[#]	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency*	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in body of evidence are similar to target population for the guideline	Populations/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[^]	Populations/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

[#]Level of evidence determined from the NHMRC evidence hierarchy

*If there is only one study, rank this component as 'not applicable'

[^]For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

There is also capacity to note any other relevant factors that were considered by the guideline developers and the respective Working Group when judging the body of evidence and developing the wording of the recommendation.

The NHMRC grades given (A-D) are intended to indicate the strength of the body of evidence underpinning the recommendation (refer to Table 6). Grade A or B recommendations are generally based on a body of evidence that can be trusted to guide clinical practice, whereas Grades C or D recommendations must be

applied cautiously to individual clinical and organisational circumstances and should be interpreted with care. A recommendation cannot be graded A or B unless evidence base and consistency of the evidence are both rated A and B respectively.[9]

Table 6: Definition of NHMRC grades of recommendations[8,9]

Note: This table is replicated in Clinical practice recommendations and practice points

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

By referring to the statements of evidence in combination with the NHMRC body of evidence matrix, a grade for each recommendation was derived from the respective grades allocated to the five key components. Grading the components of consistency, clinical impact, generalisability and applicability, was undertaken by the Working Group members, who discussed each section, and based on consensus achieved across the Working Group, arrived at these ratings.

The use of the NHMRC evidence hierarchy Table, categorises the respective study level according to the study design (refer to Table 3). This is used to determine the respective grades for evidence base and consistency of the recommendation.

Implementing the NHMRC Evidence Hierarchy, each included study in a systematic review should be assessed according to the following three dimensions of evidence:

1. Strength of evidence (level of evidence, quality of evidence (risk of bias) and statistical precision.
2. Size of effect (assessing the clinical importance of the findings of each study and hence addressing the clinical impact component of the body of evidence matrix.
3. Relevance of evidence (translation of research evidence into clinical practice and is potentially the most subjective of the evidence assessments).

Table 7: NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question[8]

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo randomised controlled trial(i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised,	A comparison with reference standard that does not meet the criteria required for Level II and III-1	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised,

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
	experimental trial • Cohort study • Case-control study • Interrupted time series with a control group	evidence			experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Appendix 2: evidence statements for grading the recommendations

SURGERY

Recommendation 1 – Surgery

In patients* with a single metastasis or limited number of brain metastases, the multidisciplinary team should consider initial surgery or radiosurgery[#] (see rec #2) for selected patients.

* Patients with good performance status with a single (or small number of metastases) accessible lesion(s), inactive/well-controlled extra-cranial disease and limited co-morbidities, and patients with raised intracranial pressure or other uncontrolled symptoms.

Hart 2011[12]; Andrews 2004[13]; Aoyama 2006[14]; Akyurek 2007[15]

Component	Grading	
1. **Evidence base** Three randomised controlled trials included in a systematic review	B	One or two Level II studies with low risk of bias or a SR/multiple Level III studies with low risk of bias
2. **Consistency**	B	Most studies consistent and inconsistency can be explained
3. **Clinical impact**	C	Moderate
4. **Generalisability** Not all trial populations had breast cancer, but findings may be applied	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. **Applicability**	B	Evidence applicable to Australian healthcare context with few caveats
Overall grade of recommendation	**B**	
Other factors None identified		
UNRESOLVED ISSUES		

Component	Grading	
None identified		
IMPLEMENTATION OF RECOMMENDATION		
Will this recommendation result in changes in usual care?		**YES** Minor changes to usual care; increased number of surgeries in some locations, little change in other areas
Are there any resource implications associated with implementing this recommendation?		**YES** Resource requirements may increase regarding surgical infrastructure and clinical staff
Will the implementation of this recommendation require changes in the way care is currently organised?		**YES** Increased communication between clinical disciplines and/or multidisciplinary teams may be required to support implementation
Are the guideline development group aware of any barriers to the implementation of this recommendation?		**YES** Increased demand for theatre time may exceed availability in some locations

Recommendation 2 – Surgery

In patients who have had local therapy (surgery or RS) for all metastases and have no measurable CNS disease, give consideration to observation alone with an appropriate salvage technique (surgery, RS or WBRT) used on brain progression. Further treatment should be based on individual patterns of relapse.

EORTC 22952-26001 (Kocher 2011 and Soffieti 2013)[16,17]

Component	Grading	
1. **Evidence base** Two randomised controlled trials	B	One or two Level II studies with low risk of bias or a SR/multiple Level III studies with low risk of bias
2. **Consistency**	B	Most studies consistent and inconsistency can be explained
3. **Clinical impact**	B	Substantial
4. **Generalisability**	B	Evidence directly generalizable to the target

Component	Grading	
Limited number of breast cancer patients, however the Working Group considered it appropriate to apply to this population		population with some caveats
5. **Applicability**	A	Evidence directly applicable to Australian healthcare context
Overall grade of recommendation	**B**	
Other factors None identified		
UNRESOLVED ISSUES None identified		
IMPLEMENTATION OF RECOMMENDATION		
Will this recommendation result in changes in usual care?		**YES** This recommendation supports delaying WBRT
Are there any resource implications associated with implementing this recommendation?		**NO** No significant resource implications associated with implementing this recommendation
Will the implementation of this recommendation require changes in the way care is currently organised?		**NO** This recommendation will not result in changes in the way care is currently organised
Are the guideline development group aware of any barriers to the implementation of this recommendation?		**NO** No barriers identified to the implementation of this recommendation

RADIOTHERAPY

Recommendation 3 – Radiotherapy

On diagnosis of brain metastases, the multidisciplinary team should consider local therapies (radiosurgery or surgery, refer to rec #1) in selected patients*.

* Patients with good performance status (KPS score above 70), small number and small size of metastases suitable for localised therapies, adequate haematological reserve and well-controlled primary disease.

Hart 2011[12]; Andrews 2004[13]; Aoyama 2006[14]; Akyurek 2007[15]

Component	Grading	
1. **Evidence base** Two randomised controlled trials	B	One or two Level II studies with low risk of bias or a SR/multiple Level III studies with low risk of bias
2. **Consistency**	B	Most studies consistent and inconsistency can be explained
3. **Clinical impact** WBRT no longer standard of care for application to all patients	B	Substantial
4. **Generalisability** Limited number of breast cancer patients, however the Working Group considered it appropriate to apply to this population	B	Evidence directly generalizable to the target population with some caveats
5. **Applicability**	A	Evidence directly applicable to Australian healthcare context
Overall grade of recommendation	**B**	
Other factors None identified		
UNRESOLVED ISSUES None identified		
IMPLEMENTATION OF RECOMMENDATION		
Will this recommendation result in changes in usual care?	**YES** WBRT the previous standard of care	
Are there any resource implications associated with implementing this recommendation?	**YES** Potentially, as more radiosurgery resources may be required	
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO** This recommendation will not result in changes in the way care is currently organised	

Component	Grading
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**YES** There may be resource allocation issues

Recommendation 4 – Radiotherapy

Consider WBRT for patients* who are not eligible for surgery or radiosurgery.

*Patients with multiple metastases, uncontrolled extra-cranial disease, limited prognosis, or not expected to benefit from radiosurgery or surgery.

Harwood 1977[25]; Kurtz 1981[26]; Andrews 2004[20]

Component	Grading	
1. **Evidence base**	D	Level IV studies, or Level I to III studies with high risk of bias
2. **Consistency**	A	All studies consistent
3. **Clinical impact**	C	Moderate
4. **Generalisability**	B	Evidence directly generalizable to the target population with some caveats
5. **Applicability**	A	Evidence directly applicable to Australian healthcare context
Overall grade of recommendation	**C**	
Other factors None identified		
UNRESOLVED ISSUES None identified		
IMPLEMENTATION OF RECOMMENDATION		
Will this recommendation result in changes in usual care?		**YES** No perceived change in standard clinical practice as WBRT was the previous standard of care

Component	Grading
Are there any resource implications associated with implementing this recommendation?	**NO** No significant resource implications associated with implementing this recommendation
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO** This recommendation will not result in changes in the way care is currently organised
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO** No barriers identified to the implementation of this recommendation

Recommendation 2 – Radiotherapy

In patients who have had local therapy (surgery or RS) for all metastases and have no measurable CNS disease, give consideration to observation alone with an appropriate salvage technique (surgery, RS or WBRT) used on brain progression. Further treatment should be based on individual patterns of relapse.

EORTC 22952-26001 (Kocher 2011 and Soffieti 2013)[16,17]

Component		Grading
6. **Evidence base** Two randomised controlled trials	B	One or two Level II studies with low risk of bias or a SR/multiple Level III studies with low risk of bias
7. **Consistency**	B	Most studies consistent and inconsistency can be explained
8. **Clinical impact**	B	Substantial
9. **Generalisability** Limited number of breast cancer patients, however the Working Group considered it appropriate to apply to this population	B	Evidence directly generalizable to the target population with some caveats
10. **Applicability**	A	Evidence directly applicable to Australian healthcare context
Overall grade of recommendation	**B**	
Other factors		

Component	Grading
None identified	
UNRESOLVED ISSUES None identified	
IMPLEMENTATION OF RECOMMENDATION	
Will this recommendation result in changes in usual care?	**YES** This recommendation supports delaying WBRT
Are there any resource implications associated with implementing this recommendation?	**NO** No significant resource implications associated with implementing this recommendation
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO** This recommendation will not result in changes in the way care is currently organised
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO** No barriers identified to the implementation of this recommendation

SYSTEMIC THERAPIES

Recommendation 5 – Systemic therapies

Avoid routine use of chemotherapy with WBRT in patients with newly diagnosed brain metastases.

Mehta 2010[28]

Component	Grading	
1. **Evidence base** Five studies included in systematic review by Mehta – four randomised, including two phase II studies. Small numbers of breast cancer patients included in trials	C	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias
2. **Consistency** Similar results shown across studies	B	Most studies consistent and inconsistency can be explained

Component	Grading	
3. **Clinical impact** No evidence of benefit shown in included studies	C	Moderate
4. **Generalisability** Most included patients from lung cancer trials, however can be applied to breast cancer patients	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. **Applicability** It is feasible to apply this recommendation	B	Evidence applicable to Australian healthcare context with few caveats
Overall grade of recommendation	**C**	
Other factors If patient is receiving chemotherapy for control of extra-cranial disease, it is not clear from the available evidence whether that should be stopped or not		
UNRESOLVED ISSUES None identified		
IMPLEMENTATION OF RECOMMENDATION		
Will this recommendation result in changes in usual care?		**NO** No perceived change in standard clinical practice and care
Are there any resource implications associated with implementing this recommendation?		**YES** Positive effect – cost savings through less medications, potential for less treatment-related morbidity
Will the implementation of this recommendation require changes in the way care is currently organised?		**NO** This recommendation will not result in changes in the way care is currently organised
Are the guideline development group aware of any barriers to the implementation of this recommendation?		**NO** No barriers identified to the implementation of this recommendation

Component	Grading

Recommendation 6 – Systemic therapies

To achieve optimal control of extra-cranial disease, HER2- targeted therapies (such as trastuzumab) should be started or continued in HER2-positive patients after the diagnosis of brain metastases.

Pestalozzi 2013[29]; Bartsch 2007[30]; Church 2008[31]; Dawood 2008[32]; Park 2009[33]; Le Scodan 2011[34]; HERA 2013[29]

Component	Grading	
1. **Evidence base** Retrospective trials	C	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias
2. **Consistency**	B	Most studies consistent and inconsistency can be explained
3. **Clinical impact** Trastuzumab does not cross blood-brain barrier but patients tend to do better with well-controlled systemic disease, minimal harm observed	B	Substantial
4. **Generalisability**	B	Evidence directly generalizable to target population with some caveats
5. **Applicability** Feasible to apply within PBS	B	Evidence applicable to Australian healthcare context with some caveats
Overall grade of recommendation	**C**	
Other factors None identified		
UNRESOLVED ISSUES None identified		
IMPLEMENTATION OF RECOMMENDATION		
Will this recommendation result in changes in usual care?	**NO** No perceived change in standard clinical practice	

Component	Grading	
		and care
Are there any resource implications associated with implementing this recommendation?		**YES** Expense associated with ongoing treatment, requires intravenous treatment, monitoring of cardiac function may be required, used for any metastatic disease
Will the implementation of this recommendation require changes in the way care is currently organised?		**NO** This recommendation will not result in changes in the way care is currently organised
Are the guideline development group aware of any barriers to the implementation of this recommendation?		**NO** No barriers identified to the implementation of this recommendation

Recommendation 7 – Systemic therapies

HER2-positive patients with progressive or residual disease following local therapy and trastuzumab may be offered lapatinib in combination with capecitabine.

Lin 2009[35]

Component	Grading	
1. **Evidence base** One phase II randomised study	D	Level IV studies, or Level I to III studies with high risk of bias
2. **Consistency**	N/A	One study only
3. **Clinical impact** Patients limited in other choices following progression after local therapy, better control over longer period of time, reluctance to change to lapatinib among oncologists	C	Moderate
4. **Generalisability** Feasible within PBS guidelines	D	Evidence not directly generalizable to target population and hard to judge whether it is sensible to apply

Component	Grading	
5. **Applicability** Feasible to apply	C	Evidence probably applicable to Australian healthcare context with some caveats
Overall grade of recommendation	**C**	
Other factors None identified		
UNRESOLVED ISSUES None identified		
IMPLEMENTATION OF RECOMMENDATION		
Will this recommendation result in changes in usual care?		**YES** Limited number of clinicians currently offering this as standard treatment, reluctance to change to lapatinib
Are there any resource implications associated with implementing this recommendation?		**YES** Oncologist time unfunded as no item number available for non-IV delivery
Will the implementation of this recommendation require changes in the way care is currently organised?		**YES** Non-IV delivery indicates there will be no chemo nurse providing regular support, increasing the supportive care burden on treating oncologist
Are the guideline development group aware of any barriers to the implementation of this recommendation?		**YES** PBS item number not available

SPINAL CORD COMPRESSION

Recommendation 8 – Spinal cord compression

In patients* with symptomatic spinal cord compression caused by metastatic disease, circumferential surgical decompression should be performed (within 24 hours), with or without fusion, followed by radiotherapy.

*Patients who are acceptable surgical candidates and have expected survival of at least three months.

Patchell 2005[40]

Component	Grading	
1. **Evidence base** One RCT	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. **Consistency**	N/A	One study only
3. **Clinical impact**	B	Substantial impact
4. **Generalisability**	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. **Applicability**	B	Evidence applicable to Australian healthcare context with few caveats
Overall grade of recommendation	**B**	
Other factors None identified		
UNRESOLVED ISSUES None identified		
IMPLEMENTATION OF RECOMMENDATION		
Will this recommendation result in changes in usual care?		**YES** Standard treatment for spinal cord compression is corticosteroids and radiotherapy
Are there any resource implications associated with implementing this recommendation?		**YES** Not all health services have access to neurosurgery and MRI
Will the implementation of this recommendation require changes in the way care is currently organised?		**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?		**YES** Demand for after-hours MRI and surgical services may be increased and this may stretch existing infrastructure and staff

Component	Grading

Recommendation 9 – Spinal cord compression

Start external beam radiotherapy as soon as possible for patients considered unsuitable for surgery.

Loblaw 2005[41]

Component	Grading	
1. **Evidence base** One systematic review	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. **Consistency**	N/A	One study only
3. **Clinical impact**	B	Moderate
4. **Generalisability**	B	Evidence directly generalisable to the target population with some caveats
5. **Applicability**	B	Evidence applicable to Australian healthcare context with some caveats
Overall grade of recommendation	**B**	
Other factors None identified		
UNRESOLVED ISSUES None identified		
IMPLEMENTATION OF RECOMMENDATION		
Will this recommendation result in changes in usual care?		**NO** Standard treatment for spinal cord compression is corticosteroids and radiotherapy
Are there any resource implications associated with implementing this recommendation?		**YES** A shortage of radiotherapy machines and specialists is currently limiting timely access to urgent radiotherapy treatment

Component	Grading
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**YES** Access to radiotherapy machines and specialists.