

# **Management of central nervous system (CNS) metastases in women with secondary breast cancer**

A systematic review

**December 2013**

Management of central nervous system (CNS) metastases in women with secondary breast cancer: a systematic review was prepared and produced by:

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## Contributors

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The management of women with CNS metastases from secondary breast cancer: a systematic review was developed with input from an expert multidisciplinary Working Group with the following members:

- |                                |                           |
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See Appendix A for more information.

## Executive summary

Breast cancer is the most common cancer among Australian women, accounting for 27% of all cancer diagnoses in 2009.<sup>1</sup> In 2013 it is estimated that 14,940 women will be diagnosed with breast cancer in Australia.<sup>2</sup>

A recent modelling study estimated the prevalence of metastatic breast cancer in Australian women.<sup>3</sup> It was estimated that in 2004, 8,284 women were alive who had been diagnosed with metastatic breast cancer, with the highest prevalence of 4,696 for women 0-4 years after metastatic diagnosis, compared with only 949 women over 20 years after metastatic detection.

Breast cancer is the second most common cancer associated with central nervous system (CNS) metastases, after lung cancer.<sup>4,5</sup> The incidence of brain metastases appears to be increasing; this is likely because patients with metastatic breast cancer are surviving longer.<sup>6</sup> Approximately 10-15% of women with metastatic breast cancer will develop CNS metastases.<sup>7,8</sup> CNS metastases are less common than bone, liver or lung metastases, however they are associated with the shortest survival time.<sup>5</sup>

In 2001 National Breast Cancer Centre\* published *Clinical practice guidelines-Management of advanced breast cancer* which included recommendations for the management of CNS metastases.<sup>9</sup> This systematic review was undertaken by Cancer Australia to update the information on the management of women with CNS metastases from the 2001 clinical practice guidelines.

A search of the literature published between January 2001 and April 2012 was undertaken using electronic databases. The primary search was limited to trials conducted in humans published in the English language. This systematic review focuses on evidence for the management of women with CNS metastases from **breast cancer** rather than CNS metastases from various primary tumours. However, some studies included in this systematic review had patient populations with mixed primary tumours and where available the results specific to the **breast cancer** populations in these primary studies are reported in this systematic review.

For this systematic review, CNS metastases from secondary breast cancer included metastases in the brain and in the spinal cord (including metastatic spinal cord compression), and both parenchymal and meningeal (leptomeningeal) metastases.

Fifty seven citations were included in the review for the five primary research questions. Fifty-one citations were included for areas identified as other issues. Seven systematic reviews, including two Cochrane reviews were also used as primary references. These systematic reviews included evidence for management for CNS metastases in populations of mixed primary cancers.

The key results for each research question on the management of CNS metastases from secondary breast cancer are summarised below.

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\* In February 2008 National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

## **What is the effectiveness of surgery in the management of CNS metastases from breast cancer?**

Two systematic reviews, including one Cochrane review, assessed the effectiveness of **surgical resection** in the management of newly diagnosed single brain metastases in patients with mixed primary tumours. The Cochrane review by Hart et al of three randomised controlled trials (RCTs) including patients with brain metastases from various primary tumours, reported no significant difference in survival between surgery plus whole brain radiotherapy (WBRT) compared with WBRT alone.

One randomised controlled trial (RCT) (Patchell 2005) was identified which assessed the efficacy of direct decompressive surgery plus postoperative radiotherapy compared with radiotherapy alone in patients with MESCC caused by metastatic cancer. Patients with MESCC treated with direct decompressive surgery plus postoperative radiotherapy had better post treatment ambulatory rates, retained the ability to walk for longer as well as regain the ability to walk more often and had improved survival compared to patients treated with radiotherapy alone.

One retrospective study was identified which reported on the surgical management of CNS metastases in breast cancer patients. One retrospective study was identified which reported on the surgical management of metastatic epidural spinal cord compression (MESCC) in breast cancer patients.

Cahill et al (2011) reported that approximately one-third of cranial surgery patients and one-half of spinal surgery patients were alive 1 year after surgery. In this study, inpatient death rates after neurosurgical treatment of metastatic disease decreased in the decade 1996-2005. Long-term postoperative survival for cranial surgery remained relatively constant, while survival after spinal fusion, but not laminectomy alone, increased in the decade 1996-2005.

Tancioni et al (2011) reported median survival of 36 months, remission of pain and recovery of neurologic deficit, for patients with metastatic epidural spinal cord compression undergoing surgery and radiation therapy, suggesting that, surgery and radiotherapy is feasible with limited morbidity and mortality.

## **What is the effectiveness of radiotherapy in the management of CNS metastases from breast cancer?**

### **Whole Brain Radiotherapy (WBRT)**

Five systematic reviews, including a Cochrane review, assessed the effectiveness of **radiotherapy** alone or in combination with other therapies. The Cochrane review by Tsao et al (2012) addressed various radiotherapy comparisons in patients with CNS metastases from mixed primary tumours. No benefit of altered dose-fractionation schedules compared to the control fractionation of standard WBRT (30 Gy delivered in 10 fractions daily) for overall survival was reported.

Three retrospective studies evaluating the effectiveness of different doses of WBRT compared to the standard dose in populations that included patients with breast cancer primaries were identified. A retrospective study by Rades et al, found dose escalation beyond 30 Gy in 10 fractions did not improve survival ( $p=0.86$ ) or local control ( $p=0.61$ ). Dose escalation was also associated with increased treatment time and cost of therapy.



In two retrospective studies by Rades et al, shorter course WBRT had similar survival and local control to longer course WBRT, with one study reporting significantly improved survival with shorter course regimens in univariate analysis. Shorter course WBRT may be preferable for the majority of these patients because it is less time consuming and more convenient.

Karnofsky Performance Status (KPS)  $\geq 70$  and no extracranial metastases were associated with longer survival in multivariate analyses across the three Rades studies.

The Tsao 2012 Cochrane review reported that the addition of radiosensitizers (in patients with mixed primary tumours) did not confer additional benefit to WBRT in either overall survival times or brain tumour response rates.

One phase III RCT, the REACH study, investigating the addition of efaproxiral to WBRT was identified. Results of the 3 analyses of the REACH randomised study indicated that the addition of efaproxiral to Whole Brain Radiotherapy (WBRT) may improve response rates and survival in patients with brain metastases and particularly in those patients with brain metastases from breast cancer. Median survival ranged from 6-9 months in patients receiving efaproxiral compared with 4.4-4.5 months without efaproxiral and efaproxiral also reduced risk of death by 25-48%. Response rates were also higher in breast cancer patients who received efaproxiral (74% vs. 49%  $p=0.007$ ) and in breast/lung cancer patients (54% vs. 41%  $p=0.01$ ).

## **Radiosurgery**

The Tsao 2012 Cochrane review included comparisons between WBRT and **radiosurgery** in patients with CNS metastases from various primary tumours. Two RCTs included in the Tsao review reported no difference in overall survival with the use of WBRT and radiosurgery boost compared to WBRT alone for selected participants with multiple brain metastases (up to four brain metastases). There was a statistically significant improvement in local control in selected patients who received radiosurgery boost compared to WBRT alone.

Two RCTs included in the Tsao review found no difference in overall survival between radiosurgery alone and radiosurgery and WBRT. The addition of WBRT to radiosurgery significantly improved locally treated brain metastases control and distant brain control.

Three retrospective studies were identified that compared SRS alone with SRS and WBRT. In two studies, in patients with newly diagnosed CNS metastases, SRS alone was associated with longer survival compared with WBRT and SRS as a focal boost ( $p=0.036$ ). SRS alone was also associated with improved local control (6.5 months vs. 4 months WBRT with SRS boost) and freedom from new brain metastases (14.8 months vs. 11.3 months for SRS + WBRT).

Three non-comparative studies of gamma knife surgery (GKS) were identified. Median overall survival after GKS was 13 months in two studies and in the third study was 16 months for newly diagnosed patients and 11.7 months for patients with recurrence brain metastases.

SRS as salvage therapy for recurrent CNS metastases, reported in three studies, was associated with median survival of between 11.7 months and 19 months.

## Subgroups

Significantly longer survival for HER2-positive compared to HER2-negative patients was reported in two retrospective studies following WBRT and in one retrospective study following GKS.

## What is the effectiveness of systemic therapies in the management of CNS metastases from breast cancer?

### Chemotherapy

A systematic review (Mehta 2010) assessing the addition of chemotherapy to WBRT in patients with newly diagnosed CNS metastases from various primary tumours, reported no survival or neurologic progression benefit compared with WBRT alone.

Eight studies were identified that investigated different chemotherapies for the management of CNS metastases, and included trials of the agents: temozolomide alone or in combination, sagopilone, patupilone and methotrexate. All these were phase I or phase II single arm studies and included small patient populations in general. Objective response rates ranged from 4 – 40% and adverse events included fatigue and diarrhoea.

### HER2-directed therapies

Six retrospective comparative studies of the use of trastuzumab in patients with brain metastases from HER2-positive breast cancer were identified. Increased survival and longer time to progression was reported in HER2-positive patients who were treated with trastuzumab or continued with trastuzumab, after diagnosis of CNS metastases compared to patients who did not receive trastuzumab.

One single arm phase II study was identified which investigated the use of lapatinib in combination with capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer. Overall survival at 6 months was 90.9% (95% CI 77.6-96.5) and the median overall survival for the 44 patients who were assessable for efficacy outcomes was 17.0 months (13.7–24.9). Objective response rate of 65.9% was reported, all of which were partial responses. At the time of analysis, 36 (82%) patients had received radiotherapy to the brain and median time to radiotherapy was 8.3 months.

Eight studies investigating the use of lapatinib, or lapatinib in combination with other agents, including capecitabine, for previously treated CNS metastases from HER2 positive metastatic breast cancer were identified. These included two prospective phase II trials and one randomised phase II trial. Objective response rates reported ranged from 2.6% to 6% in patients who received lapatinib alone and from 20% to 38% in patients who received lapatinib in combination with capecitabine, while no objective responses were observed in patients receiving lapatinib and topotecan. Adverse events reported included diarrhoea, palmarplantar erythrodysesthesia (lapatinib + capecitabine), nausea and fatigue.

One small study has suggested lapatinib, compared with trastuzumab, may improve overall survival in patients after completion of local therapy.

## Subgroups

Results from one retrospective study indicated that systemic therapy following WBRT appears to improve survival in patients with luminal A, luminal B and HER2-positive breast cancer subtypes. Targeted therapy was found to have an additional positive impact on survival. In patients with triple negative breast cancer, the role of systemic therapy after WBRT appears to be less clear and therefore requires further investigation.

### **What is the effectiveness of combinations of treatments in the management of CNS metastases from breast cancer?**

Two non-comparative phase II trials investigated the combination of radiotherapy and chemotherapy. Both combinations of radiotherapy and chemotherapy (one study patients received temozolomide and other study patients received concurrent cisplatin and vinorelbine) appeared to be active and well tolerated. In the two studies, objective response rates were 58% and 76%, and complete response rates were observed in 7.4% and 12% of patients. In the two studies, median survival was 6.5 months and 8.8 months and 1 year survival was 18.5% and 28%; median progression free survival (PFS) was 5.2 months and 6 months.

One retrospective study reported significantly longer survival for surgery + radiotherapy vs. radiotherapy alone ( $p=0.001$ ) as well as longer survival in patients who receive systemic chemotherapy after radiotherapy ( $p=0.015$ ).

One retrospective study that included 15% patients with breast cancer primary tumour reported that surgery + 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 ( $p<0.001$ ).

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

### **Are there specific requirements for the management of the sub-group of patients diagnosed with asymptomatic CNS metastases?**

One prospective study was identified that investigated asymptomatic compared with symptomatic brain metastases in HER2-positive breast cancer patients. The study concluded that in HER2-positive breast cancer patients with visceral and brain metastases, WBRT performed during the asymptomatic period had no influence on survival but decreased the risk of cerebral death. The study showed visceral (lung/liver) metastases to be a significant predictor (univariate analysis) of brain metastasis development and cause of death in majority of patients.



# 1 Background

## 1.1 Breast cancer in Australia

Breast cancer is the most common cancer among Australian women, accounting for 27% of all cancer diagnoses in 2009.<sup>1</sup> In 2013 it is estimated that 14,940 women will be diagnosed with breast cancer in Australia.<sup>2</sup> It is estimated that in 2007 there were 151,200 Australian women alive who had been diagnosed with breast cancer in the previous 26 years.<sup>10</sup>

A recent modelling study estimated the prevalence of metastatic breast cancer in Australian women.<sup>3</sup> It was estimated that 8,284 women were alive in 2004 who had been diagnosed with metastatic breast cancer, with the highest prevalence of 4,696 women for 0-4 years after metastatic diagnosis, compared with only 949 alive over 20 years after metastatic detection.

## 1.2 CNS metastases from breast cancer

Breast cancer is the second most common cancer associated with central nervous system (CNS) metastases, after lung cancer.<sup>4,5</sup> The incidence of CNS metastases appears to be increasing; this is because patients with metastatic breast cancer are surviving longer.<sup>6</sup> Approximately 10-15% of women with metastatic breast cancer will develop CNS metastases.<sup>7,8</sup> CNS metastases are less common than bone, liver or lung metastases, however, they are associated with the shortest survival time.<sup>5</sup> The median time from diagnosis of the primary cancer to the development of CNS metastasis is approximately between 2 and 3 years.<sup>4</sup>

Breast cancer cells metastasize to the brain through the vasculature where they proliferate and subsequently invade the brain parenchyma, while most therapeutic agents with a high-molecular weight are excluded by the diffusion barrier. The blood brain barrier (BBB) is the protective mechanism for the exclusion of toxic agents.<sup>8</sup> The BBB consists of endothelial cells sealed by tight junctions. Around the capillary is a layer of basement membrane, as well as, pericytes and astrocyte foot processes. It is not clear how tumour cells compromise the highly restrictive structure of the BBB, invade the parenchyma, and grow to become macrometastases.<sup>4</sup>

Women with HER2-positive or triple negative breast cancer have been reported to have an increased risk of developing CNS metastases.<sup>6</sup> Other risk factors associated with an increased likelihood of CNS metastases include young age (<40 years), pulmonary metastases, BRCA1 mutation carriers and ER-negative tumours.

There have been a number of theories proposed as to why there is a higher incidence of brain metastases in patients who receive adjuvant trastuzumab, as reviewed by Viani et al 2007.<sup>11</sup> One theory suggests that HER2 overexpression endows tumour cells with increased metastatic access to the CNS and lungs. Secondly, by allowing patients to live longer, trastuzumab may allow micrometastatic brain metastases to become symptomatic as a natural consequence of the patient's extended life span. A third

theory speculates that trastuzumab is effective against systemic metastases but relatively ineffective against CNS metastases due to its poor penetration of the BBB. That hypothesis may extend to cytotoxic chemotherapy as well as trastuzumab.<sup>11</sup>

The appropriate management of CNS metastases from breast cancer should consider the following factors:

- Performance status
- Number, size and site of lesions
- Status of systemic metastases
- Expected toxicities of treatment<sup>5,6</sup>

For patients with brain metastases from lung, breast and other solid tumours, the Radiation Therapy Oncology Group (RTOG) has defined, using recursive partitioning analysis (RPA), prognostic groups, which are based upon Karnofsky performance status (KPS), age, disease status of the primary site, and extent of extracranial metastases.<sup>6</sup> The three RPA classes are:

- Class 1 (favourable prognosis): patients with KPS  $\geq 70$ , < 65 years of age with controlled primary and no extracranial metastases (median survival 7 months)
- Class 3 (poor prognosis): KPS < 70 (median survival 2 months)
- Class 2 (intermediate prognosis): all others (median survival 4 months)<sup>6</sup>

The RTOG-RPA prognostic classes are used to stratify patients into favourable and poor prognosis in order to determine the appropriate therapeutic approach.<sup>6,12</sup>

A disease-specific Graded Prognostic Assessment (GPA) score has recently been developed, which takes into account tumour subtype. For breast cancer, the GPA score included KPS, ER/PR status, HER2 status and age. Median survival ranges from 3.4 months GPA 0-1 (worst prognosis) group to 25.3 months GPA 3.5-4.0 (best prognosis) group.<sup>6,13</sup> In contrast to the RPA, more patients were allocated to the good prognosis group, suggesting that the GPA may be more useful clinically than the RPA.<sup>6</sup>

CNS metastases are associated with poor outcomes including survival, morbidity and quality of life. The prognosis of women with brain metastases from breast cancer is poor; median survival is 2.3-7.1 months.<sup>4</sup>

## 1.3 Current clinical practice guidelines

In 2001 National Breast Cancer Centre<sup>†</sup> published guidelines on the management of women with advanced breast cancer which included recommendations for the management of CNS metastases.<sup>9</sup> The 2001 guidelines made the following recommendations:

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<sup>†</sup> In February 2008 National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

Cerebral metastases:

1. Treatment of cerebral metastases with radiotherapy should be considered, as it leads to improvement in symptoms.<sup>9</sup>
2. Systemic chemotherapy may be an alternative to cerebral radiation therapy, particularly in patients with symptomatic metastases outside the brain.<sup>9</sup>
3. Resection of solitary cerebral metastases followed by radiotherapy potentially results in increased local control and a longer disease-free survival than radiotherapy alone.<sup>9</sup>

Spinal cord compression:

1. Treatment of spinal cord compression with radiotherapy is considered as equally effective as surgery in achieving symptomatic relief.<sup>9</sup>
2. Radiotherapy is recommended following surgical treatment of spinal cord compression.<sup>9</sup>
3. Patients with spinal cord compression who are ambulatory and retain bladder or bowel function prior to the commencement of radiotherapy, have the most favourable neurological outcome.<sup>9</sup>

Meningeal carcinomatosis: treatment of meningeal carcinomatosis involves intrathecal chemotherapy, and may be supplemented with whole-brain or spinal irradiation, depending on the location of focal abnormalities. The optimum combination of intrathecal chemotherapy and irradiation has not been defined.<sup>9</sup>

## **1.4 Current systematic review**

This systematic review of the literature was undertaken to identify any revisions required and to ensure currency of the 2001 guidelines on the management of women with advanced breast cancer. Following consultation with a multidisciplinary working group, it was agreed that the scope of the review would include metastases in the brain and in the spinal cord (including metastatic spinal cord compression), and both parenchymal and meningeal (leptomeningeal) metastases.

## 2 Methods

This systematic review addresses five research questions which were developed with input from a multidisciplinary working group. The questions addressed were:

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?

### 2.1 Inclusion criteria

This systematic review will focus on evidence for the management of women with CNS metastases from **breast cancer** not CNS metastases from various primary tumours. However, some studies included in this systematic review have patient populations with mixed primary tumours and therefore only results specific to the **breast cancer** populations of these studies will be reported in this systematic review.

#### 2.1.1 Participants

For questions 1 to 4: women with CNS metastases from secondary breast cancer.

For question 5: asymptomatic women with CNS metastases from secondary breast cancer.

#### 2.1.2 Intervention/Comparison

For question 1: various types of surgery in comparison to other surgery or other treatment modalities or no surgery

For question 2: various radiotherapy regimens (including whole brain radiotherapy, stereotactic radiosurgery, stereotactic radiotherapy) in comparison with other radiotherapy regimens or other treatment modalities or no radiotherapy

For question 3: various systemic therapies in comparison with other systemic therapies or other treatment modalities or a placebo



For question 4: various combinations of surgery/radiotherapy/ systemic therapies

For question 5: active treatment in comparison with no treatment / surveillance

### **2.1.3 Outcome measures**

Outcome measures of interest were:

- overall survival
- recurrence of CNS metastases
- neurocognitive and psychological impairments
- quality of life
- adverse events

### **2.1.4 Additional issues of interest**

The following topics were considered as additional issues of interest, and although they were not specifically searched for in the systematic review, as this was not feasible within the available timeframe and resources, any information on these topics identified was reported:

- 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 secondary 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 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 secondary breast cancer
- Use of other medications including steroids and anticonvulsants.

## 2.2 Literature search

A systematic literature search was conducted in April 2012 to identify relevant studies which address the inclusion criteria. The search was conducted using several databases (see appendix B), including:

- Medline
- Embase
- Pubmed

Additional papers identified from personal files and the reference lists of included papers were also sourced.

The search strategy, developed with input from a multidisciplinary working group, used combined key terms which described breast cancer, CNS and metastases. The search was limited to papers published between January 2001 and April 2012, conducted in humans and in the English language, see appendix C.

After the removal of duplicates a total of 1315 citations remained. The titles and abstracts of these citations were assessed by two reviewers independently to determine eligibility for the current review based on the inclusion criteria described previously. Ineligible studies were classified using the exclusion criteria below. For citations which provided insufficient information to assess eligibility, the full text was retrieved for assessment, by the same two reviewers.

In addition to the above database, guideline and clinical trial websites were searched for relevant information. Specific internal guideline organisations were searched as well as the National Guidelines Clearinghouse and the Guidelines International Network (GIN) guideline library. Clinical trials site searched included the [clinicaltrials.gov](http://clinicaltrials.gov) (USA) and [controlledtrials.com](http://controlledtrials.com) (UK). Further information on sites searched can be found in appendix D.

The following conference websites were searched from January 2008 to June 2012 to identify recently presented abstracts about CNS metastases from breast cancer:

- American Society of Clinical Oncology (ASCO)
- San Antonio Breast Cancer Symposium (SABCS)

### 2.2.1 Exclusion criteria

Papers were excluded if they met any of the following criteria:

- Not an original clinical study: publications not reporting the findings of original clinical studies including non-systematic reviews, editorials, opinion pieces and letters.
- Inappropriate population: studies in a population other than as defined in the inclusion criteria. Studies with less than 10% breast cancer patients and/or less than 10 breast cancer patients were excluded

- Inappropriate interventions: studies not investigating the management of women with CNS metastases from secondary breast cancer
- Inappropriate outcomes
- Not published in the English language
- Published prior to 2001
- Molecular profile studies and clinicopathologic characteristics studies.
- Prognostic studies on risk of metastases
- Non comparative studies
- Non-comparative retrospective studies

Based on these criteria, 909 articles were excluded. The full texts of the remaining 406 citations were retrieved and assessed to identify which met the inclusion criteria for the review. Non-systematic overview papers were sourced and reference lists were checked for further articles of interest. After full text assessment, 108 citations and one abstract were identified as eligible for the current review (see Appendix E).

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

Six randomised studies were included in the review for the primary research questions. Seven previously published systematic reviews, including six Cochrane reviews were also used as primary references.

## 2.3 Data extraction

Data extraction was performed by one reviewer and verified by a second reviewer to ensure accuracy. Descriptive data extracted from the studies included characteristics such as population, interventions and primary outcomes.

Outcome data extracted from the studies included overall survival, progression-free survival, treatment compliance, response to chemotherapy, adverse events and quality of life.

## 3 Results

### 3.1 International guidelines and recommendations

In 2001 National Breast Cancer Centre<sup>‡</sup> published guidelines on the management of women with advanced breast cancer which included recommendations for the management of CNS metastases.<sup>9</sup> Please see section 1.3 for detailed recommendations.

Six international guidelines were identified that address **CNS metastases from breast cancer** in their recommendations, specific recommendations are presented below.

#### 1. National Comprehensive Cancer Network (NCCN)

*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)*.<sup>14</sup> These are consensus-based guidelines.

Treatment flow charts are available for limited (1-3) metastatic lesions, multiple (>3) metastatic lesions, leptomeningeal metastases and metastatic spine tumours. Each flowchart includes recommendations for clinical presentations, workup, primary treatment, follow up and recurrence. The guidelines include treatment recommendations for systemic therapy, radiotherapy and surgery.

The NCCN guidelines include the following recommendations specific to the management of CNS metastases from breast cancer primary tumours:

Limited (1-3) metastases or multiple (>3) metastatic lesions:

Organ specific treatment:

- High dose methotrexate (breast and lymphoma).
- Capecitabine, cisplatin, etoposide (breast).

Leptomeningeal metastases:

- Patients with breast or lymphoma may receive high-dose methotrexate or craniospinal radiotherapy.

#### 2. National Institute for Health and Care Excellence (NICE)

*Advanced breast cancer: diagnosis and treatment (2009)*.<sup>15</sup> These guidelines are based on a systematic review.

The NICE guidelines include the following recommendations specific to the management of CNS metastases from breast cancer primary tumours:

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<sup>‡</sup> In February 2008 National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

Offer surgery followed by WBRT to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well-controlled other metastatic disease.

Offer WBRT to patients for whom surgery is not appropriate, unless they have a very poor prognosis.

Offer active rehabilitation to patients who have surgery and/or WBRT.

Offer referral to specialist palliative care to patients for whom active treatment for brain metastases would be inappropriate.

Qualifying statement: These recommendations are based on evidence from retrospective case series.

### **3. European Society of Medical Oncology (ESMO)**

*Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2011)*<sup>16</sup> These are consensus-based guidelines.

The ESMO guidelines include the following recommendations specific to the management of CNS metastases from breast cancer primary tumours:

Radiation therapy is an integral part of palliative treatment. The most common indications for palliative radiotherapy include:

- Brain metastases: in patients with single or few metastatic foci, SRS can be used as an alternative to surgical resection, with improvement in local control and fewer side effects than WBRT.

### **4. European Federation of Neurological Societies (EFNS)**

*Brain metastases: EFNS guidelines on brain metastases (2011)*.<sup>17</sup> These guidelines are based on a systematic review.

The EFNS guidelines include the following recommendations specific to the management of CNS metastases from breast cancer primary tumours:

Chemotherapy may be the initial treatment for patients with brain metastases from chemosensitive tumours, like small - cell lung cancers, lymphomas, germ cell tumours, and breast cancers, especially if asymptomatic, chemo – naïve, or an effective chemotherapy schedule for the primary is still available.

### **5. Central European Cooperative Oncology Group**

*Third consensus on medical treatment of metastatic breast cancer (2009)*.<sup>18</sup> These guidelines are based on a literature review.

The Central European Cooperative Oncology Group guidelines include the following recommendations specific to the management of CNS metastases from breast cancer primary tumours:

Recommendation: Lapatinib as a single agent or in combination with capecitabine should be considered in Her-2/neu-positive patients with CNS metastases and those who progressed after previous therapy including trastuzumab.

## **6. German Society of Radiation Oncology (DEGRO)**

*DEGRO Practical Guidelines for palliative radiotherapy of breast cancer patients: brain metastases and leptomeningeal carcinomatosis (2010).*<sup>19</sup> These guidelines are based on a systematic review.

The DEGRO guidelines include the following recommendations specific to the management of CNS metastases from breast cancer primary tumours:

### Brain metastases

Systemic application of corticosteroids is the standard treatment for brain edema. With dexamethasone, symptoms of intracranial pressure are rapidly alleviated within 4-24 hours. A dose of 4 mg is adequate to start with and may be increased according to remaining symptoms. Doses of 4, 8, or 16 mg showed equivalent effectiveness after 1 week of medication; however side effects after 4 weeks were more pronounced with 16 mg. As symptoms may recur in case of rapid reduction, the dose should be reduced stepwise over a period of weeks.

Prophylactic administration of anticonvulsant drugs is not recommended; when necessary, interactions with other drugs such as chemotherapeutic agents or steroids have to be taken into consideration and dose monitoring is mandatory

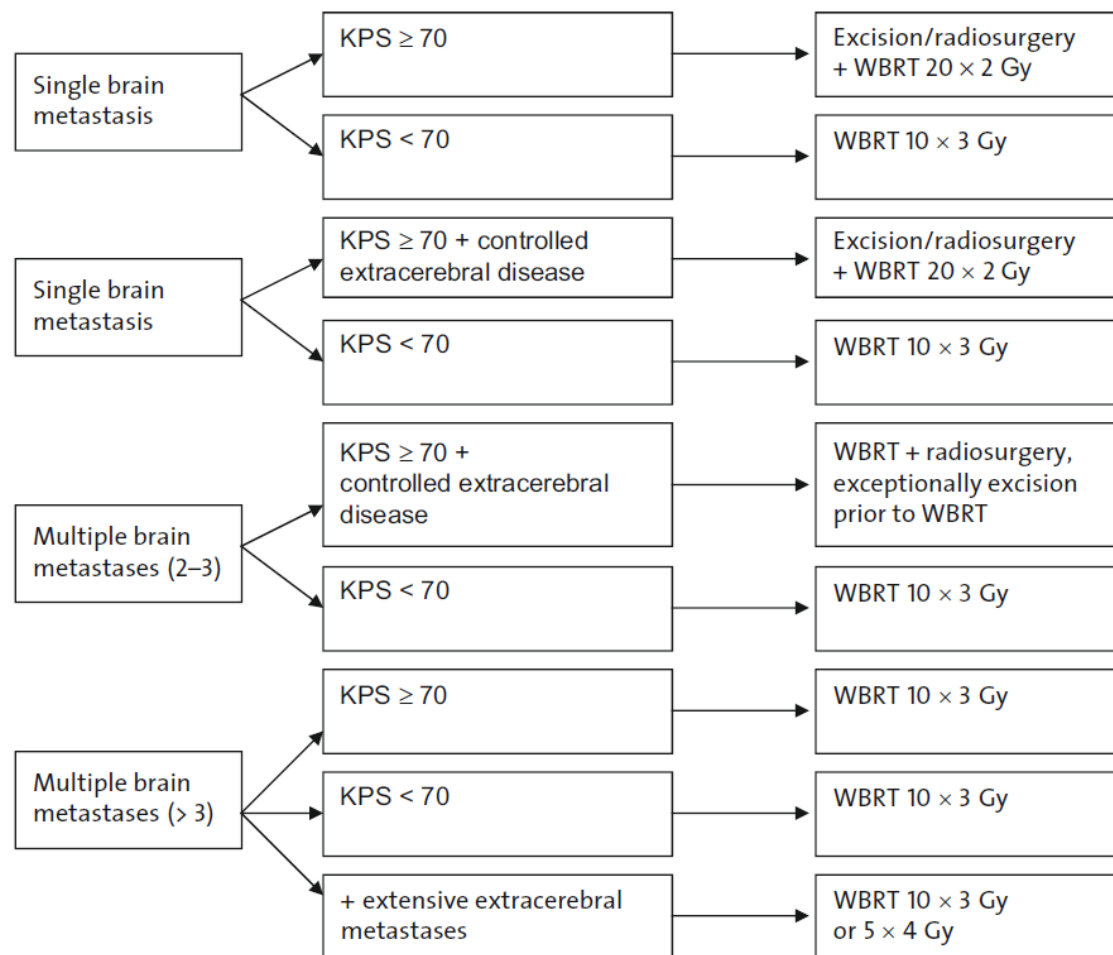
In patients with low performance status (KPS <50%) for whom specific tumour treatment is not indicated and steroids are not effective, pain medication and sedative treatment should be administered as supportive care.

The DEGRO guidelines included the following treatment algorithm for brain metastases from breast cancer, see figure 1. The algorithm outlines treatment options for single brain metastasis, multiple brain metastases (2-3) and multiple brain metastases (>3) and different options depending on KPS and extracerebral disease.

The guideline also includes systemic therapy, however does not make recommendations. The guideline states that the role of chemotherapy for brain metastases remains limited. Also, new drugs as targeted therapies show promising results.

No standard treatment has been established for patients with recurring brain metastases after radiotherapy. Re-excision, radiosurgery or re-irradiation of the whole brain may be considered as well as systemic treatment options. Retreatment seems reasonable only in cases with a progression-free interval of at least 4 months after initial treatment. The neurologic symptoms, KPS, extracranial tumour control, and the patients desire are relevant criteria for the treatment decision.

**Figure 1 DEGRO guidelines treatment algorithm for brain metastases**



### Leptomeningeal carcinomatosis (LC)-radiotherapy and chemotherapy

Both treatment modalities are effective in LC according to the sparse data. Their sequence is determined according to the predominant clinical symptoms. Chemotherapy after radiotherapy bears an increased risk of leukoencephalopathy.

Chemotherapy may be administered systemically or intrathecally. For intrathecal injection, methotrexate, thiotepea and cytarabine are most commonly applied. Intrathecal chemotherapy is effective for diffuse meningeal spread, however, may be ineffective in bulky disease.

Radiotherapy is an effective palliative treatment for LC. For WBRT, the clinical target volume encompasses the cerebellum and brain stem. In case of leptomeningeal manifestation and intratentorial metastases, the treatment volume should include the spinal cord down to the caudal margin of the second vertebral body. For LC, it is important to cover the meningeal space including the lamina cribrosa and basal cisterns. A total dose of 30 Gy in daily fractional doses of 3 Gy and five fractions per week is most commonly used. In patients with a predicted survival exceeding 12 months, reduction of the single fraction to 2 Gy may be preferable (20 x 2 Gy) in order to reduce

brain toxicity. In cases of a more limited prognosis, acceleration of treatment time and single dose may be an alternative (5 x 4 Gy).

These recommendations apply to both LC and brain metastases.

- For stereotactic irradiation, the gross tumour volume in MRI is regarded as clinical target volume, an additional safety margin of 1-2mm for the planning target volume is recommended, depending on reproducibility and immobilisation technique. Single-dose treatment is suitable for lesions up to 3.5cm in size. A tumour encompassing dose of 20-25 Gy (80-90% isodose) is recommended, provided no WBRT has recently preceded or is planning consecutively. For tumours with a volume >4ml (i.e. diameter >2cm), the reference dose should not exceed 18 Gy. When combined with WBRT, the radiosurgical dose should be restricted to 18 Gy and in larger tumours to 15 Gy. Dose prescription refers to the 80-90% isodoses.
- Fractionated SRS is feasible for tumours >2cm and lesions in critical anatomic sites such as the cerebellum with increased risk of incarceration. Moreover, fractionation is preferable for metastases of the brain stem to avoid late reactions with dismal outcome. Depending on the treatment volume, fractionation schedules of 4 x 8.7 Gy, 5 x 7 Gy, 6 x 5 Gy, or 10 x 4 Gy are in use. In case of additional WBRT, 6 x 5 Gy are recommended.

*DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer. Bone metastases and metastatic spinal cord compression (MSCC) (2009).*<sup>20</sup> These guidelines are based on a systematic review.

Emergency measures in MSCC:

- The initial intervention should be an i.v. application of high-dose steroids up to doses of 96 mg/d. A potential remission of neurologic symptoms can be expected as early as 4-6 hours post administration.

Guidelines for the treatment of MSCC:

- Instability of vertebral column, bony compression and/or paresis/paraplegia
  - Immediate (within maximally 24-48hour) surgical intervention and postoperative radiotherapy
- Spinal cord compression without neurologic deficits
  - In ambulatory patients; radiotherapy
  - In case of analgesia as additional goal: short course of radiotherapy with increased single doses
  - In case of remineralisation as additional goal: fractionated radiotherapy with conventional single doses
- Acute onset of paresis/paraplegia
  - Surgical decompression followed by radiotherapy



- Radiotherapy when decompression is not possible
- Inoperability
  - Radiotherapy; choice of fractionation depending on life expectancy
- After surgical decompression
  - Radiotherapy
- In case of (in field) recurrence after previous radiotherapy
  - Surgery (when possible)
  - Reirradiation (using high-precision techniques)

Supportive care: the early use of physical therapy and rehabilitation measures are of importance in addition to medication (steroids bisphosphonates, etc.)

### **Additional international clinical practice guidelines**

Several international guidelines on the management of CNS metastases from **mixed primary tumours** were identified. Recommendations from these guidelines as well as additional recommendations from the guidelines presented above (CNS metastases from breast cancer) are presented in **appendix F**, including:

- American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS). *The role of emerging and investigational therapies for metastatic brain tumours: a systematic review and evidence-based clinical practice guideline of selected topics (2010).*
- AANS/CNS. *The role of prophylactic anticonvulsants in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline (2010);* AANS/CNS. *The role of steroids in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline (2010).*
- AANS/CNS. *The role of retreatment in the in the management of recurrent/progressive brain metastases: A systematic review and evidence-based clinical practice guideline (2010).*
- AANS/CNS. *The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline (2010).*
- AANS/CNS. *The role of whole-brain radiation therapy in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline (2010);* AANS/CNS. *The role of stereotactic radiosurgery in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline (2010).*
- American College of Radiology (ACR). *ACR appropriateness criteria multiple brain metastases (2011) and single brain metastases (2010).*

- American Society for Radiation Oncology (ASTRO). *Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline (2012)*.
- Cancer Care Ontario (CCO). *Management of Brain Metastases: Role of radiotherapy alone or in combination with other treatment modalities(2004)*.
- CCO. *Management of single brain metastases: a clinical practice guideline (2006)*.
- CCO. *Management of single brain metastases: A clinical practice guideline (2006)*.
- CCO. *The use of prophylactic anticonvulsants in patients with brain tumours: A clinical practice guideline (2006)*.
- German Society of Radiation Oncology (DEGRO). *DEGRO practical guidelines for palliative radiotherapy of breast cancer patients: brain metastases and leptomeningeal carcinomatosis (2010)*.
- European Federation of Neurological Societies (EFNS). *Brain metastases: EFNS guidelines on brain metastases (2011)*.
- International RadioSurgery Association (IRSA). *Stereotactic radiosurgery for patients with metastatic brain tumours (2008)*.
- National Institute for Health and Care Excellence (NICE). *Advanced breast cancer: diagnosis and treatment (2009)*.

## 3.2 Research questions

### 3.2.1 What is the effectiveness of surgery in the management of CNS metastases from breast cancer?

#### Systematic reviews

No systematic reviews on the effectiveness of surgery in the management of CNS metastases from breast cancer were identified.

Two systematic reviews, including one Cochrane review, were identified which assessed the effectiveness of surgical resection in the management of newly diagnosed brain metastases in patients with mixed primary tumours.<sup>21,22</sup> Two additional systematic reviews were identified, however, these were considered to be superseded by the Cochrane review and therefore are not reported any further.<sup>23,24</sup>

The **Cochrane review by Hart et al (2011)** aimed to assess if resection of single brain metastasis followed by WBRT holds any clinical advantage over WBRT alone.<sup>22</sup> Three RCTs were identified that included a total of 195 patients. Of note, the RCTs by Mintz et al 1996, Patchell et al 1990 and Vetch et al 1993, included in the systematic 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. Details on total number of patients and number of breast cancer patients in individual trials are presented in appendix G.

No significant difference in survival was found (HR 0.72; 95% CI 0.34-1.55;  $p=0.40$ ) although there was heterogeneity between trials ( $I^2 = 83\%$ ).<sup>22</sup> One trial found surgery and WBRT increased the duration of Functionally Independent Survival (FIS) (HR 0.42; 95% CI 0.22-0.82;  $p=0.01$ ). There was some indication that surgery and WBRT might reduce the risk of deaths due to neurological cause: (relative risk (RR) 0.68; 95% CI 0.43-1.09;  $p=0.11$ ). The risk of adverse events was not statistically proven to be different between arms although actual event numbers were higher in the surgery arm.

The authors concluded that the addition of surgery may improve the length of time patients remained independent from others for support and there is a suggestion it may also reduce the risk of death due to neurological causes.<sup>22</sup> Patients undergoing surgery were not reported to have a higher risk of adverse events than patients who only had WBRT. Decisions on the treatment for an individual patient are best made as part of a multidisciplinary team.

**The systematic review by Ammirati et al (2010)** addressed the treatment of patients who develop recurrent/progressive brain metastases after initial therapy.<sup>21</sup> The associated clinical practice guideline recommendations included in the paper by Ammirati et al, are outlined in appendix F for recurrent disease.

The review addressed the question: *what evidence is available regarding the use of WBRT, SRS, surgical resection or chemotherapy for the treatment of recurrent/progressive brain metastases?*<sup>21</sup>

Four case series were identified that addressed the use of surgical resection for recurrent/progressive brain metastases. Median survival ranged from 8.9 months to 11.5 months. The populations in the studies were not limited to patients with breast cancer primary tumours.

## **Randomised controlled trials**

From hand searching an additional randomised controlled study was identified which met the inclusion criteria. Patchell et al (2005) assessed the efficacy of direct decompressive surgery plus postoperative radiotherapy compared with radiotherapy alone in patients with spinal cord compression caused by metastatic cancer.<sup>25</sup>

### **Study characteristics**

Patchell et al (2005) randomised 101 patients to direct decompressive surgery followed by radiotherapy ( $n=50$ ) or radiotherapy alone ( $n=51$ ).<sup>25</sup> After an interim analysis the study was stopped early because of proven superiority of surgical treatment. The primary endpoint of the study was the ability to walk after treatment. Secondary endpoints were survival time after treatment, urinary continence, changes in Frankel functional scale scores and American Spinal Injury Association (ASIA) motor scores, and the use of corticosteroids and opioid analgesics.<sup>25</sup>

### **Outcomes**

### **Ambulatory rate**

Patchell et al (2005) reported the combined post-treatment ambulatory rate in the surgery group was 84% compared with 57% in the radiation group (OR= 6.2; 95% CI 2.0-19.8;  $p=0.001$ ).<sup>25</sup> The surgical group retained the ability to walk for significantly longer than the radiation group, median 122 days vs. 13 days, respectively ( $p=0.003$ ). Both surgery and pre-treatment Frankel score were found to be significantly associated with longer ambulatory time on multivariate analysis,  $p=0.0017$  and  $p=0.0008$  respectively.<sup>25</sup>

In a subgroup analysis of the RCT by Patchell et al (2005) patients who could walk at study entry, 94% (32/34) in the surgery group continued to walk after treatment compared to 74% (26/35) in the radiation groups ( $p=0.024$ ).<sup>25</sup> The surgical group were also able to walk for a significantly longer period, 153 days versus 54 days for the radiation group (OR= 1.82, 95% CI 1.08-3.12;  $p=0.024$ ). Multivariate analysis demonstrated surgery ( $p=0.0048$ ), Frankel score ( $p=0.016$ ) and breast primary tumour ( $p=0.029$ ) to be associated with longer ambulatory times. Thirty-two patients (16 in each group) were unable to walk at study entry; of these, ten patients (62%) in the surgery group regained the ability to walk compared with 19% (three patients) in the radiation group ( $p=0.012$ ). Non-ambulatory patients treated with surgery walked for a median of 59 days compared with a median of 0 days for patients in the radiation group ( $p=0.04$ ).<sup>25</sup>

### **Mortality**

Patchell et al (2005) reported 30-day mortality rates of 6% in the surgery group and 14% in the radiation group ( $p=0.32$ ).<sup>25</sup> The surgical group also had significantly increased survival, 126 days compared with 100 days in the radiation group (RR= 0.60; 95% CI 0.38-0.96;  $p=0.033$ ) (see table X).<sup>25</sup>

### **Secondary endpoints**

Surgical treatment resulted in significant differences in maintenance of continence, muscle strength (ASIA scores), and functional ability (Frankel scores) in the study by Patchell et al (2005).<sup>25</sup> See table X. A substantial reduction in the use of corticosteroids and opioid analgesics was reported among the surgical group. At 30 days, surgery group patients maintained or improved their pre-treatment ASIA muscle strength scores at a significantly higher rate than patients in the radiation group, 86% and 60% respectively ( $p=0.0064$ ). Also, at day 30 after treatment, the percentage of patients with Frankel scores at or above study entry level was significantly higher in the surgery group than in the radiation group (91% vs. 61%,  $p=0.0008$ ).<sup>25</sup>

The median mean daily dexamethasone equivalent dose was 1.6mg in the surgical group compared with 4.2mg in the radiation group ( $p=0.0093$ ). The median mean equivalent dose of morphine was also significantly less in the surgical group compared with the radiation group, 0.4mg and 4.8mg respectively ( $p=0.002$ ).<sup>25</sup>

Median hospital stay was not prolonged in the surgery group, both the surgery and radiation group had a median hospital stay of 10 days ( $p=0.86$ ). Extended hospital stays (greater than 20 days) occurred in seven patients in the surgery group and 11 in the radiation group.<sup>25</sup>

Ten patients in the radiation group (20%) had a substantial decline in motor strength during radiotherapy and crossed over to receive surgery (no patients with primary breast

cancer). None of the patients were able to walk at time of surgery. Following surgery, three (30%) patients regained the ability to walk.<sup>25</sup>

**Table 1 Secondary endpoints reported by Patchell et al (2005)<sup>25</sup>**

	Radiation group (n=51) median days	Surgery group (n=50) median days	Relative risk	95% CI	p	Significant predictors
Maintenance of continence	17	156	0.47	0.25-0.87	0.016	Surgery RR= 0.51 (0.29-0.90) Baseline Frankel score RR= 0.56 (0.3-0.73)
Maintenance of ASIA score	72	566	0.28	0.13-0.61	0.001	Surgery RR= 0.30 (0.14-0.62) Stable spine RR= 0.43 (0.22-0.83) Cervical spinal level RR= 0.49 (0.26-0.90) Baseline Frankel score RR= 0.65 (0.46-0.91)
Maintenance of Frankel score	72	566	0.24	0.11-0.54	0.0006	Surgery RR= 0.26 (0.12-0.54) Stable spine RR= 0.39 (0.20-0.75) Cervical spinal level RR= 0.53 (0.74-0.98) Baseline Frankel score RR= 0.62 (0.44-0.88)
Survival time	100	126	0.60	0.38-0.96	0.033	Surgery RR= 0.60 (0.4-0.92) Breast primary tumour RR= 0.29 (0.13-0.62) Lower thoracic spinal level RR= 0.65 (0.43-0.99)

Abbreviations: ASIA=American Spinal Injury Association , RR=relative risk

## Retrospective studies

One retrospective studies was identified which reported on the surgical management of CNS metastases in breast cancer patients. A second retrospective study was identified

which reported on surgery and radiotherapy in patients with metastatic epidural spinal cord compression (MESCC).

### **Study characteristics**

Cahill et al (2011) conducted a retrospective study to determine population-based estimates of postoperative survival after the neurosurgical treatment of metastatic breast cancer, including both intracranial and spinal column disease.<sup>26</sup> Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, 643 patients who had undergone neurosurgical treatment between 1986 to 2005 were identified. Two-hundred and sixty four (41%) underwent cranial surgery and 379 (59%) underwent spinal surgery. Of the patients who underwent spinal surgery, 174 (46%) underwent laminectomy without fusion and 205 (54%) underwent a spinal fusion procedure. It was noted by Cahill et al (2011) as a limitation of the study, that no information regarding additional treatments such as postoperative radiation and chemotherapy could be obtained.<sup>26</sup>

Tancioni et al (2011) undertook a retrospective analysis of breast cancer patients with metastatic epidural spinal cord compression (MESCC) undergoing surgery and radiation therapy.<sup>27</sup> Between 2004 and 2009 a total of 26 surgical procedures were performed on 23 consecutive breast cancer patients with MESCC. Three different surgical procedures were performed:

1. Minimal resection (palliative surgery) with instrumented fixation in cases unsuitable for extensive surgery (n=5; 19.2%)
2. Curettage (subtotal tumorectomy) leaving microscopic residual tumour, performed through different surgical approaches and followed by stabilisation procedures (n=18; 69.2%)
3. Total tumorectomy performed via the anterior or posterior approach (or both), depending on the site of metastases (this surgery included spondilectomy or vertebrectomy), and requiring stabilisation of the spine (n=3; 11.5%).

Within 30 days after surgery, radiotherapy was performed.<sup>27</sup>

### **Outcomes**

#### **Survival**

In the study by Cahill et al (2011), there was a significant difference in overall postoperative survival for cranial and spinal procedures ( $p < 0.01$ ).<sup>26</sup> Observed rates of postoperative survival according to type of surgery and decade in which surgery was performed are present in table 1.

**Table 2 Trends in overall postoperative survival after neurosurgical treatment of metastatic breast cancer (Cahill 2011<sup>26</sup>)**

	Median post-surgical survival (95% CI), months	Surgery before 1996 (95% CI), months	Surgery after 1996 (95% CI), months	P value
All surgeries	9.9 (8.5-11.5)	9.7 (7.6-11.8)	10.2 (8.5-12.9)	0.1
Cranial	7.8 (6.2-9.2)	7.5 (5.3-10.0)	8.1 (5.8-9.6)	1.0
Laminectomy (no fusion)	9.4 (6.3-15.7)	9.2 (5.9-14.6)	15.1 (4.6-20.1)	0.8
Fusion	15.7 (11.9-18.5)	12.4 (8.4-15.7)	19.6 (12.1-27.2)	<0.01
P value	<0.01			

Abbreviations= CI=confidence interval

Prognostic factors of postoperative survival were determined from univariate and multivariate Cox regression models.<sup>26</sup> For cranial surgery, the significant predictors of increased hazards for postoperative death in unadjusted analyses were:

- increasing age at the time of surgery (HR 1.03; 95% CI 1.01-1.05 per 1-year increase in age)
- increasing Charlson comorbidity score (HR 1.18; 95% CI 1.10-1.27 per 1-unit increase)
- the presence of stage 4 disease at the initial diagnosis of breast cancer (HR 1.81; 95% CI 1.22-2.69)
- short time between diagnosis of breast cancer and surgical treatment (HR 0.96; 95% CI, 0.93-0.98 per 1-year increase in time).<sup>26</sup>

After multivariate analysis all factors remained associated with increased hazards for postoperative death.

For spinal surgery, in unadjusted analyses presence of estrogen or progesterone receptors compared with respective negative receptor status was associated with decreased hazards for postoperative death (HR 0.47; 95% CI 0.28-0.79 for the presence of estrogen receptors; HR 0.48; 95% CI 0.32-0.72 for the presence of progesterone receptors.<sup>26</sup> After multivariate analysis, increasing time from the initial diagnosis of breast cancer to neurosurgical treatment was also associated with decreased hazards for death (adjusted HR 0.97; 95% CI 0.95-0.99 per 1-year increase). Prognostic factors of increased hazards for postoperative death on univariate and multivariate analyses were:

- admission to the hospital through the emergency room (unadjusted HR 1.41; 95% CI 1.10-1.79 and adjusted HR 1.53; 95% CI 1.20-1.97 respectively)
- poorly differentiated or undifferentiated tumour histology compared with well-differentiated or moderately differentiated histology (unadjusted HR 1.51; 95% CI 1.17-1.95 and adjusted HR 1.49; 95% CI 1.19-1.95).<sup>26</sup>

Cahill et al (2011) also reported 1-, 3-, and 5-year Kaplan-Meier survival estimates.<sup>26</sup> Approximately 50% of younger patients who underwent cranial surgery and 50% of all spinal surgery patients survived for at least 1 year after surgery. Patients >70 years of age who underwent cranial surgery had 1-year survival rates of 25% to 30%. Approximately



25% of spinal surgery patients survived for at least 3 years from the time of surgery. See table 2.

**Table 3 Perioperative survival estimates according to type of surgery (Cahill 2011<sup>26</sup>)**

Surgery	Cumulative survival estimate (95% CI)		
	Year 1	Year 3	Year 5
Cranial surgery, age 65-69yr (n=88)	47.5 (36.8-57.5)	15.5 (8.5-24.4)	6.3 (2.2-13.8)
Cranial surgery, age 70-74yr (n=97)	29.5 (20.8-38.8)	12.3 (6.5-20.1)	5.6 (2.0-12.3)
Cranial surgery, age >75yr (n=79)	24.9 (16-34.9)	11.6 (5.6-19.9)	3.6 (0.8-10)
Spinal surgery, laminectomy (n=174)	47.6 (40-54.8)	22.7 (16.7-29.3)	9 (5.2-14.1)
Spinal surgery, fusion (n=205)	57 (50-63.5)	22.3 (16.7-28.5)	12.2 (7.8-17.7)

Abbreviations= CI=confidence interval

Tancioni et al (2011) reported median overall survival of 36 months (range 3-60).<sup>27</sup> At a median observation time of 26 months (range 3-60), 10 patients (43.4%) were alive and 13 had died. The one-year survival rate was 70%, two-year survival was 60%, three-year survival was 42%, four and five-years survival was 34%.

Evidence of other bone (vertebral or other site) metastases was the only factor which affected survival. In patients with other bone metastases one, two and three-years survival was 53.3% (vs. 100%), 46.7% (vs. 100%) and 19.4% (vs. 85.7%), respectively.<sup>27</sup>

All patients treated with minimal resection died within a median time of 5 months; of 18 cases undergoing curettage, eight (44.4%) were still alive at last follow-up and 10 (55.6%) were dead. Among patients treated with total tumorectomy, two (66.7%) were alive at the last follow-up.<sup>27</sup>

### Inpatient death

Cahill et al (2011) reported a postoperative death rate of 6.2% for all patients and no significant difference between the overall rates of postoperative inpatient death for cranial compared with spinal surgeries (6.4% vs. 6.1% respectively;  $p=0.9$ ).<sup>26</sup> There were significant differences in postoperative inpatient death rates according to decade of surgery ( $p=0.03$ ). See table 3.

The study reported that the declines in the postoperative inpatient death rates corresponded to a decrease in the mean postoperative inpatient length of stay overtime (17.7 days before 1996 vs. 7.2 days after 1996;  $p<0.01$ ).<sup>26</sup>

There was no significant difference between cranial and spinal surgery for 30-day mortality rates (9.1% vs. 9.8% respectively;  $p=0.8$ ).<sup>26</sup> The 30-day mortality rate has remained constant for all types of neurosurgical procedures over time. See table 4.



**Table 4 Trends in in-hospital death rates after neurosurgical treatment of metastatic breast cancer (Cahill 2011<sup>26</sup>)**

Surgery	Median post-survival, % (n/N)	Surgery before 1996, % (n/N)	Surgery after 1996, % (n/N)	P value
All surgeries	6.2 (40/603)	8.4 (25/273)	4.4 (15/330)	0.03
Cranial	6.4 (17/247)	9.4 (10/97)	4.5 (7/150)	0.1
Laminectomy (no fusion)	<6*	<7*	<3*	0.2
Fusion	8.3 (17/188)	<9*	<6*	0.3

\*actual value not reportable because of SEER-Medicare patient confidentiality restrictions on reporting results with n <11.

**Table 5 Trends in 30-day mortality after neurosurgical treatment of metastatic breast cancer (Cahill 2011<sup>26</sup>)**

Surgery	30-day mortality, % (n/N)	30-day mortality, % (n/N)	30-day mortality, % (n/N)	P value
All surgeries	9.0 (58/585)	10.1 (30/268)	8.1 (28/317)	0.4
Cranial	9.1 (24/240)	11.2 (12/95)	7.6 (12/145)	0.3
Laminectomy (no fusion)	9.8 (17/157)	<10*	<10*	1.0
Fusion	8.3 (17/188)	<9*	<8*	0.8

\*actual value not reportable because of SEER-Medicare patient confidentiality restrictions on reporting results with n <11.

### Clinical remission

The median duration of clinical remission was 26 months in the study by Tancioni et al (2011).<sup>27</sup> Clinical remission of pain, complete or partial was obtained in all cases after combined treatment. All 17 patients with neurologic deficit at presentation had complete recovery of neurologic deficit.

### Summary

- The Cochrane review by Hart et al (2011) reported no significant difference in survival between surgery and WBRT vs. WBRT alone (HR 0.72; 95% CI 0.34-1.55; p=0.40) although there was heterogeneity between trials ( $I^2 = 83\%$ ).<sup>22</sup> Two trials reported better survival among patients having surgery and WBRT and one trial reported better survival among patients receiving WBRT alone.
- One RCT (Patchell 2005) was identified which assessed the efficacy of direct decompressive surgery plus postoperative radiotherapy compared with radiotherapy alone in patients with MESCC caused by metastatic cancer.
- Patients with MESCC treated with direct decompressive surgery plus postoperative radiotherapy had better post treatment ambulatory rates, retained the ability to walk for longer as well as regain the ability to walk more often and had improved survival compared to patients treated with radiotherapy alone.

- One retrospective study was identified which reported on the surgical management of CNS metastases in breast cancer patients.
- Cahill et al (2011) reported that approximately one-third of cranial surgery patients and one-half of spinal surgery patients were alive 1 year after surgery. In this study, inpatient death rates after neurosurgical treatment of metastatic disease decreased in the decade 1996-2005. Long-term postoperative survival for cranial surgery, however, has remained relatively constant, while survival after spinal fusion, but not laminectomy alone, has increased in the decade 1996-2005.
- One retrospective study was identified which reported on the surgical management of MESCC in breast cancer patients.
- Tancioni et al (2011) reported median survival of 36 months, remission of pain and recovery of neurologic deficit, for patients with metastatic epidural spinal cord compression undergoing surgery and radiation therapy, suggesting that, surgery and radiotherapy are feasible with limited morbidity and mortality.

### 3.2.2 What is the effectiveness of radiotherapy in the management of CNS metastases from breast cancer?

#### *Systematic reviews*

No systematic reviews on the use of radiotherapy for the management of CNS metastases from breast cancer were identified.

Five systematic reviews, including a Cochrane review, were identified which assessed the effectiveness of radiotherapy either alone or in combination with other therapies for management of CNS metastases, in populations of **mixed primary cancers**. Some additional systematic reviews were identified, however, these were considered to be superseded by the Cochrane review and therefore are not reported any further.<sup>28-32</sup>

The **Cochrane review by Tsao et al (2012)** assessed the effectiveness and adverse effects of whole brain radiotherapy (WBRT) either alone or in combination with other therapies in adult participants with newly diagnosed multiple brain metastases. The review published in 2012 updates a previous 2006 Cochrane review.<sup>33</sup> Nine new randomised control trials (RCTs) involving 1420 participants were added to the updated review. The updated review included a total of 39 trials involving 10,835 participants.<sup>33</sup> Details on total number of patients and number of breast cancer patients in individual trials are presented in appendix G.

The review addressed the following comparisons:

- **Altered WBRT dose-fractionation schedules versus conventional WBRT fractionation schedules.** Eight published reports (nine RCTs) showed no benefit of altered dose-fractionation schedules as compared to the control fractionation (3000 cGy in 10 fractions daily) of WBRT for overall survival. These studies also showed no improvement in symptom control nor neurologic improvement among the different dose-fractionation schemes as compared to 3000 cGy in 10 daily fractions of WBRT. The review also included two trials comparing 4000 cGy in 20

fractions given twice daily versus 2000 cGy in 4 or 5 daily fractions. Overall, there was no survival advantage (HR 1.18; 95% CI 0.89-1.56;  $p=0.25$ ) with the use of 4000 cGy in 20 fractions given twice daily compared to 2000 cGy in 4 or 5 daily fractions.

- **WBRT plus radiosensitizers versus WBRT.** The addition of radiosensitizers in six RCTs did not confer additional benefit to WBRT in either the overall survival times (HR 1.08; 95% CI 0.98-1.18;  $p=0.11$ ) or brain tumour response rates (HR 0.87; 95% CI 0.60-1.26;  $p=0.46$ ).
- **WBRT plus radiosurgery versus WBRT.** Two RCTs found no benefit in overall survival (HR 0.61; 95% CI 0.27-1.39;  $p=0.24$ ) with the use of WBRT and radiosurgery boost as compared to WBRT alone for selected participants with multiple brain metastases (up to four brain metastases). Overall, there was a statistically significant improvement in local brain control (HR 0.35; 95% CI 0.20-0.61,  $p=0.0003$ ) favouring the WBRT and radiosurgery boost arm. Only one trial of radiosurgery boost with WBRT reported an improved Karnofsky performance score outcome and improved ability to reduce the dexamethasone dose.
- **Radiosurgery plus WBRT versus radiosurgery.** In the updated review, a total of three RCTs reported on selected patients (with up to three or four brain metastases) treated with radiosurgery alone versus WBRT and radiosurgery. Based on two trials, there was no difference in overall survival (HR 0.98; 95% CI 0.71-1.35;  $p=0.88$ ). The addition of WBRT when added to radiosurgery significantly improved locally treated brain metastases control (HR 2.61; 95% CI 1.68-4.06;  $p<0.0001$ ) and distant brain control (HR 2.15; 95% CI 1.55-2.99;  $p<0.0001$ ). On the other hand, one trial concluded that patients treated with WBRT and radiosurgery boost were significantly more likely to show a decline in learning and memory function as compared to those treated with radiosurgery alone. Further detail on recurrence of brain metastases for individual trials is presented at Appendix G.

Conclusions of the Cochrane review by Tsao et al (2012):

- Altered WBRT dose-fractionation schedules versus conventional WBRT fractionation schedules. None of the RCTs with altered WBRT dose-fractionation schemes as compared to standard (3000 cGy in 10 daily fractions or 2000 cGy in 4 or 5 daily fractions) found a benefit in terms of overall survival, neurologic function, or symptom control.<sup>33</sup>
- WBRT plus radiosensitizers versus WBRT. The addition of radiosensitisers did not confer additional benefit to WBRT in either overall survival times or brain tumour response rates.
- WBRT plus radiosurgery versus WBRT. Radiosurgery boost with WBRT may improve local disease control in selected participants as compared to WBRT alone, although survival remains unchanged for participants with multiple brain metastases.
- Radiosurgery alone or radiosurgery plus WBRT. The addition of WBRT to radiosurgery improves local and distant brain control but there is no difference in overall survival. Patients treated with radiosurgery alone were found to have

better neurocognitive outcomes in one trial as compared to patients treated with WBRT and radiosurgery.<sup>33</sup>

**The systematic review by Linskey et al 2010** addressed the question whether patients with newly diagnosed brain metastases should undergo stereotactic radiosurgery (SRS), compared with other treatment modalities.<sup>34</sup> The associated clinical practice guideline recommendations included in the paper by Linskey et al, are outlined in appendix F. The review included different comparisons of SRS with other therapies including SRS vs. WBRT. Other comparisons are reported in research question 4 or have been superseded by the 2012 Cochrane review.

For the comparison of SRS alone vs. WBRT alone the review found no RCTs. Four class II evidence studies (one prospective cohort study and three retrospective cohort studies) and two class III evidence studies (retrospective studies with historical control) were identified.<sup>34</sup> The four class II evidence studies all demonstrated a statistically significant survival advantage for single-dose SRS alone compared with WBRT alone for patients with either single or multiple brain tumors.<sup>34</sup> However, one study was confounded by the inclusion of SCLC patients who are normally excluded from solid metastatic brain tumor analysis, particularly in a study in which WBRT is not included in one of the arms. A second study included a very small number of patients and was limited by selective rare histology (epithelial ovarian cancer only), and poor intergroup comparative analysis. Consistent with these results, one class III evidence study showed a significant survival advantage for single-dose SRS alone for RPA class I and II, but not RPA class III patients. Only one class III evidence study showed similar survival results for both treatment strategies. While different studies evaluated patients with differing numbers of brain metastases, all studies included patients with up to three metastatic brain tumours.<sup>34</sup>

**The systematic review by Kalkanis et al 2010** addressed the question of surgery alone versus surgery plus radiotherapy.<sup>24</sup> The associated clinical practice guideline recommendations included in the paper by Kalkanis et al, are outlined in appendix F.

One RCT and three retrospective cohort studies were identified which evaluated surgical resection alone compared to surgery plus post-operative WBRT for the initial management of a single brain metastasis.<sup>24</sup> In the randomized study, fewer patients who received post-operative WBRT experienced a recurrence in the brain compared to those who had surgical resection alone (surgery + WBRT: 18% vs. surgery: 70%;  $p=0.001$ ). Recurrence in the WBRT group was less frequent both at the original site of the brain metastasis (surgery + WBRT: 10% vs. surgery: 46%;  $p=0.001$ ) and at distant sites in the brain (surgery + WBRT: 14% vs. surgery: 37%;  $p=0.01$ ) compared to patients who did not receive post-operative WBRT. The time to any recurrence in the brain was significantly longer in the group that had post-operative WBRT compared to the group that did not (log-rank;  $p=0.001$ ). Overall survival did not differ significantly between the two groups. Median survival in the surgery + WBRT group was 48 weeks compared to 43 weeks in the group that received no further treatment following surgical resection. This study was not powered for survival, however, which was a secondary endpoint.

**The systematic review by Gasper et al 2010** addressed the question if WBRT is used, what impact does tumour histopathology have on treatment outcomes.<sup>23</sup> Other comparisons in the review have been superseded by the 2012 Cochrane review. Only one small case series was included. There were no statistically significant differences in overall survival by

tumour histology. Local control by tumour type was not reported. The authors concluded further studies in the area are needed before any recommendations are made.

**The systematic review by Ammirati et al (2010)** addressed the treatment of patients who develop recurrent/progressive brain metastases after initial therapy.<sup>21</sup> The associated clinical practice guideline recommendations included in the paper by Ammirati et al, are outlined in appendix F.

The review addressed the questions:

1. What evidence is available regarding the use of WBRT, SRS, surgical resection or chemotherapy for the treatment of recurrent/progressive brain metastases? Thirty studies were identified. Three studies addressed the use of WBRT and these were case series and include 52, 72 and 86 patients with limited data. No studies were identified that specifically addressed the question of the benefit of further SRS, surgery or chemotherapy in recurrent/progressive brain metastases.<sup>21</sup>
2. If WBRT is used in this setting, what impact does tumour histopathology have on treatment outcomes? No studies were identified that met the eligibility criteria for this question.<sup>21</sup>

## **Whole brain radiotherapy (WBRT)**

### **Prospective studies**

One phase III randomised controlled trial (RCT), the REACH study, investigating the addition of Efaproxiral (Efaproxyn) to whole-brain radiotherapy (WBRT) was identified.<sup>35-37</sup>

Yaneva et al (2006) assessed the effect of palliative radiotherapy on quality of life (QoL) in patients with brain metastases from breast and lung cancer.<sup>38</sup>

### **Study characteristics**

The REACH study included patients with brain metastases from solid tumours and a Karnofsky performance score of  $\geq 70$ . Three analyses were reported.<sup>35-37</sup> Patients were randomised to receive WBRT with supplemental oxygen and either efaproxiral (intervention arm n=265; breast cancer patients n=58) or no efaproxiral (control arm n=250; breast cancer patients n=49). Patients were stratified to one of four strata depending on their Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification and primary tumour: (1) RPA Class I, (2) RPA Class II non-small cell lung cancer (NSCLC) (3) RPA Class II breast cancer, (4) RPA Class II other than NSCLC or breast cancer. See table 5.

Yaneva et al (2006) assessed the effect of palliative radiotherapy on quality of life (QoL) in patients with brain metastases from primary cancer including breast cancer.<sup>38</sup> Two schedules of radiotherapy were applied to 65 patients (33 breast cancer, 50.8%); 30 Gy in 15 fractions or 30 Gy in 10 fractions. Radiation was performed concomitantly with corticosteroid treatment.<sup>38</sup> See table 5.

**Table 6 Study characteristics of WBRT prospective studies**

Study	Patients	Arm 1	Arm 2
<b>REACH study</b>			
Suh 2006	RPA class I or II patients with BM originating from NSCLC, BC or other (excluding small-cell lung cancer, germ cell tumours and lymphomas). Included a NSCLC/BC subgroup	WBRT plus supplemental oxygen and efaproxiral	WBRT plus supplemental oxygen and no efaproxiral
Stea 2006 Efaproxiral red blood cell (E-RBC) and number of doses analysis	RPA class I or II patients with BM originating from NSCLC, BC or other (excluding small-cell lung cancer, germ cell tumours and lymphomas). Included a BC subgroup	WBRT plus supplemental oxygen and efaproxiral	WBRT plus supplemental oxygen and no efaproxiral
Scott 2007 QoL and QAS	Subgroup of 106 eligible breast cancer patients with baseline SQLI	WBRT plus supplemental oxygen and efaproxiral	WBRT plus supplemental oxygen and no efaproxiral
<b>Yaneva 2006</b> Quality of life before and after palliative radiotherapy	Patients with cerebral metastases from breast, lung, renal cancer and unidentified primary location	WBRT 30 Gy. QoL was assessed using EORTC-QOL-C30 before and after WBRT	

Abbreviations: BC=breast cancer, BM=brain metastases, EORTC-QOL-C30=European Organisation for Research and Treatment of Cancer for Cancer patients, NSCLC=non-small cell lung cancer, RPA=recursive partitioning analysis, SQLI=Spitzer Quality of Life Index, QAS=Quality adjusted survival, QoL=Quality of Life, WBRT=whole brain radiotherapy.

### Retrospective studies

Three retrospective studies reporting results of various radiotherapy regimens in patients with CNS metastases were identified.

Rades et al published three retrospective studies, two comparing shorter course WBRT with longer course<sup>39,40</sup> and the third investigated the potential benefit of dose escalation beyond the standard 30 Gy treatment.<sup>41</sup>

### Study characteristics

Rades et al (2007) investigated the potential benefit of dose escalation beyond the standard 30 Gy treatment in patients with  $\geq 2$  brain metastases from breast, lung and other primaries.<sup>41</sup> 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 (15 fractions of 2.5 Gy each over 3 weeks; 57 patients) and 40 Gy in 20 fractions (20 fractions of 2 Gy each over 4 weeks; 102 patients).<sup>41</sup> See table 6.

Rades and Lohrynska et al (2007) retrospectively compared survival and local control for short-course WBRT compared with longer programs in breast cancer patients.<sup>40</sup> Sixty-nine

patients received short course WBRT with 20 Gy given in 5 fractions (5 fractions of 4 Gy each, with a treatment time of 5 days). Long course WBRT with either 30 Gy given in 10 fractions (10 fractions of 3 Gy each, with a treatment time of 2 weeks) or 40 Gy given in 20 fractions (20 fractions of 2 Gy each, with a treatment time of 4 weeks) was given to 138 patients.<sup>40</sup> See table 6.

In another retrospective study by Rades et al (2011) shorter course and longer course WBRT were compared for elderly patients ( $\geq 65$  years) treated between 2001 and 2010 for brain metastases.<sup>39</sup> The analysis compared 62 patients (23 breast cancer patients) who received 5 x 4 Gy in 1 week to 293 patients (53 breast cancer patients) who received 10 x 3 Gy in 2 weeks, the analysis included patients with primary tumours from breast, lung and other sites.<sup>39</sup> See table 6.

**Table 7 Study characteristics of retrospective studies (Rades<sup>38, 39, 40</sup>)**

Study	Patients	Arm 1	Arm 2
Rades 2007	Patients treated with WBRT alone for $\geq 2$ BM from primary tumours including breast, lung and other	Higher doses: 45 Gy in 15 fractions (15 fractions of 2.5 Gy over 3 weeks n=57) and 40 Gy in 20 fractions (20 fractions of 2 Gy over 4 weeks n=102)	30 Gy in 10 fractions (10 fractions of 3 Gy each, with an overall treatment time of 2 weeks n=257)
Rades and Lohynska 2007	BC patients who were treated with WBRT for BM	20 Gy in 5 fractions (5 fractions of 4 Gy each, with a treatment time of 4 days n=69)	30 Gy in 10 fractions (10 fractions of 3 Gy each, with a treatment time of 2 weeks) or 40 Gy given in 20 fractions (20 fractions of 2 Gy each, with a treatment time of 4 weeks) n=138
Rades 2011	Elderly patients treated with WBRT alone for BM from BC, lung cancer or other tumours	5 x 4 Gy in 1 week n=162	10 x 3 Gy in 2 weeks n=293

Abbreviations: BC=breast cancer, BM=brain metastases, WBRT=whole brain radiotherapy.

## Outcomes

### Survival

The REACH randomised study of WBRT and efaproxiral reported three analyses of overall survival.<sup>35-37</sup>

Suh et al (2006) reported median overall survival for the whole study population of 5.4 months for the efaproxiral arm vs. 4.4 months for control (HR 0.87;  $p=0.16$ ).<sup>37</sup> Median survival and HR estimates for the effect of treatment from multiple regression analysis with prognostic covariates for the breast cancer/NSCLC subgroup are presented in table 7. The largest efaproxiral treatment effect was observed in breast cancer patients (HR 0.51;  $p=0.003$ ).<sup>37</sup>



Stea et al (2006) compared Efaproxiral red blood cell (E-RBC) concentrations and number of efaproxiral doses administered for primary tumour type (breast, NSCL and all eligible patients) and patient body weight.<sup>36</sup> High E-RBC was associated with increased survival compared with low E-RBC and control arm for all three population groups.<sup>36</sup> Median survival and HR estimates for the effect of treatment from multiple regression analysis with prognostic covariates for breast cancer patients are presented in table 7.<sup>36</sup>

Scott et al (2007) reported survival, QoL and quality-adjusted survival (QAS) analysis of patients with brain metastases from primary breast cancer from the REACH study (n=106).<sup>35</sup> Median survival time was 9 months in the efaproxiral arm and 4.47 months in the control arm, this represented a 101% improvement in median survival (unadjusted p=0.004) for the comparative drug arm. Median survival and HR estimates for the effect of treatment from multiple regression analysis with prognostic covariates are presented in table 7. Quality-adjusted survival was statistically significantly improved in the efaproxiral arm compared to control arm (p=0.001).<sup>35</sup>

**Table 8 Survival outcomes in REACH randomised study. Outcomes shown are for breast cancer patient group, unless otherwise indicated**

Author	Intervention WBRT + supplemental oxygen + Efaproxiral	Comparator WBRT + supplemental oxygen	p-value
<b>Median survival time</b>			
Suh 2006 <sup>*37</sup>	6 months	4.4 months	HR=0.82; p=0.07
Stea 2006 <sup>36</sup>	9 months	4.5 months	HR=0.51; p=0.003
Scott 2007 <sup>35</sup>	9 months	4.47 months	P=0.004
<b>Multiple regression analysis: effect of treatment</b>			
Suh 2006 <sup>*37</sup>	HR=0.75	HR=1.00	0.01
Stea 2006 <sup>36</sup>	HR=0.52	HR=1.00	0.006
Scott 2007 <sup>35</sup>	HR=0.542	HR=1.00	0.0086

\*Breast cancer or NSCLC subgroup. Abbreviations: HR=hazard ratio, WBRT=whole brain radiotherapy

Survival outcomes were reported for the retrospective studies of various WBRT regimens Rades et al (2007) reported for the entire cohort median survival after radiotherapy was 7.5 months.<sup>41</sup> Radiotherapy schedule did not appear to have significant impact on overall survival in univariate analysis. Univariate and multivariate analyses of survival are presented in table 8.<sup>41</sup>

Median survival for the entire cohort in the retrospective analysis by Rades and Lohynska was 5 months, median survival for those patients receiving short course WBRT was 5.5 months compared with 4.5 months in patients who received longer course WBRT.<sup>40</sup> During the follow up period, 54 of the 69 patients in the shorter course group and 114 of the 138 patients in the longer course group died of their disease (p=0.807). In univariate analysis, WBRT regimen and survival were not found to be significantly associated. Further univariate and multivariate analyses of survival are presented in table 8.<sup>40</sup>

Rades et al (2011) reported median overall survival of 2.5 months and 1 year survival 13%.<sup>39</sup> On univariate analysis WBRT regimen of 5 x 4Gy compared with 10 x 3Gy was significantly associated with improved overall survival (p=0.020), however on multivariate



analysis this did not remain significant ( $p=0.13$ ).<sup>39</sup> Further univariate and multivariate analyses are presented in table 8. WBRT regimen of 5 x 4 Gy was also significantly associated with improved survival in subgroup analysis of RPA class 2 patients ( $p=0.004$ ), but not in RPA class 3 patients ( $p=0.78$ ).<sup>39</sup>

For all three retrospective studies by Rades, KPS  $\geq 70$ , lower RPA class, lower number of brain metastases and no extracranial metastases were significantly associated with improved survival in univariate analyses. On multivariate analysis KPS  $\geq 70$  and no extracranial metastases remained significant across all three analyses.<sup>39-41</sup> Lower RPA class also remain significant when included in multivariate analysis.<sup>39</sup> See table 8.

In the analysis by Yaneva et al (2006) median survival was 9.8 months for breast cancer patients.<sup>38</sup>

**Table 9 Results of univariate and multivariate analyses of treatment and potential prognostic factors, and survival from three studies of WBRT schedules (Rades<sup>38, 39, 40</sup>)**

Study	Treatment or Prognostic factor (associated with improved survival)	Univariate analysis; p value	Multivariate analysis; p value
Rades 2007 <sup>41</sup>	<b>Radiation schedule</b> (30 Gy/10 fractions vs. higher doses)	0.86	NR
Rades, Lohynska 2007 <sup>40</sup>	<b>Radiation schedule</b> (5 x 4 Gy vs. higher doses)	0.254	NR
Rades 2011 <sup>39</sup>	<b>Radiation schedule</b> (5 x 4 Gy vs. 10 x 30 Gy)	<b>0.02</b>	0.13
Rades 2007 <sup>41</sup>	Age (<60 years vs. $\geq 60$ years)	<b>&lt;0.001</b>	<b>0.026</b>
Rades, Lohynska 2007 <sup>40</sup>	Age ( $\leq 58$ years vs. $\geq 59$ years)	0.147	NR
Rades 2011 <sup>39</sup>	Age (65-70 years vs. >70 years)	<b>0.021</b>	0.66
Rades 2007 <sup>41</sup>	KPS (<70 vs. $\geq 70$ )	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Rades, Lohynska 2007 <sup>40</sup>	KPS (<70 vs. $\geq 70$ )		
Rades 2011 <sup>39</sup>	KPS (<70 vs. $\geq 70$ )		
Rades 2007 <sup>41</sup>	RPA class (1 vs. 2 vs. 3)	<b>&lt;0.001</b>	Not included
Rades, Lohynska 2007 <sup>40</sup>	RPA class (1 vs. 2 vs. 3)	<b>&lt;0.001</b>	Not included
Rades 2011 <sup>39</sup>	RPA class (class 2 vs. class 3)	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Rades 2007 <sup>41</sup>	Number brain metastases (2-3 vs. 4)	<b>&lt;0.001</b>	0.07
Rades, Lohynska 2007 <sup>40</sup>	Number brain metastases (1 vs. $\geq 2$ )	<b>0.023</b>	0.614
Rades 2011 <sup>39</sup>	Number brain metastases (1-3 metastases vs. $\geq 4$ )	<b>&lt;0.001</b>	<b>0.029</b>
Rades 2007 <sup>41</sup>	Extracranial metastases (no vs. yes)	<b>&lt;0.001</b>	<b>0.003</b>
Rades, Lohynska 2007 <sup>40</sup>	Extracranial metastases (no vs. yes)	<b>&lt;0.001</b>	<b>0.024</b>
Rades 2011 <sup>39</sup>	Extracranial metastases (no vs. yes)	<b>&lt;0.001</b>	<b>0.012</b>
Rades 2007 <sup>41</sup>	Interval from tumour diagnosis to RT ( $\leq 12$ months vs. >12 months)	0.06	NR

Rades, Lohynska 2007 <sup>40</sup>	Interval from tumour diagnosis to RT ( $\leq 24$ months vs. $> 24$ months)	0.794	NR
Rades 2011 <sup>39</sup>	Interval from tumour diagnosis to RT ( $\leq 12$ months vs. $> 12$ months)	0.18	NR
Rades 2007 <sup>41</sup>	Type of primary tumour ( <i>breast</i> vs. lung vs. other tumours)	0.09	NR
Rades, Lohynska 2007 <sup>40</sup>	Type of primary tumour	NR	NR
Rades 2011 <sup>39</sup>	Type of primary tumour ( <i>breast</i> vs. lung vs. other)	0.35	NR

Abbreviations: KPS=Karnofsky Performance Status, NR=not reported, RPA= recursive partitioning analysis, RT=radiotherapy. Bold p values indicate statistical significance

Table 9 presents univariate and multivariate analysis from three retrospective studies of WBRT in patients with brain metastases from breast cancer, which did not have further comparative data.<sup>42-44</sup>

**Table 10 Univariate and multivariate analysis of survival of three additional retrospective studies**

Study	Prognostic factors	Univariate analysis; p value	Multivariate analysis; p value
Johansen 2008 <sup>42</sup> (n=99)	<b>Radiation schedule</b> ( $\geq 30$ Gy vs. $\leq 20$ Gy)	<b>&lt;0.01</b>	ND
Liu 2006 <sup>43</sup> (n=48)	<b>Radiation schedule</b> (30 Gy/10 fractions vs. 37.5 Gy/15 fractions vs. 40 Gy/20 fractions)	0.5146	NR
Mahmoud-Ahmed 2002 <sup>44</sup> (n=116)	<b>Radiation schedule</b> ( $> 3000$ cGy vs. $< 3000$ cGy vs. 3000cGy)	<b>0.0001</b>	ND
Johansen 2008 <sup>42</sup>	Age ( $> 60$ years vs. $\geq 65$ years)	0.7	ND
Liu 2006 <sup>43</sup>	Age ( $\leq 50$ years vs. $> 50$ years)	<b>0.0452</b>	0.340
Mahmoud-Ahmed 2002 <sup>44</sup>	Age ( $\leq 65$ years vs. $> 65$ years)	0.37	ND
Johansen 2008 <sup>42</sup>	KPS ( $\geq 70$ vs. $< 70$ )	0.17	ND
Liu 2006 <sup>43</sup>	KPS ( <i>high</i> 90-100 vs. medium 70-80 vs. low $< 70$ )	<b>&lt;0.0001</b>	<b>&lt;0.001</b>
Mahmoud-Ahmed 2002 <sup>44</sup>	KPS ( <i>high</i> 90-100 vs. medium 70-80 vs. low $\leq 60$ )	<b>0.008</b>	ND
Johansen 2008 <sup>42</sup>	RPA class (class 1 vs. class 2 vs. class 3)	0.6	ND
Liu 2006 <sup>43</sup>	RPA class ( <i>class 1</i> vs. class 2 vs. class 3)	<b>&lt;0.0001</b>	NR
Mahmoud-Ahmed 2002 <sup>44</sup>	RPA class ( <i>class 1</i> vs. class 2 vs. class 3)	<b>0.014</b>	ND
Johansen 2008 <sup>42</sup>	Number brain metastases ( <i>single</i> vs. multiple)	<b>&lt;0.01</b>	ND
Liu 2006 <sup>43</sup>	Number brain metastases	<b>0.0149</b>	<b>0.039</b>

	(single vs. $\geq 2$ )		
Mahmoud-Ahmed 2002 <sup>44</sup>	Number brain metastases (1 vs. 2-3 vs. 4-9 vs. $>9$ )	0.61	ND
Johansen 2008 <sup>42</sup>	Extracranial metastases (yes vs. no)	0.6	ND
Liu 2006 <sup>43</sup>	Extracranial metastases (absent vs. present)	0.3013	NR
Mahmoud-Ahmed 2002 <sup>44</sup>	Extracranial metastases (absent vs. present)	0.80	ND

Abbreviations: KPS=Karnofsky Performance Status, ND= not done, NR=not reported, RPA= recursive partitioning analysis, RT=radiotherapy. Bold p values indicate statistical significance

### Local control

All three retrospective studies by Rades reported results of both univariate and multivariate analyses of local control of brain metastases.<sup>39-41</sup> WBRT regimen was not associated with improved local control in any of the three studies, see table 10.

In the study of shorter-course WBRT in elderly patients by Rades 2011, subgroup analysis of RPA class 2 patients showed a trend towards improved local control for the shorter WBRT regimen 5 x 4Gy (p=0.11), however WBRT regimen for RPA class 3 patients was not associated with improved local control (p=0.60).<sup>39</sup>

For all three studies, KPS  $\geq 70$ , lower RPA class and primary tumour being breast cancer (for two studies reported) were significantly associated with improved local control in univariate analysis. KPS  $\geq 70$  and primary tumour being breast cancer remained significantly associated with improved local control in multivariate analyses for all three studies.<sup>39-41</sup> Lower RPA class also remain significant when included in multivariate analysis.<sup>39</sup>

**Table 11 Results of univariate and multivariate analyses of treatment and potential prognostic factors, and local control from three studies of WBRT schedules (Rades<sup>38, 39, 40</sup>)**

Author	Prognostic factors	Univariate analysis; p value	Multivariate analysis; p value
Rades 2007 <sup>41</sup>	<b>Radiation schedule</b> (30 Gy/10 fractions vs. <i>higher doses</i> )	0.61	NR
Rades and Lohynska 2007 <sup>40</sup>	<b>Radiation schedule</b> (5 x 4 Gy vs. higher dose)	0.397	NR
Rades 2011 <sup>39</sup>	<b>Radiation schedule</b> (5 x 4 Gy vs. 10 x 3 Gy)	0.32	NR
Rades 2007 <sup>41</sup>	Age (<60 years vs. $\geq 60$ years)	0.06	NR
Rades and Lohynska 2007 <sup>40</sup>	Age ( $\leq 58$ years vs. $\geq 59$ years)	0.433	NR
Rades 2011 <sup>39</sup>	Age (65-70 years vs. $>70$ years)	<b>0.001</b>	0.11
Rades 2007 <sup>41</sup>	KPS (<70 vs. $\geq 70$ )		
Rades and Lohynska 2007 <sup>40</sup>	KPS (<70 vs. $\geq 70$ )		

Rades 2011 <sup>39</sup>	KPS (<70 vs. ≥70)	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Rades 2007 <sup>41</sup>	RPA class (class 1 vs. class 2 vs. class 3)	<b>&lt;0.001</b>	Not included
Rades and Lohynska 2007 <sup>40</sup>	RPA class (class 1 vs. class 2 vs. class 3)	<b>&lt;0.001</b>	Not included
Rades 2011 <sup>39</sup>	RPA class (class 2 vs. class 3)	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Rades 2007 <sup>41</sup>	Number brain metastases (2-3 vs. 4)	<b>0.001</b>	Borderline significance
Rades and Lohynska 2007 <sup>40</sup>	Number brain metastases (1 vs. ≥2)	0.135	NR
Rades 2011 <sup>39</sup>	Number brain metastases (1-3 vs. ≥4)	<b>0.001</b>	0.12
Rades 2007 <sup>41</sup>	Extracranial metastases (no vs. yes)	0.87	
Rades and Lohynska 2007 <sup>40</sup>	Extracranial metastases (no vs. yes)	0.159	NR
Rades 2011 <sup>39</sup>	Extracranial metastases (no vs. yes)	0.49	NR
Rades 2007 <sup>41</sup>	Interval from tumour diagnosis to RT (≤12 months vs. >12 months)	<b>0.004</b>	0.17
Rades and Lohynska 2007 <sup>40</sup>	Interval from tumour diagnosis to RT (<24 months vs. ≥24 months)	0.575	NR
Rades 2011 <sup>39</sup>	Interval from tumour diagnosis to RT (≤12 months vs. >12 months)	0.39	NR
Rades 2007 <sup>41</sup> (breast cancer)	Type of primary tumour (breast vs. lung vs. other)	<b>&lt;0.001</b>	<b>0.012</b>
Rades and Lohynska 2007 <sup>40</sup>	Type of primary tumour	NR	NR
Rades 2011 <sup>39</sup> (breast cancer)	Type of primary tumour (breast vs. lung vs. other)	<b>0.054</b>	<b>0.029</b>

Abbreviations: KPS=Karnofsky Performance Status, NR=not reported, RPA= recursive partitioning analysis, RT=radiotherapy. Bold p values indicate statistical significance

### Progression Free Survival

The REACH randomised study reported no statistically significant differences between arms.<sup>37</sup> Median progression free survival (PFS) for all patients was 4 months in the efaproxiral arm vs. 3.5 months in the control arm (HR 0.89; p=0.21). In the NSCLC/breast cancer population, median PFS was 4.8 months in the treatment arm compared with 3.7 months in the control arm (HR 0.81; p=0.06).

Rades and Lohynska et al (2007) reported that progression of intracerebral disease and symptoms during or directly after radiotherapy were observed in 12% of the patients who received 5 fractions of 4 Gy each and in 9% of the higher dose group patients, respectively.<sup>40</sup>

### Neurologic progression

The REACH randomised study reported there was no statistically significant difference between arms for the proportion of deaths caused by neurologic progression (p=0.46).<sup>37</sup> Of the 206 deaths in the control arm, 30 (15%) were a result of neurologic progression, 124

(60%) were a result of non-neurologic progression, and 52 (25%) were indistinguishable. Of the 215 deaths in the efaproxiral arm, 37 (17%) were a result of neurologic progression, 126 (59%) were a result of non-neurologic progression, and 52 (24%) were indistinguishable ( $p=0.46$ ). Similar results were observed for the NSCLC/breast cancer population.<sup>37</sup>

### **Recurrence of brain metastases**

Recurrence of brain metastases was observed in 62% of patients after median interval of 3 months in the study of dose escalation by Rades et al (2007).<sup>41</sup>

### **Response rate**

Two analyses of the REACH randomised study reported response rate data.<sup>36,37</sup>

Suh et al (2006) reported point estimates of response rate (complete plus partial response) were 46% for the efaproxiral arm and 38% for the control arm ( $p=0.10$ ).<sup>37</sup> Twenty-eight patients in the efaproxiral arm had a complete response, twice the number in the control arm ( $n=14$ ). Analysis of the NSCLC/breast cancer population demonstrated a 13% increase in the response rate of the intervention arm (54%) compared with the control arm (41%), ( $p=0.01$ ).<sup>37</sup>

Stea et al (2006) reported response rates for the breast cancer subset, finding a statistically significant difference between the efaproxiral arm (74%) compared with the control arm (49%) ( $p=0.007$ ).<sup>36</sup>

### **Neurocognitive and psychological impairments**

Yaneva et al (2006) reported significantly improvement after whole brain radiotherapy for intracranial pressure (elevated pressure was corrected), headache and sensory dysfunctions.<sup>38</sup> While not significant, improvements were also observed for motor function and convulsions. There was also a reduction in patient's complaints and it was reported that patients felt socially adapted.<sup>38</sup>

Rades et al (2007) reported neurocognitive dysfunction/dementia in 6 patients (2.3%) who were treated with standard 30 Gy WBRT and in 8 patients (5.0%) treated with higher doses ( $p=0.24$ ).<sup>41</sup>

### **Adverse events**

The REACH randomised study reported that for both treatment arms the majority of treatment-emergent adverse events were grade 1 (mild) to grade 2 (moderate) in severity.<sup>37</sup> Hypoxaemia was the most commonly reported grade 3 adverse event in the efaproxiral arm (11%), and was the most commonly reported adverse event related to study drug. Overall, grade 4 adverse events were reported at comparable frequencies; 12% in efaproxiral arm vs. 11% in control arm. All adverse events were treatable; the majority of adverse events were resolved by the 1-month follow-up period.<sup>37</sup>

Rades et al (2007) reported mild acute WBRT-related toxicity for both groups.<sup>41</sup> There was no significant difference in grade 3 acute toxicity between 30 Gy arm (5.8%) and higher doses (5%) ( $p=0.92$ ).

Rades and Lohynska et al (2007) observed no significant difference in grade 3 radiotherapy-related acute toxicity rates between shorter and longer course arms, 9% and 4% respectively ( $p=0.359$ ).<sup>40</sup>

Rades et al (2011) reported acute WBRT related toxicity was mild in both shorter-course and standard therapy groups, however the patients treated with the shorter-course received higher doses of dexamethasone than those treated with standard therapy (median 24 mg per day vs. 20 mg per day).<sup>39</sup>

### **Quality of life**

Scott et al (2007) reported quality of life (QoL) results for breast cancer patients in the REACH randomised study.<sup>35</sup> QoL was improved in the efaproxiral arm compared with the control arm ( $p=0.019$ ), although there was a rapid drop-off in compliance for the completion of QoL assessment in follow-up beyond 1 month post WBRT. Suh et al (2006) also reported that in both the whole study population, and the NSCL/breast cancer population, a larger percentage of patients in the efaproxiral arm had stable or improving QoL scores over the course of the follow-up visits.<sup>37</sup>

Yaneva et al (2006) reported significant improvement ( $p<0.001$ ) over the time course: before radiotherapy, end of radiotherapy, and 1 month after radiotherapy, in all functional parameters of the EORTC-C30 questionnaire, including: global, physical, role, emotional, cognitive and social. Health-related quality of life recovered within a month after radiotherapy.<sup>38</sup>

### **Radiosurgery**

The American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons published a position statement and support the following definition of stereotactic radiosurgery (SRS) developed by the AANS, Congress of Neurological Surgeons, and the American Society for Therapeutic Radiology and Oncology (ASTRO)<sup>45</sup>:

Stereotactic Radiosurgery is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate defined target(s) in the head or spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist. Stereotactic Radiosurgery (SRS) typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five. Technologies that are used to perform SRS include linear accelerators, particle beam accelerators, and multisource Cobalt 60 units. In order to enhance precision, various devices may incorporate robotics and real time imaging.<sup>45</sup>

### **Retrospective analyses**

Five retrospective studies reporting results of SRS in patients with CNS metastases were identified.<sup>46-48</sup>

## Study characteristics

Combs et al (2004) retrospectively reviewed patients with cerebral metastases from breast cancer treated with SRS.<sup>47</sup> For analysis, the patients were divided into three treatment groups. The first group (group 1 n=10) consisted of ten patients with one to three brain metastases who received SRS alone, the second group (group 2, n=13) received WBRT and SRS as a focal boost to one to three brain metastases, and the third group (group 3 n=39) contained 39 patients treated with WBRT as an initial treatment who received SRS for recurrent metastases at a later time point.<sup>47</sup>

Goyal et al (2005) evaluated the effectiveness and limitations of gamma knife surgery (GKS) in the treatment of intracranial breast cancer lesions.<sup>49</sup> Forty-three breast cancer patients with a total of 84 lesions who were treated between 1989 and 2000 were included. All patients who received treatment were included in the study. Imaging studies were available in 35 patients with 67 treated lesions.

Akyurek et al (2007) undertook a retrospective study to evaluate the outcome of patients undergoing SRS as primary or salvage treatment of brain metastases from breast cancer.<sup>46</sup> The analysis included 49 patients with breast cancer who underwent SRS for brain metastases, 34 patients were treated initially with SRS and 15 patients were treated with salvage SRS for brain metastasis recurrence after initial WBRT. The number of brain metastases at time of SRS ranged from one to  $\geq 4$  and 23 patients (47%) presented with a single brain metastasis.

Kased et al (2009) reported on how the size and number of metastases and the omission of WBRT affect median survival time and local freedom from progression in a retrospective review of gamma knife SRS in 176 patients with brain metastases from breast cancer.<sup>48</sup> Three major subgroups were included:

- newly diagnosed brain metastases undergoing SRS alone initially (n=64; including 3 patients who also had undergone surgical resection of a metastasis before SRS),
- patients with newly diagnosed brain metastases undergoing SRS and upfront WBRT (n=31; including 3 patients who also had undergone surgical resection of a metastasis),
- patients with recurrent brain metastases (n=81: after previous WBRT, n=59; after surgery and WBRT, n=18; and after surgery alone, n=4).

The number of brain metastases ranged from one to  $>6$ . For the newly diagnosed patients, the proportion of patients with  $\geq 4$  metastases was 25% in the SRS alone group, 25%, compared with 52% in the SRS + WBRT group.

Matsunaga et al (2010) analysed prognostic factors for local tumour control and survival and indications for initial treatment with Gamma Knife in patients with up to 10 metastatic brain tumours from primary breast cancer.<sup>50</sup> One-hundred and one patients underwent a total of 160 GKS procedures for a total of 600 lesions, including 354 lesions at the initial treatment and 246 lesions at additional treatments.



## Outcomes

### Survival

In the retrospective analysis by Combs et al (2004) median overall survival after SRS was 15 months (range 1–276).<sup>47</sup> The median total survival time from primary diagnosis was 64 months (range 14–408). Median overall survival from the time point of SRS was 9, 6, and 19 months for group 1 (SRS alone), group 2 (WBRT and SRS as a focal boost to one to three brain metastases), and group 3 (SRS for recurrent metastases), respectively. In a univariate analysis of impact of prognostic factors on overall survival, type of radiation ( $p=0.0116$ ) and age ( $p=0.04$ ) were found to significantly influence overall survival. When overall survival of groups 1 and 2 were compared, patients treated with SRS only showed an increase in overall survival compared to WBRT with a focal boost ( $p = 0.036$ ). There was no significant difference in median overall survival when patients were divided into subgroups according to the RTOG RPA classes ( $p=0.47$ ). Median overall survival for RPA class 1 patients was 72 months, for class 2 was 64 months and for class 3 was 48 months, respectively.<sup>47</sup>

Goyal et al (2005) reported the overall duration of median survival was 13 months (95% CI 7-16 months) after GKS.<sup>49</sup> A univariable Cox regression analysis revealed that a single lesion ( $p=0.03$ ), a high Karnofsky Performance Scale (KPS) score ( $p=0.0009$ ), and a high Score Index for Radiosurgery (SIR) ( $p=0.00033$ ) were predictive of survival. The median duration of survival for patients grouped according to the SIR as low, middle, and high was 3, 8, and 21 months, respectively ( $p = 0.00033$ ). A multivariable analysis showed that a high KPS score ( $p=0.006$ ), a high SIR ( $p=0.014$ ), and advanced age ( $p=0.038$ ) were predictive of survival. The 1-, 2-, 3-, and 5-year survival rates were 49, 23, 12, and 2%, respectively.

Akyurek et al (2007) reported median survival of all patients to be 19 months and 1- and 2-year overall survival to be 59% and 46% respectively.<sup>46</sup> For patients who underwent initial SRS-alone, median survival was 25 months compared with 14 months in patients who received salvage SRS. The 1-year overall survival rate was 60% for SRS alone group and 55% for SRS salvage group, and 2-year overall survival was 56% for SRS alone and 23% for SRS salvage group. These rates were not statistically significant between groups ( $p=0.99$ ). Univariate analysis found high KPS score ( $p=0.02$ ), higher score index for radiosurgery (SIR) ( $p=0.004$ ) and pre-menopausal status ( $p=0.02$ ) to be significant prognostic factors for survival. In multivariate analysis all significant prognostic factors in the univariate analysis remained significant, with the addition of positive estrogen receptor ( $p=0.004$ ).<sup>46</sup>

Kased et al (2009) reported median survival time of 16 months from the start of brain metastasis treatment, for patients treated for newly diagnosed brain metastases ( $n=95$ ).<sup>48</sup> Median survival time for patients treated with SRS alone was 17.1 months while for patients treated with SRS and upfront WBRT, median survival time was 15.9 months ( $p=0.20$ ). In univariate analysis, longer survival time was significantly associated with age <50 years ( $p=0.015$ ), primary tumour control ( $p<0.001$ ), ER positivity ( $p=0.028$ ), and HER2/neu overexpression ( $p=0.007$ ). On multivariate analysis KPS >70 ( $p=0.021$ ), primary tumour control ( $p=0.057$ ), ER positivity ( $p = 0.032$ ), and HER2/neu overexpression ( $p=0.037$ ) were associated with improved survival. After adjusting for these four factors, upfront WBRT and the number of brain metastases remain insignificant ( $p=0.65$  and  $p=0.60$ , respectively) on multivariate analysis.<sup>48</sup>



Kased et al (2009) reported median survival time for patients with recurrent metastases of 11.7 months from the date of SRS.<sup>48</sup> Age <50 years ( $p<0.001$ ), KPS  $\geq 70$  ( $p=0.005$ ), a longer interval between the primary diagnosis and SRS ( $p=0.036$  for <4 years vs.  $\geq 4$  years;  $p=0.029$  by quartile), and smaller total target volume ( $p=0.01$  for  $<3\text{ cm}^3$  vs.  $\geq 3\text{ cm}^3$ ;  $p=0.004$  by quartile) were associated with longer survival. Age <50 years, longer interval from the primary diagnosis to SRS and a smaller total target volume remained significantly associated with longer survival on multivariate analysis.<sup>48</sup>

Matsunaga et al (2010) reported median overall survival time to be 13 months after the diagnosis of brain metastases and initial GKS treatment and 73 months after the diagnosis of primary breast cancer.<sup>50</sup> A multivariate analysis showed that the presence of extracranial metastatic disease at the time of the initial GKS ( $p=0.041$ ) and phenotype other than HER2-positive ( $p=0.001$ ) were significantly correlated with adverse overall survival time. The number of brain metastases was not statistically significant, except for a single metastasis.

### **Local and locoregional control**

Combs et al (2004) reported a median local control of 9 months and locoregional tumour control of 6 months for the whole populations studied.<sup>47</sup> The median local tumour control interval for group 1 (SRS alone) was 6.5 months and for group 2 (WBRT with SRS boost) was 4 months. The difference between group 1 and 2 was not significant ( $p=0.66$ ). The median local control interval after SRS in group 3 was 9 months. The median overall locoregional brain control was 6.5 months for group 1, 4 months for group 2, and 7 months for group 3. There was no statistically significant difference in locoregional control between group 1 and 2 ( $p=0.66$ ).<sup>47</sup>

In the study by Goyal et al (2005) the overall median time to local treatment failure was 10 months (95% CI 6-14 months) after GKS.<sup>49</sup> A univariable analysis demonstrated that a single lesion, higher KPS score, and a higher SIR were associated with a significantly longer time until local treatment failure. A multivariable analysis showed that a higher KPS score and SIR and patients who had received chemotherapy were associated with a significantly longer time to local treatment failure. Neuroimaging scores given for the enhancement pattern (ring-enhancing, heterogeneous, and homogeneous signal), amount of necrosis (none, < 50%, and > 50%), and mass effect (none, mild, moderate, and severe) of each treated lesion did not correlate with survival or local treatment failure.

Akyurek et al (2007) reported 1- and 2- year local control rates of brain tumour of 78% and 48% respectively for all patients.<sup>46</sup> The 1-year local control rate was 79% for SRS alone group and 77% for SRS salvage group, and 2-year local control was 49% for SRS alone and 46% for SRS salvage group. The rates were not statistically significant between groups ( $p=0.99$ ). Initial number of metastases at presentation, tumour volume, SRS dose ( $\leq 18\text{ Gy}$  vs.  $>18\text{ Gy}$  and  $\leq 20\text{ Gy}$  vs.  $>20\text{ Gy}$ ) and cone diameter were not significant in a log-rank analysis of local tumour control.<sup>46</sup>

Kased et al (2009) reported freedom from progression (FFP) including local FFP, freedom from new brain metastases and brain FFP.<sup>48</sup> There were no significant differences in the newly diagnosed patients between SRS alone and SRS plus WBRT groups for 1-year local FFP probability ( $p=0.68$ ), freedom from new brain metastases (median 14.8 months vs. 11.3 months for SRS alone vs. SRS + WBRT;  $p=0.83$ ) or brain FFP (median 8.6 months vs. 10.5

months for SRS alone vs. SRS + WBRT;  $p=0.75$ ). Data was presented in this study for patients treated for recurrent brain metastases, however there were no comparative analyses.

Matsunaga et al (2010) reported local tumour control.<sup>50</sup> Neuroimaging studies showed complete remission in 214 tumours (35.7%), partial remission in 280 tumours (46.7%), no change in 88 tumours (14.7%) and progression in 18 tumours (3%). Overall, the local tumour control rate, which was defined as suppression of tumour growth, was 97%, and the tumour response rate with volume reduction was 82.3%.<sup>50</sup> Multivariate analysis indicated that larger tumour volume and lower margin dose were significantly correlated with poor local tumour control ( $p=0.001$ ).

### **Freedom from progression (FFP)**

In the study by Kased et al (2009) no significant differences were seen in the FFP endpoints between SRS alone initially and SRS with upfront WBRT in the newly diagnosed patients.<sup>48</sup> The 1-year local FFP probability by patient was 78% (95% CI, 60–89%) for SRS alone vs. 77% (95% CI, 50–91%) for SRS plus WBRT ( $p=0.68$ ). The median freedom from new brain metastases was 14.8 months for SRS alone vs. 11.3 months for SRS plus WBRT ( $p=0.83$ ), and the median brain FFP was 8.6 months for SRS alone vs. 10.5 months for SRS plus WBRT, with a 1-year probability of 44% (95% CI, 29–59%) for SRS alone vs. 36% (95% CI, 15–58%) for SRS plus WBRT ( $p=0.75$ ). Salvage SRS was required 3 years later, and surgery was performed for a combination of tumour and necrosis 4.4 years after the first SRS session.

Symptomatic necrosis occurred in 10 patients, including 6 of 64 patients treated with SRS alone initially for newly diagnosed brain metastases (at 2.5, 5.2, 22.1, 32.4, 39.3, and 52.0 months after SRS), 1 of 31 patients treated with SRS and WBRT initially (11.5 months after SRS), and 3 of 81 patients treated with SRS for recurrent brain metastases (4.3, 7.4, and 12.4 months after SRS).<sup>48</sup> Of the 10 patients, 5 underwent surgical resection, with histologic examination showing only necrosis in 3 and predominantly necrosis in 2.

### **New lesion-free survival**

In the study by Matsunaga et al (2010) new brain metastases developed in 47 patients after the initial GKS, and additional WBRT and/or GKS were performed in 39 patients.<sup>50</sup> The median new lesion-free survival time after the initial GKS was 9 months. Survival rates were 74.8% at 6 months and 52.1% at 1 year. Patients with 4 or fewer lesions had significantly more favourable outcomes. Five or more lesions at initial GKS ( $p=0.007$ ) and younger patient age ( $p=0.008$ ) reduced survival significantly.

### **Distant brain metastases-free survival (DBMFS)**

For all patients in retrospective analysis by Akyukek et al (2007), the 1 year DBMFS rate was 69%.<sup>46</sup> The 1-year DBNFS was 64% in the group that received initial SRS alone and 57% in the group that received SRS salvage ( $p=0.62$ ). The median time between WBRT and salvage SRS was 11 months. Multivariate analysis found primary controlled disease ( $p=0.03$ ), age ( $p=0.02$ ) and positive estrogen receptor ( $p=0.05$ ) to have significant effect on DBMFS. Of the 34 patients treated with initial SRS alone, 10 (29%) later received WBRT. The actuarial 1-year freedom from WBRT was 62%.<sup>46</sup>

## Neurological survival

Matsunaga et al reported at the time of last follow-up, 78 patients had died of brain metastasis.<sup>50</sup> The causes of death were systemic disease in 68 patients and neurological disease in 10 patients. The survival rate at 1 year was 93.9%. An evaluation of prognostic factors for neurological survival showed only lower KPS score was significantly associated with poor survival ( $p=0.009$ ). The number of brain metastases had no effect on neurological survival.

## Adverse events

Combs et al (2004) reported SRS was very well tolerated in nearly all the patients. Ten of the 62 patients developed perifocal oedema without clinical symptoms, in one patient nausea and vomiting developed, and one patient suffered from intermittent neurological deficits (reduction of visual acuity).<sup>47</sup>

## Subgroups

### Retrospective analyses

Three retrospective studies examined the influence of HER2 status on outcomes in breast cancer patients following WBRT for brain metastases.

### Study characteristics

In a retrospective study, Wolstenholme et al (2008) assessed whether HER2 status had an effect on outcomes after WBRT.<sup>51</sup> 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) conducted a retrospective study to determine survival after WBRT in a cohort of women with brain metastases from breast cancer and confirm the prognostic significance of HER2 status.<sup>52</sup> Two hundred twenty-three women with breast cancer who developed brain metastases with known HER2 status were included; 30.2% hormone receptor-positive/HER2-negative, 45.5% HER2-positive, and 24.3% had triple receptor-negative disease. All women received WBRT and in addition, 33 (15%) women underwent surgery and 8 (3.6%) underwent radiosurgery as part of their initial treatment.<sup>52</sup>

Matsunaga et al (2010) analysed prognostic factors for local tumour control and survival and indications for initial treatment with Gamma Knife in patients with up to 10 metastatic brain tumours from primary breast cancer and analysed the impact of the tumours histological phenotype.<sup>50</sup> The phenotypes were HER2-positive in 28 patients, luminal in 37 patients, and triple negative in 36 patients.

## Outcomes

### Survival

Wolstenholme et al (2008) reported Kaplan-Meier estimation for median survival after diagnosis of brain metastases was 8 months in HER2-positive group compared with 4 months in the HER2-negative group ( $p=0.008$ ).<sup>51</sup> Only performance status was found to be a significant predictor of longer survival on univariate analysis ( $p=0.01$ ). On multivariate analysis, after adjusting for performance status, bone and lung metastases, surgery,

radiation dose, chemotherapy and trastuzumab, HER2 status remains an independent prognostic factor ( $p=0.02$ ).

In the study by Dawood et al (2010), from the entire cohort 82.5% had died at time of analysis.<sup>52</sup> The median time to brain metastases was 12 months (0-134 months) while median survival after diagnosis of brain metastases was 6 months (0-93 months) with one year overall survival rate of 30%. Univariate analysis found significant association between breast tumour subtype and survival, with significantly longer survival in HER2-positive patients (median survival 9 months) compared with hormone receptor-positive/HER2-negative disease and triple receptor negative disease (both median survival 5 months) ( $p=0.0069$ ). Poor median survival was associated with WBRT without surgery or radiosurgery and lower radiation doses ( $<30\text{Gy}$ ) ( $p=<0.0001$  for both). RPA class 3 was also found to have poorer survival compared with RPA class 1 or 2 ( $p=<0.0001$ ).<sup>52</sup>

In a multivariate analysis, HER2-positive disease had a lower risk of death in comparison to hormone receptor-positive/HER2-negative disease (HR 0.63; 95% CI 0.42-0.94;  $p=0.02$ ).<sup>52</sup> Radiation dose of  $<30\text{ Gy}$  had a significantly higher risk of death compared with  $\geq 30\text{ Gy}$  (HR 3.41; 95% CI 1.56-7.50;  $p=0.002$ ). WBRT alone vs. WBRT and surgery or radiosurgery was no longer significant. RPA class 3 was significantly associated with higher risk of death compared to RPA class 1 or 2 (HR 3.47; 95% CI 2.35-5.14;  $p=<0.0001$ ).<sup>52</sup>

Matsunaga et al (2010) reported patients whose lesions had the HER2-positive phenotype had longer survival times from detection of the first brain metastasis (median 25 months) than patients whose lesions had the luminal (median 12 months;  $p<0.0001$ ) or triple-negative (median 5 months;  $p<0.0001$ ) phenotype; however, the difference between patients with luminal-type lesions and those with triple-negative-type lesions was not statistically significant ( $p=0.569$ ).<sup>50</sup>

### **New lesion-free survival**

Matsunaga et al (2010) reported there were no significant differences between patients harbouring HER2-positive tumours (median 20 months) and those with luminal lesions (median 41 months;  $p=0.404$ ), patients with HER2-positive tumours and those with triple-negative lesions (median 11 months;  $p=0.092$ ), and patients with luminal tumours and those with triple-negative lesions ( $p=0.511$ ).<sup>50</sup>

### **Treatment received**

Wolstenholme et al (2008) reported no significant difference between HER2-positive and HER2-negative patients in the radiation doses received for treatment of brain metastases at presentation.<sup>51</sup> On progression of brain metastases, there were significant differences between the two groups regarding management. The HER2-positive group were more likely to receive further cranial radiation (19% HER2-positive vs. 6% HER2-). HER2-positive group also received more systemic therapy for cerebral disease progression compared with HER2-negative patients (64% vs. 42% respectively). Of the HER2-positive patients who developed brain metastases while receiving trastuzumab, 77% continued on the drug following local treatment for cerebral disease.

## Summary

### WBRT

- WBRT has been standard therapy for the treatment of CNS metastases from breast cancer.
- Results of the 3 analyses of the REACH randomised study indicated that the addition of efaproxiral to WBRT may improve response rates and survival in patients with brain metastases and particularly in those patients with brain metastases from breast cancer. Median survival ranged from 6-9 months in patients receiving efaproxiral compared with 4.4-4.5 months without efaproxiral. Efaproxiral also reduced risk of death by 25-48%. Response rates were also higher in breast (breast/lung cancer patients) who received efaproxiral (74% vs. 49%;  $p=0.007$  and in breast/lung cancer patients 54% vs. 41%;  $p=0.01$ ).
- A retrospective study by Rades et al, found dose escalation beyond 30 Gy in 10 fractions did not improve survival ( $p=0.86$ ) or local control ( $p=0.61$ ). Dose escalation was also associated with increased treatment time and cost of therapy.
- In two retrospective studies by Rades et al, short course WBRT had similar survival and local control to longer course WBRT, with one reporting significantly improved survival with shorter course regimens in univariate analysis. Shorter course may be preferable for the majority of these patients because it is less time consuming and more convenient.
- Karnofsky performance status (KPS)  $\geq 70$  and lack of extracranial metastases were associated with longer survival in multivariate analyses across the three Rades studies.

### Radiosurgery

- Five retrospective studies reporting results of SRS in patients with CNS metastases from breast cancer were identified.
- In two studies, patients with newly diagnosed CNS metastases, SRS alone was associated with longer survival compared with WBRT and SRS as a focal boost ( $p=0.036$ ) or WBRT and SRS ( $p=0.20$ ). SRS alone was also associated with improved local control (6.5 months vs. 4 months WBRT with SRS boost) and freedom from new brain metastases (14.8 months vs. 11.3 months for SRS + WBRT).
- Three non-comparative studies of gamma knife surgery (GKS) were identified. Median overall survival after GKS was 13 months in two studies and in the third study was 16 months for newly diagnosed patients and 11.7 months for patients with recurrence brain metastases.
- SRS as salvage therapy for recurrent CNS metastases reported in three studies, was associated with median survival of between 11.7 months and 19 months.

## Subgroups

Significantly longer survival for HER2-positive compared to HER2-negative patients was reported in two retrospective studies following WBRT and in one retrospective study following gamma knife surgery.

### 3.2.3 What is the effectiveness of systemic therapies in the management of CNS metastases from breast cancer?

#### Chemotherapy

##### Systematic reviews

No systematic reviews were identified which addressed the effectiveness of systemic therapies in the management of CNS metastases from breast cancer.

Two systematic reviews were identified which addressed the effectiveness of systemic therapies in the management of CNS metastases from various primary tumours, including breast cancer.

**The systematic review by Mehta et al (2010)** addressed the role of chemotherapy in the management of newly diagnosed brain metastases.<sup>53</sup> The associated clinical practice guideline recommendations included in the paper by Mehta et al, are outlined in appendix F. The use of chemotherapy for brain metastases was investigated in four questions, however, only the comparison of chemotherapy plus WBRT vs. WBRT alone will be reported as the other questions included studies of only lung cancer patients. Details on total number of patients and number of breast cancer patients in individual trials are presented in appendix G.

Five studies met the inclusion criteria for the question chemotherapy plus WBRT vs. WBRT alone. Four were class I evidence (two phase III randomised controlled trial (RCT's) and two phase II RCT's) and one was a retrospective cohort study. The systematic review concluded:

- Lack of clear and robust survival benefit with the addition of chemotherapy to WBRT
- Enhanced response rates, specifically in non-small cell lung cancer (NSCLC) with the addition of chemotherapy to WBRT
- In terms of secondary endpoints such as time to neurologic progression, steroid dose, etc., the data and results are mixed and do not permit robust conclusions

**The systematic review by Ammirati et al (2010)** addressed the treatment of patients who develop recurrent/progressive brain metastases after initial therapy.<sup>21</sup> The associated clinical practice guideline recommendations included in the paper by Ammirati et al, are outlined in appendix F.

The review addressed the question: *what evidence is available regarding the use of WBRT, SRS, surgical resection or chemotherapy for the treatment of recurrent/progressive brain metastases?* Thirty studies were identified.

Ten studies evaluated the role of chemotherapy in patients with recurrent/progressive metastatic brain disease. Median survival ranged from 3.5 months to 6.6 months and median time to recurrence after retreatment with chemotherapy ranged from 2 months to 4 months. The review concluded that the studies indicate that some patients with recurrent or progressive brain metastases will have an objective radiographic response and/or improvement in functional status after treatment with chemotherapy.<sup>21</sup>

### ***Prospective trials***

Eight studies were identified which investigated different chemotherapies for the management of CNS metastases.<sup>54-61</sup> Six studies were in populations with CNS metastases from breast cancer only,<sup>54,56-60</sup> while two studies were in populations with CNS metastases from various primary cancers, including breast cancer.<sup>55,61</sup>

### **Study characteristics**

Studies investigated the use of the following chemotherapies:

- temozolomide either alone or in combination with other chemotherapies: four studies<sup>55,58,60,61</sup>
- sagopilone alone: one study<sup>56</sup>
- patupilone alone: one study<sup>59</sup>
- methotrexate either alone or in combination with other chemotherapies: two studies<sup>54,57</sup>

Details for each of the included studies are presented in table 11

**Table 12 Characteristics of studies investigating chemotherapy**

Study	Patients, n	Treatment	Response rate	PFS or TTP	Median OS
<b>Temozolomide (TMZ) studies</b>					
Rivera 2006 <sup>60</sup> Phase I	Brain metastases (n=14 newly diagnosed, n=10 recurrent) from breast cancer n=24	Capecitabine (1800mg/m <sup>2</sup> /day starting dose) and TMZ (75mg/m <sup>2</sup> /day starting dose) (days 1-5 and 8-12) every 21 days	ORR: 18% CR: 4% PR: 14% SD: 50% PD: 32%	TTP: 12 weeks (range 3-70 weeks)	NR
Christodoulou 2005 <sup>55</sup> Phase II	Brain metastases from solid tumours n=32 (15 BC)	TMZ 150 mg/m <sup>2</sup> for 5 days, if they had received prior chemotherapy or 200 mg/m <sup>2</sup> /day for 5 days if they were chemotherapy naïve, combined with cisplatin 75mg/m <sup>2</sup> on day 1, every 28 days	For BC patients: ORR: 40% CR: 0% PR: 40%	For all patients: TTP: 2.9 months	For all patients: OS: 5.5 months
Siena 2010 <sup>61</sup> Phase II	Brain metastases from solid tumours n=157 (51 BC)	TMZ 150mg/m <sup>2</sup> /day (days 1-7 and 15-21 every 28- or 35- day cycle)	For BC patients: ORR: 4% CR: 0% PR: 4% SD: 16% PD: 80%	PFS: 58 days for BC	Not reached in BC
Melisko 2009 <sup>58</sup> Phase II Conference abstract	Brain metastases from breast cancer n=17 (brain metastases: n=9 leptomeningeal: n=1 brain and leptomeningeal n=7)	Irinotecan 125mg/m <sup>2</sup> intravenously every 14 days with TMZ 100mg/m <sup>2</sup> orally on days 1-7 and 15-21	SD: 64%	TTP in the CNS: 11.5 weeks TTP for patients with BM only: 16 weeks TTP with leptomeningeal : 4.5 weeks	NR



<b>Sagopilone studies</b>					
Freedman 2011 <sup>56</sup> Phase II	Brain metastases from breast cancer n=15	Sagopilone at 16mg/m <sup>2</sup> or 22mg/m <sup>2</sup> intravenously every 21 days	ORR: 13.3% CR: 0% PR: 2% SD (> 12 weeks): 0%	PFS: 1.4 months	5.3 months
<b>Patupilone studies</b>					
Murphy 2009 <sup>59</sup> Phase II Conference abstract	Brain metastases from breast cancer n=36 of 55 planned patients	Patupilone is given by 20 minute infusion at 10mg/m <sup>2</sup> every 3 weeks	PR: 19% SD: 29% PD: 52%	Median CNS PFS: 84 days	NR
<b>Methotrexate (MTX) studies</b>					
Jacot 2010 <sup>57</sup> Retrospective study	Brain metastases from breast cancer n=50	Carmustine 100mg/m <sup>2</sup> on day 1 and methotrexate 600mg/m <sup>2</sup> on day 1 and 15 of a 28 day cycle.	ORR: 23%	PFS: 4.2 months	6.9 months
Bazan 2011 <sup>54</sup> Phase II Conference abstract	Brain metastases from breast cancer n=22 (parenchymal metastases: n=17 leptomeningeal metastases: n=8)	High dose intravenous MTX (3g/m <sup>2</sup> ) during 3 hours infusion and concomitant hyper alcalin hydration.	PR: 9% SD: 45% PD: 45%	TTP: 2.1 months	6.3 months

Abbreviations: BC=breast cancer, CNS=central nervous system, CR=complete response, MTX=methotrexate, ORR=objective response rate, OS=overall survival, PD=progressive disease, PFS=progression free survival, PR=partial response, SD=stable disease, TMZ=temozolomide, TTP=time to progression

## Outcomes

All studies were phase I or phase II single arm studies and included small patient populations in general including newly diagnosed and recurrent, and meningeal. Median survival ranged from 5.3 months to 6.9 months. PFS/TTP ranged from 1.4-4.2 months. Objective response rates ranged from 4 – 40%.

## Adverse events

The most commonly reported adverse events reported in the trials were: thrombocytopenia, nausea, vomiting, headache, fatigue, leukopenia, anaemia and neutropenia.<sup>54-61</sup>

## Neurocognitive effects

Rivera et al (2006) reported that approximately half of the patients exhibited impairments in fine motor dexterity, 40% had impaired learning ability, and one-fourth had deficits in executive function and cognitive processing speed at baseline.<sup>60</sup> However, none had deficits in excess of the general cancer population. After 1 month of treatment (capecitabine and temozolomide), significant improvements in attention span ( $p=0.047$ ) and emotional function ( $p=0.016$ ) were observed, suggesting that the treatment was not neurotoxic and may have had a beneficial effect due to improved tumour control. There was a trend for improved graphomotor speed ( $p=0.09$ ). In addition, there was a significant improvement in emotional function as measured by the FACT-Br ( $p=0.016$ ) and no increase in adverse symptoms in the M.D. Anderson Symptom Inventory (MDAS). There were no significant differences between the baseline and end-of-study assessment on any measure, although the sample size ( $n=7$ ) may have been too small to detect a difference.<sup>60</sup> It appears that the treatment had no negative impact on cognitive function or QoL and may even have had a beneficial effect in those patients who had not progressed at the time of the neurocognitive assessment.<sup>60</sup>

Changes in neurologic signs and symptoms for women receiving sagopilone in the study by Freedman et al (2011) are presented in table 12.<sup>56</sup>

**Table 13 Changes in neurologic signs and symptoms for women receiving Sagopilone (n=15)<sup>a</sup> (Freedman 2011<sup>56</sup>)**

Study time point	Overall status of neurologic signs and symptoms (n)			Worsening of $\geq 1$ neurologic domain <sup>b</sup>
	Improved	Stable	Worsening	
Midtherapy	1	8	2 <sup>c</sup>	7 (of 11)
Progression/withdrew from study	0	5	9 <sup>c</sup>	10 (of 14) <sup>d</sup>

a Three patients had progression at second assessment and did not have "midtherapy" evaluations; 1 patient did not have assessments beyond baseline.

b Domains included level of consciousness, symptoms, cranial nerves, language, strength, sensation, and ataxia.

c At midtherapy and progression in 1 woman and 5 women, respectively, the signs and symptoms were felt to be possibly, probably, or definitely related to therapy.

d Seven of these patients had worsening overall status.

## HER2-directed therapies

### Trastuzumab

Six retrospective studies compared the use of trastuzumab in Human epidermal growth factor receptor 2 positive (HER2-positive) breast cancer patients with brain metastases to patients who did not receive trastuzumab to determine if trastuzumab is beneficial to survival and other outcomes.<sup>62-67</sup>

#### Study characteristics

Table 13 presents study characteristics of the six retrospective studies.

Five of the studies evaluated the use of trastuzumab in patients with brain metastases from HER2-positive breast cancer.<sup>62-65</sup> The remaining study reported outcomes for patients with metastatic breast cancer who then developed brain metastases.<sup>66</sup>

**Table 14 Study characteristics of trastuzumab studies**

Study	Patients	Arm 1	Arm 2
Bartsch et al 2007 <sup>62</sup>	HER2-positive BC and BM	Patients treated from 2003-2006 with WBRT for BM from HER2-positive BC, who received further T n=17	HER2-positive disease and BM, who were treated before 2002 WBRT, without T n=36
Church et al 2008 <sup>63</sup>	HER2-positive BC and BM	HER2-positive patients who received T after BM n=18	HER2-positive patients who did not receive T after BM n=8
Dawood et al 2008 <sup>64</sup>	HER2-positive BC and BM (91% parenchymal metastases, 1% leptomeningeal metastases, 8% parenchymal and leptomeningeal metastases)	Patients with HER2-positive disease who received T before, at or after the time of CNS metastases diagnosis n=228	Patients with HER2-positive disease who did not receive T n=32
Park et al 2009 <sup>65</sup>	HER2-positive BC and BM (92% multiple parenchymal metastases, 13% leptomeningeal and parenchymal metastases); 94% received WBRT	Patients with HER2-positive BC treated with T after BM diagnosis or continued T treatment after BM detected n=29	Patients with HER2-positive BC who did not receive T n=11 Patients with HER2-positive BC who received T before BM diagnosis n=38
Le Scodan et al 2011 <sup>67</sup>	HER2-positive BC and BM	HER2-positive patients treated with T n=32	HER2-positive patients not treated with T n=20
Park, Park et al 2009 <sup>66</sup>	HER2-positive MBC	MBC patients treated with T (2003-2006) n=111	MBC patients not treated with T (1999-2002) n=140

Abbreviations: BC=breast cancer, BM=brain metastases, MBC=metastatic breast cancer, METS=metastases, T=trastuzumab, WBRT=whole brain radiotherapy

## Outcomes

### Overall survival

Five retrospective studies reported on overall survival.<sup>62-65,67</sup>

#### *Trastuzumab vs. no trastuzumab in HER2-positive patients*

Five retrospective studies reported increased survival in HER2-positive patients who were treated with trastuzumab, or continued with trastuzumab after diagnosis of CNS metastases. See table 14.<sup>62-65</sup>

**Table 15 Median survival in retrospective studies comparing trastuzumab and no trastuzumab in HER2-positive patients**

Study	Trastuzumab received	No trastuzumab	P value
Bartsch 2007 <sup>62</sup>	21 months	9 months: chemotherapy, no T 3 months: no further systemic therapy	p=<0.001
Church 2008 <sup>63</sup>	11.9 months	3 months	p=0.05
Dawood 2008 <sup>64</sup>	11.6 months	6.1 months	p=0.03
Park 2009 <sup>65</sup>	4.0 months: T before BM 13.6 months: T after BM	5.5 months	p=<0.001
Le Scodan 2011 <sup>67</sup>	19.53 months	5.65 months	

Abbreviations: BM=brain metastases, T=trastuzumab

Bartsch et al (2007) reported a significant influence of trastuzumab treatment on overall survival in multivariate analysis (p=0.001).<sup>62</sup>

Dawood et al (2008) reported in a multivariate model adjusting for clinical and tumour characteristics patients who had HER2-positive disease and had never received trastuzumab had an increased hazard of death compared with patients with HER2-positive disease who had received trastuzumab before or at the time of CNS diagnosis (HR 1.34; 95% CI 0.78-2.30; p=0.28).<sup>64</sup>

In the study by Park et al (2009) of 78 tumours, 32 (41%) were ER or PgR positive, and 46 (59%) tumours were negative for both receptors.<sup>65</sup> In hormone receptor negative 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 (13.6 versus 3.2 months; p=<0.001). There was no significant survival advantage after trastuzumab treatment in hormone receptor-positive patients (median survival 13.2 versus 7.1 months; p=0.228).

Le Scodan et al (2011) reported 1-year survival rates to be 62.6% in HER2-positive patients treated with trastuzumab compared with 29.2% in HER2-positive patients not treated with trastuzumab.<sup>67</sup>

### *Trastuzumab after brain metastases vs. trastuzumab before brain metastases in HER2-positive patients*

In the study by Park et al (2009), for patients receiving trastuzumab after diagnosis, overall survival was significantly longer in comparison to patients who received trastuzumab before brain metastases (13.6 months vs. 4 months respectively;  $p < 0.001$ ).<sup>65</sup> Trastuzumab treatment after brain metastasis diagnosis compared with trastuzumab before brain metastases remained significantly associated with better survival in a multivariate cox regression model (HR 0.50; 95% CI 0.29-0.88;  $p = 0.017$ ).

In the study by Le Scodan et al (2011), the median survival for the 10 HER2-positive patients who stopped trastuzumab before or after the diagnosis of brain metastases and the 22 patients who continued a trastuzumab-based therapy after WBRT were 9.2 months and 20.9 months respectively ( $p > 0.1$ ).<sup>67</sup> The 1-year survival rates were 43.6% and 87.1% respectively ( $p = 0.13$ ).

### *HER2-positive patients who received trastuzumab vs. HER2-negative patients*

In the study by Church et al (2008), median survival was significantly longer in HER2-positive patients receiving trastuzumab compared with HER2-negative patients (11.9 months vs. 3.8 months;  $p = 0.002$ ).<sup>63</sup> Patients who received chemotherapy after brain metastases had improved survival in both groups, and median survival remained longer for trastuzumab-treated patients compared with HER2-negative patients (16.3 months vs. 9.6 months respectively;  $p = 0.04$ ).<sup>63</sup>

Dawood et al (2008) reported median survival to be significantly longer in HER2-positive patients who received trastuzumab before or at the time of CNS metastasis diagnosis compared with HER2-negative patients (11.6 months vs. 6.3 months respectively;  $p < 0.001$ ).<sup>64</sup> In a multivariate model adjusting for clinical and tumour characteristics, patients with HER2-negative disease had an increased hazard of death compared with patients with HER2-positive disease who had received trastuzumab before or at the time of CNS diagnosis (HR 1.66; 95% CI 1.31-2.12;  $p < 0.0001$ ).

In the study by Le Scodan et al (2011) the median survival of HER2-patients was 5.9 months compared with 19.53 months in HER2-positive patients treated with trastuzumab.<sup>67</sup> One-year survival rates were 26.1% vs. 62.6% respectively.

### **Time to death from brain metastases**

Park, Park et al (2009) reported time to death from brain metastases to be significantly longer in the patients who received trastuzumab compared to patients who did not receive trastuzumab (14.9 months vs. 4 months respectively;  $p = 0.0005$ ). Multivariate cox regression analysis indicated a high hazard ratio for trastuzumab treatment after brain metastases, though it was not significant (HR 3.597, 95% CI 0.834-15.523;  $p = 0.086$ ).<sup>66</sup>

### **Time to progression (TTP)**

Two retrospective studies reported on time to progression (TTP).<sup>62,65</sup>

#### *1. Trastuzumab vs. no trastuzumab in HER2-positive patients*

All two studies reported significantly longer median TTP in HER2-positive patients who received trastuzumab, see table 15.

**Table 16 Median TTP in retrospective studies comparing trastuzumab and no trastuzumab in HER2-positive patients**

Study	Trastuzumab received	No trastuzumab	P value
Bartsch 2007 <sup>62</sup>	9 months	6 months: chemotherapy, no T 2 months: no further systemic therapy	p=0.001
Park 2009 <sup>65</sup>	7.8 months	3.9 months	p=0.006

Abbreviations: T=trastuzumab

Bartsch et al (2007) reported a trend toward prolonged in-brain TTP in patients receiving trastuzumab in a multivariate analysis, however it did not reach significance (p=0.068).<sup>62</sup>

## 2. Trastuzumab after brain metastases vs. trastuzumab before brain metastases in HER2-positive patients

In the study by Park et al (2009), median TTP was 7.8 months in patients who received trastuzumab after brain metastases compared with 2.9 months in patients who received trastuzumab before brain metastasis diagnosis (p=0.006).<sup>65</sup>

### Time to treatment failure (TTF)

In the study by Park et al (2009) time to treatment failure (TTF), defined as the time from trastuzumab administration to disease progression or death, was not different between patients who received trastuzumab before brain metastases compared with patients who received trastuzumab after brain metastases (5.6 months vs. 5.8 months respectively; p=0.771).<sup>65</sup> Kaplan–Meier survival analysis showed a trend toward longer survival in patients with TTF >5.8 months (median survival 20.2 versus 8.4 months; p=0.085).

## Lapatinib

### 1. Previously untreated CNS metastases

One study was identified which investigated the use of lapatinib in combination with capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer.<sup>68</sup> The search undertaken for this systematic review identified a conference abstract for this study. A full paper of the study was published after the search and has been included in this systematic review.

### 2. Previously treated CNS metastases

Eight studies, investigating the use of lapatinib for the treatment of CNS metastases in HER2 positive metastatic breast cancer patients previously treated were identified.<sup>69-76</sup>

## Study characteristics

### 1. Previously untreated CNS metastases

In the LANDSCAPE single arm, phase II study, Bachelot et al (2013) evaluated the combination of lapatinib plus capecitabine for the treatment of previously **untreated** brain metastases from HER2-positive breast cancer.<sup>68</sup> Exclusion criteria included single brain metastases amenable to surgical resection, previous WBRT or SRS, current radiation therapy or current systemic treatment for breast cancer.

## 2. Previously treated CNS metastases

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.<sup>72,73</sup> In Lin 2009 a subset of patients who progressed on lapatinib went on to receive lapatinib and capecitabine.<sup>73</sup> A subsequent randomised phase II trial comparing lapatinib in combination with capecitabine or topotecan was undertaken.<sup>74</sup> Patient characteristics are presented in table 16. 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 reports<sup>69</sup>), however none included a control arm of capecitabine alone.<sup>69,75,76</sup> Patient characteristics are presented in table 6.

Two further phase I studies (conference abstract reports) reported outcomes for use of lapatinib with temozolomide and lapatinib with WBRT.<sup>70,71</sup> Patient characteristics are presented in table 16.

**Table 17 Study characteristics of lapatinib studies**

Study	Patients	Arm 1	Arm 2
<i>Previously untreated patients</i>			
Bachelot (LANDSCAPE) 2013 <sup>68</sup>	HER2-positive BC with BM not previously treated with WBRT n=45	C 2000mg/m <sup>2</sup> /day from day 1-14 every 21 days, in combination with L 1250mg/day continuously (days 1-21)	
<i>Previously treated patients</i>			
Lin 2008 <sup>72</sup>	HER2-positive BC, prior T was required. CNS progression after WBRT, SRS, or both. Patients also eligible if no prior radiotherapy provided they were asymptomatic n=39	L 750mg orally twice a day in continuous 4wk cycles. L dose was held, then reduced to 500mg twice a day for grade 3 to 4 toxicity or clinically significant grade 2 toxicity.	
Lin 2009 <sup>73</sup>	HER2-positive BC, new or progressive BM after completion of WBRT or SRS. Prior T required n=242	L 750mg twice daily (n=242)	Extension phase: C 1000mg/m <sup>2</sup> for 14 days in each 21 day cycle in combination with L 1250mg (n=50)
Lin 2011 <sup>74</sup>	HER2-positive BC, new and/or progressive BM, prior WBRT and/or SRS. Prior T required. n=22	L 1250mg orally once daily and C 2000mg/m <sup>2</sup> orally divided twice daily on days 1-14 of a 21 day cycle (n=13)	L 1250mg orally once daily and topotecan 3.2mg/m <sup>2</sup> intravenously on days 1, 8 and 15 of a 28 day cycle (n=9)
Boccardo (LEAP/ATU) 2008 <sup>69</sup>	HER2-positive BC with BM, disease progression after prior taxane,	L and C	

Study	Patients	Arm 1	Arm 2
Abstract	anthracycline and T n=138		
Metro 2011 <sup>75</sup>	HER2-positive BC with BM pre-treated with a taxane, an anthracycline and T. Patients were considered evaluable for response of BMs: (i) in the presence of progressive BMs (ii) in presence of measurable BMs $\geq 1$ cm in diameter (iii) in case of prior neurosurgery residual disease had to be documented radiologically (iv) if cranial radiotherapy and/or SRS had been completed $\geq 2$ months before start of LC	L 1250mg orally once daily plus C 1000mg/m <sup>2</sup> orally twice per day for days 1-14 every 3 weeks (n=30)	Patients treated consecutively with T-based therapies only beyond brain progression (n=23)
Sutherland 2010 <sup>76</sup>	HER2-positive BC who previously received anthracycline, taxane and T. Patients with CNS disease were allowed in study if asymptomatic and on $\leq 2$ mg dexamethasone (or equivalent) per day. n=34 patients with CNS metastases	C 2000mg/m <sup>2</sup> per day in two divided doses for 14 days, followed by a 7-day rest and lapatinib 1250mg once daily continuously	
De Azambuja 2011 <sup>70</sup> Abstract	HER2-positive BC and recurrent or progressive BM. Previous chemotherapy, T, L and brain radiotherapy/surgery/radiosurgery were allowed n=17	L and temozolomide	
Lin 2010 <sup>71</sup> Abstract	HER2-positive BC and at least 1 BM n=35	L 750mg BID on day 1, followed by 1000mg, 1250mg or 1500mg QD, beginning 1-8 day prior to WBRT (37.5 Gy in 15 fractions) and continuing through radiotherapy	

Abbreviations: BC=breast cancer, BM=brain metastases, C=capecitabine, CNS=central nervous system, L=Lapatinib, T= trastuzumab



## Outcomes

### Overall survival

#### 1. Previously untreated CNS metastases

Bachelot et al (2013) reported 26 (58%) of the 45 study participants died during the LANDSCAPE study (none of the deaths were thought to be treatment-related): 24 (53%) patients died from disease progression, one (2%) patient died from diabetic ketoacidosis, and one patient (2%) died from unknown cause.<sup>68</sup> Overall survival at 6 months was 90.9% (95% CI 77.6–96.5) and the median overall survival for the 44 patients who were assessable for efficacy outcomes was 17.0 months (13.7–24.9).

#### 2. Previously treated CNS metastases

Lin et al (2009) reported on overall survival, for lapatinib treatment.<sup>73</sup> In total 110 patients (46%) had died by the time of the analysis. The median survival was 6.37 months (95% CI 5.49-8.25).<sup>73</sup>

In the study by Metro et al (2011), overall survival was measured from start of lapatinib and capecitabine (OS1) and from the time of development of brain metastases (OS2) to the date of death for any cause.<sup>75</sup> In the OS1 analysis, 18 patients had died and median survival was 11 months (95% CI 4.3-17.6). In OS2 analysis, patients treated with lapatinib and capecitabine had a median overall survival significantly longer compared with patients treated with trastuzumab-based therapies only beyond brain progression (27.9 months vs. 16.7 months, respectively;  $p=0.01$ ). Two-year survival was 66% for responsive patients compared with 44% for patients with stable or progressive brain metastases ( $p=0.11$ ).

### Response rate

#### 1. Previously untreated CNS metastases

Bachelot et al (2013) reported an objective response rate of 65.9% ( $n=29$ ; 95% CI 50.1-79.5), all of which were partial responses, among the 44 (98%) of assessable patients.<sup>68</sup> See table 17. The median time from inclusion to first documented response was 1.8 months (1.1-5.8 months) among the 29 patients.<sup>68</sup>

Seven (16%) patients had progressive disease.<sup>68</sup> Of these patients, one withdrew from the study (with no post-baseline assessment) because of non-compliance with treatment. Of the remaining six patients one had extra-CNS progression only and five had CNS progression (one had neurological signs and symptoms at neither baseline nor progression, one had baseline neurological signs and symptoms that slightly improved at the time of progression, and three patients had baseline neurological signs and symptoms that worsened at progression). Of the three patients with neurological signs and symptoms that worsened at progression, WBRT was given 0.8 months, 1.1 months and 3.7 months after inclusion-they died at 6.2 months, 4.1 months and 6.6 months respectively.<sup>68</sup>

Forty-two (96%) of 44 patients were evaluable for CNS response according to Response Evaluation Criteria in Solid Tumors (RECIST).<sup>68</sup> Twenty-four (57%, 95% CI 41-72) had an objective CNS response; two patients (5%) had a complete response and 22 patients

(52%) had a partial response. Fifteen (36%) patients had stable disease and three (7%) had progressive disease. The authors noted high agreement between disease progression determined by RECIST and disease progression determined by volumetric assessments: all but one patient with a complete or partial response according to RECIST criteria also had an objective CNS response measured by volumetric criteria.<sup>68</sup>

Of the 24 patients assessable for efficacy and with neurological signs and symptoms at baseline, improvement of symptoms was reported in 14 (58%) patients (95% CI 37-78).<sup>68</sup> In 34 (77%) patients with assessable extra-CNS metastatic sites, RECIST-based assessment showed that 15 patients (44.1%; 95% CI 27.2-62.1) had an objective extra-CNS response, 16 (47%) patients had stable disease and three (9%) patients had progressive disease. Median time to progression was 5 + 5 months (95% CI 4.3-6.0).<sup>68</sup>

Objective CNS response according to ECOG performance status showed that 13 (77%) of 17 patients with an ECOG performance status of 0 had objective CNS response compared with 15 (58%) of 26 patients with a 1-2 ECOG status.<sup>68</sup>

## 2. Previously treated CNS metastases

The three studies by Lin et al reported response rate.<sup>72-74</sup> The objective response rate was 2.6% to 6% in patients who received lapatinib alone.<sup>72,73</sup> In patients who received lapatinib in combination with capecitabine the objective response rate was 20% to 38%.<sup>73,74</sup> While no objective responses were observed in patients who received lapatinib with topotecan.<sup>74</sup> The three lapatinib and capecitabine studies also reported response rates; 18-32%.<sup>69,75,76</sup> See table 17.

Lin et al 2009 also reported response rates for 130 patients with measurable extra-CNS disease at baseline.<sup>73</sup> Nineteen (15%) patients experienced an objective response by RECIST guidelines in those sites. Of the 19 patients, 3 experienced a CNS objective response.<sup>73</sup>

Lin et al 2008 reported that 16 patients (41%) had measurable non-CNS disease at baseline. Four patients (25%) achieved a PR in non-CNS sites.<sup>72</sup> All of the patients that responded in non-CNS sites were taken off study for CNS progression.

**Table 18 Response rates of studies**

Study	Arm	ORR (%)	CR (%)	PR (%)	SD (%)	PD (%)
<i>Previously untreated patients</i>						
Bachelot 2013 <sup>68</sup>	Lapatinib + capecitabine	29 (65.9)	NR	29 (65.9)	NR	7 (16%)*
<i>Previously treated patients</i>						
Lin 2008 <sup>72</sup>	Lapatinib only	1 (2.6)	0	1 (2.6)	6 (15.4)	NR
Lin 2009 <sup>73</sup>	Lapatinib only	15 (6)	0	15 (6)	88 (37)	108 (46)
	Lapatinib + capecitabine extension	10 (20)	NR	10 (20)	NR	NR
Lin 2011 <sup>74</sup>	Lapatinib + capecitabine	5 (38)	0	5 (38)	6 (46)	2 (15)
	Lapatinib + topotecan	0	0	0	3 (33)	1 (11)

Study	Arm	ORR (%)	CR (%)	PR (%)	SD (%)	PD (%)
Boccardo 2008 <sup>69</sup>	Lapatinib + capecitabine	NR	3(2)	22(16)	65(47)	19(14)
Metro 2011 <sup>75</sup>	Lapatinib + capecitabine	NR	NR	7(31.8)	6(27.3)	9(40.9)
Sutherland 2010 <sup>76</sup>	Lapatinib + capecitabine	7(21)	1(3)	6(18.2)	19(57.6)	6(18.2)

Abbreviations: BC=breast cancer, BM=brain metastases, C=capecitabine, CNS=central nervous system, CR=complete response, L=Lapatinib, NR=not reported, ORR=objective response rate, PD=progressive disease, PR=partial response, SD=stable disease, T= trastuzumab

\*Two patients had progression outside of the CNS

Boccardo et al (2008) noted that 42% of patients with progressive brain metastases at entry received capecitabine before lapatinib; 36% of patients with complete response or partial response in the CNS received prior capecitabine.<sup>69</sup>

Metro et al (2011) reported response of brain metastases to be related to the local treatment delivered prior to lapatinib and capecitabine: three responses (75%) and one disease stabilization (25%) in the brain were observed in patients who did not receive any local treatment for brain metastases.<sup>75</sup>

In the study by Sutherland et al (2010), the objective response rate in CNS was lower in those previously treated with capecitabine (16.7%) compared with 30% in the patients who had not received prior capecitabine ( $p=0.2$ ).<sup>76</sup>

### **Time to progression (TTP)**

#### *1. Previously untreated CNS metastases*

In the LANDSCAPE study (Bachelot et al 2013), the median time to progression (TTP) was 5.5 months (95% CI 4.3-6.0) and median time to CNS progression was 5.5 months (95% CI 4.5-6.1).<sup>68</sup> TTP was greater in patients who responded to treatment (6 months; 95% CI 5.5-7.4) compared with patients who did not respond to treatment (2.8 months; 95% CI 1.4-4.2) ( $p<0.0001$ ).<sup>68</sup>

#### *2. Previously treated CNS metastases*

In the 2008 study by Lin et al median TTP was 3 months (95% CI 2.3-3.7 months) and TTP was 11.3 months for the patient with CNS objective response. At 16 weeks, seven patients (18%) were free of any progression.<sup>72</sup>

Sutherland et al (2010), reported a median TTP of 22 weeks (95% CI 15-28) for the 34 patients with CNS metastases (most of who had progressed despite previous radiotherapy).<sup>76</sup> Median TTP for those previously treated with capecitabine was 17 weeks compared with 30 weeks for the capecitabine naive group ( $p=0.06$ ).

Bachelot et al (2011) observed a median TTP of 5.5 months and median time to WBRT of 8.3 months.<sup>77</sup>

## Progression free survival (PFS)

### 1. Previously treated CNS metastases

Lin et al 2009 reported median PFS and the percentage of patients free of disease progression at 2, 4 and 6 months for patients receiving lapatinib alone and for the extension phase of lapatinib and capecitabine. Results are presented in table 18.<sup>73</sup>

**Table 19 PFS and disease progression (Lin 2009<sup>73</sup>)**

		Lapatinib alone	Lapatinib and capecitabine
Median PFS (95% CI)		2.40 months (1.87-2.79)	3.65 months (2.43-4.37)
Free of disease	2 months (95% CI)	53.5% (47.1-59.9)	66.3% (53.2-79.4)
	4 months (95% CI)	14.7% (10.1-19.3)	37.3% (23.8-50.9)
	6 months (95% CI)	5.9% (2.2-9.6)	19.7% (7.6-31.7)

Abbreviations: PFS=progression free survival

In the study by Metro et al (2011), median PFS was 5.1 months (95% CI 2.6-7.5) and median brain-specific PFS was 5.6 months (95% CI 4.4-6.8) from the start of lapatinib and capecitabine.<sup>75</sup> The median duration of brain response was 6 months (range 3-25). It was 18 months in the three patients who had not received any prior local treatment for brain metastases, compared with 4.5 months (range 3-6) in the four patients who had received prior local therapy. At 6 months, 57% of responsive patients were alive and free from brain progression compared with 27% of patients with stable or progressive brain metastases ( $p=0.02$ ). At 1 year, 67% of responsive patients were alive compared with 33% of patients with stable or progressive brain metastases ( $p=0.02$ ).

## Volumetric analysis of CNS lesions

### 1. Previously untreated CNS metastases

Bachelot et al (2013) reported a CNS volumetric reduction of 80% or greater for 20% of patients in the LANDSCAPE study.<sup>68</sup> The study also reported overall 84% of patients had a reduction in tumour volume from baseline.<sup>68</sup> See table 19.

**Table 20 CNS volumetric reduction in the LANDSCAPE study<sup>68</sup>**

CNS volumetric reduction	Patients (n=44)
≥80% reduction	9 (20%)
50-<80% reduction	20 (45%)
20-<50% reduction	6 (14%)
0-<20% reduction	2 (5%)

### 2. Previously treated CNS metastases

In the two prospective trials of lapatinib by Lin et al, volumetric changes in CNS target lesions, including TTP and PFS, were reported.<sup>72,73</sup>

Lin et al 2008 reported three patients achieved at least 30% volumetric reductions in CNS target lesions and an additional seven patients achieved reductions of 10% to 30%.<sup>72</sup> A

trend toward a longer TTP for patients with at least 30% volumetric reduction versus others (median TTP from 8-week MRI, 1.8 v 5.4 months;  $p=0.16$ ) was observed. Similar results were seen when patients were dichotomized according to at least 10% volumetric reduction versus others (median TTP from 8-week MRI, 1.8 v 3.5 months;  $p=0.04$ ).

In the 2009 study by Lin et al, volumetric reduction in CNS lesions were reported for patients who received lapatinib only as well as in the subset of patients who received lapatinib and capecitabine.<sup>73</sup> Table 20 presents the number of patients who experienced volumetric reductions of either  $\geq 50\%$  or  $\geq 20\%$  as well as median PFS for these subgroups.

**Table 21 Volumetric changes and PFS (Lin 2009<sup>73</sup>)**

	Patients experiencing a ≥20% CNS volumetric reduction		Patients experiencing a ≥50% CNS volumetric reduction	
	Yes	No	Yes	No
Lapatinib alone				
n	50	186	19	217
Median PFS, months (95% CI)	3.61 (3.19-3.71)	1.87 (1.84-2.14)	3.38 (2.79-5.36)	2.07 (1.87-2.73)
PFS HR (95% CI)	0.51 (0.36-0.72)		0.61 (0.37-1.01)	
Lapatinib and capecitabine extension phase				
n	20	30	11	39
Median PFS, months (95% CI)	4.60 (3.68-8.15)	1.89 (1.48-3.65)	6.21 (3.94-n/e)	3.12 (1.68-3.75)
PFS HR (95% CI)	0.34 (0.17-0.68)		0.33 (0.14-0.76)	

Abbreviations: CNS=central nervous system, HR=hazard ratio, PFS=progression free survival

### **Sites of first progression**

#### *1. Previously untreated CNS metastases*

In the LANDSCAPE study (Bachelot et al 2013) among the 41 (93%) patients with available data, the site of first progression was CNS alone in 32 (78%) patients, extra-CNS alone in two (5%) patients and both CNS and extra-CNS lesions in five (12%) patients.<sup>68</sup> Median time to radiotherapy was 8.3 months (95% CI 5.4-9.1). At the time of analysis, 36 (82%) patients had received radiotherapy to the brain.

#### *2. Previously treated CNS metastases*

Seventy-three per cent of patients in the lapatinib only study by Lin et al (2009) experienced progression of disease.<sup>73</sup> The initial site of disease progression in 66% of patients overall was in the CNS, with or without extra-CNS disease progression. Only 7% of patients experienced disease progression exclusively outside of the CNS. The 2011 study by Lin also reported the CNS to be the most common site of initial disease progression.

### **Improvement in neurological signs and symptoms (NSS)**

#### *1. Previously treated CNS metastases*

In the study by Lin et al (2009), of the 198 patients with NSS at baseline, improvements in NSS were reported in 11.6% of patients at week 8 (lapatinib alone).<sup>73</sup> Dizziness, ataxia or

headache, visual problems or vertigo, cranial nerves or strength, and nausea, consciousness or seizure, were the most common NSS reported as improved. Improvement in NSS was reported in 22.9% of patients who experienced a  $\geq 20\%$  reduction in the volume of their CNS lesions compared with only 7.3% of patients who did not experience a decrease in the volume of the CNS lesions.

In the study of lapatinib and capecitabine by Boccardo et al (2008), investigators reported improvement in NSS in 25% of patients.<sup>69</sup>

### **Treatment compliance**

#### *1. Previously untreated CNS metastases*

Bachelot et al (2013) reported that 16 patients required a lapatinib dose reduction. Of these, 11 had their dose reduced in their first two cycles of treatment.<sup>68</sup> Twenty-six patients needed a capecitabine dose reduction, mostly during the second (six patients), third (six patients) and fourth (four patients) cycle. Four (9%) patients discontinued treatment due to an adverse event.<sup>68</sup>

#### *2. Previously treated CNS metastases*

All three studies by Lin et al reported on treatment received, treatment discontinuation and dose reductions.<sup>72-74</sup>

In the 2008 lapatinib only study, 136 4-week cycles of treatment were administered, with 74% of cycles administered at full dose.<sup>72</sup> Fifteen patients (38%) required at least one dose reduction, in 23% of cycles lapatinib was reduced to 500mg twice a day, and one patient required a further reduction to dose of 1250mg once a day. At the time of final study analysis, all patients had completed protocol-directed therapy. Patients were removed from the study for progressive disease (PD) in the CNS only (n=24); PD in non-CNS sites only (n=4), PD in both CNS and non-CNS sites (n=5), toxicity (n=3), death (n=1) or other (n=2).<sup>72</sup>

Lin et al 2009 (lapatinib only) reported that the median duration of exposure to lapatinib alone was 84 days (range 1-336 days).<sup>73</sup> Initial dose modification from 750 mg b.i.d. (twice daily) to 1500mg once daily (q.d.) was required by 30 patients (12%), and 14 patients (6%) required a second dose modification to 1250mg q.d. Dose delays were required by 21% of patients (n=50), mostly as a result of non-hematologic toxicity. The most common reason for study medication discontinuation was disease progression (74%).<sup>73</sup>

In the 2011 Lin study all patients had discontinued therapy as of the data cut-off date.<sup>74</sup> The most common reason for discontinuation in the lapatinib plus capecitabine arm was disease progression (62%). Reasons for treatment discontinuation in the lapatinib plus topotecan arm were more variable, however progressive disease was still most common (32%) followed by adverse events (22%). In the lapatinib plus capecitabine arm 4 patients (31%) required dose reductions of capecitabine, with no reductions required for lapatinib. In the lapatinib plus topotecan arm three patients (33%) required dose reductions of topotecan and three patients (33%) also required dose reductions for lapatinib. In addition, dose delays for topotecan were common (89%).

## Adverse events

### 1. Previously untreated CNS metastases

In the LANDSCAPE study (Bachelot et al 2013), 22 (49%) patients had at least one grade 3 or grade 4 adverse event with the most common being diarrhoea and hand-foot syndrome.<sup>68</sup> Fourteen (31%) patients had at least one serious adverse event. No toxic deaths were reported. See table 21.

**Table 22 Treatment-related adverse events in the LANDSCAPE study<sup>68</sup>**

	Any grade	Grade 3-4
Diarrhoea	38 (84%)	9 (20%)
Hand-foot syndrome	34 (76%)	9 (20%)
Fatigue	22 (49%)	6 (13%)
Rash	21 (47%)	2 (4%)
Nausea	23 (51%)	1 (2%)
Bilirubin increase	21 (47%)	1 (2%)
Vomiting	16 (36%)	2 (4%)
Stomatitis	13 (29%)	1 (2%)

### 2. Previously treated CNS metastases

The three studies by Lin et al reported on adverse events.<sup>72-74</sup> In patients receiving lapatinib only, the most common adverse event was diarrhoea, see table 22 for most common adverse events.<sup>72</sup> In the 2008 study, three patients were removed from the study due to toxicity and one patient died suddenly while receiving the third cycle. In the 2009 study, 17 patients (7%) had serious or non-serious adverse events that led to withdrawal from the study. One fatal serious event was reported in a patient.<sup>73</sup>

In patients receiving lapatinib in combination with capecitabine, the most commonly reported adverse events were diarrhoea, palmarplantar erythrodysesthesia (PPE), nausea and fatigue, see table 22 for most common adverse events.<sup>73,74</sup> There was one death due to adverse event in the 2009 study.<sup>73</sup> In the 2011 randomised study, one patient was withdrawn from the study and one patient died due to adverse events. In the lapatinib plus topotecan arm of the 2011 study, the most commonly reported adverse events were diarrhoea, nausea, fatigue and thrombocytopenia.<sup>74</sup> Excess toxicity and lack of efficacy led to closure of the lapatinib plus topotecan arm of the study.



**Table 23 Most commonly reported adverse events in the three studies (Lin<sup>70,71,72</sup>)**

Study	Adverse event	Patients, number. (%)				
		Grade 1	Grade 2	Grade 3	Grade 4	Unknown
Lapatinib only						
Lin 2008 <sup>72</sup>	Diarrhoea		(23)	(21)	(0)	
	Fatigue		(15)	(15)	(0)	
	Headache		(8)	(10)	(0)	
	Rash		(10)	(5)	(0)	
	Anorexia		(8)	(3)	(0)	
	AST/ALT		(5)	(8)	(0)	
	Nausea		(5)	(3)	(0)	
Lin 2009 <sup>73</sup>	Diarrhoea	65 (27)	61 (25)	30 (13)	2 (<1)	
	Rash	50 (21)	15 (6)	6 (3)	1 (<1)	
	Nausea	36 (15)	21 (9)	7 (3)	0	
	Vomiting	32 (13)	16 (7)	9 (4)	0	
	Fatigue	27 (11)	19 (8)	6 (3)	0	
	Headache	28 (12)	13 (6)	4 (2)	0	
Lapatinib plus capecitabine						
Lin 2009 <sup>73</sup>	PPE					(45)
	Diarrhoea					(37)
	Nausea					(29)
Lin 2011 <sup>74</sup>	Diarrhoea	3 (23)	4 (31)	2 (23)	1 (8)	0
	PPE	2 (15)	4 (31)	2 (15)	0	0
	Fatigue	4 (31)	4 (31)	0	0	0
	Headache	4 (31)	2 (15)	0	0	0
	Rash	4 (31)	1 (8)	0	0	0
	Peripheral edema	2 (15)	1 (8)	0	0	2 (15)
	Vomiting	3 (23)	1 (8)	0	0	0
	Dry skin	3 (23)	1 (8)	0	0	0
	Mucosal inflammation	3 (23)	0	1 (8)	0	0
Lapatinib plus topotecan						
Lin 2011 <sup>74</sup>	Diarrhoea	2 (22)	3 (33)	3 (33)	0	0
	Nausea	3 (33)	1 (11)	1 (11)	0	0
	Fatigue	2 (22)	1 (11)	2 (22)	0	0
	Thrombocytopenia	1 (11)	2 (22)	2 (22)	0	0
	Neutropenia	1 (11)	0	1 (11)	1 (11)	0

PPE= palmar-plantar erythrodysesthesia

Bachelot et al (2011) reported that 20 patients (44%) treated with lapatinib and capecitabine experienced grade 3 or 4 treatment related toxicity and treatment was discontinued due to toxicity in 3 patients.<sup>77</sup>

Lin et al (2010) reported none of the three patients receiving lapatinib 1,000 mg and none of the five patients receiving lapatinib 1,250 mg experienced a dose limiting toxicity (DLT). At lapatinib 1,500 mg, DLTs were observed in 2 patients: grade 3 diarrhoea and grade 3 rash, each associated with lapatinib dose hold of 16 days during cycle 1. An additional 22 patients were enrolled at the maximum tolerated dose (MTD) (1,250 mg); DLT were observed in 5/24 patients with ≥8 weeks data (21%; 95% CI 7-42%); 2 cases of



pulmonary embolus (PE), 1 patient with grade 3 herpes simplex rash, 1 patient with grade 3 hypoxia, 1 patient with grade 3 hyponatremia/hypokalemia. No grade 3/4 neurological toxicity were reported.<sup>71</sup>

De Azambuja et al (2011) reported a DLT was observed in the cohort receiving lapatinib 1500 mg/d and temozolomide 200 mg/m<sup>2</sup> days 1-5, with an extension to 6 patients in this cohort. The most common toxicities reported in the study were fatigue, diarrhoea, thrombocytopenia, and liver enzymes alterations.<sup>70</sup>

### **Lapatinib versus Trastuzumab**

A retrospective study was identified which investigated whether lapatinib-based treatment may improve survival in patients with brain metastases from HER2-positive breast cancer.<sup>78</sup>

#### **Study characteristics**

Bartsch et al (2012) compared patients receiving lapatinib and trastuzumab (either sequentially or concomitantly) plus/minus chemotherapy after completion of local therapy (n=15) with individuals who only received trastuzumab plus/minus chemotherapy (n=28) and a historical control group of HER2-positive patients without any further targeted therapy (n=37).<sup>78</sup>

#### **Outcomes**

##### **Survival**

Median overall survival in all patients was 10 months (95% CI 6.31-13.69) in the study by Bartsch et al (2012).<sup>78</sup> In patients who received trastuzumab with or without chemotherapy, median survival was 13 months (95% CI 8.85-17.15). Median survival was 9 months for patients treated with chemotherapy without anti-HER2 therapy and 3 months in patients without further systemic therapy after local treatment. After a median follow-up of 24 months, median overall survival was not reached in the lapatinib group.

On univariate model, trastuzumab after completion of local therapy compared with no anti-HER2 targeted treatment significantly improved survival ( $p < 0.001$ ).<sup>78</sup> The addition of lapatinib compared with trastuzumab-based treatment plus/minus chemotherapy significantly improved survival ( $p = 0.002$ ). In multivariate Cox proportional hazards model, HER2 targeted therapy remained a highly significant predictor for longer survival.<sup>78</sup>

In patients with anti-HER2 targeted therapy after local therapy, median survival was 18 months (95% CI 12.49-23.51). Additional treatment with lapatinib after completion of local therapy remained a significant predictor of longer overall survival (HR 0.279; 95% CI 0.1-0.76;  $p = 0.012$ ). See table 23.

**Table 24     Multivariate Cox proportional hazards model (Bartsch 2012<sup>78</sup>)**

Prognostic factor	Total population			Patients receiving HER2-targeted therapy after completion of local treatment		
	N=80			N=43		
	HR	95% CI	P value	HR	95% CI	P value
Hormone receptor-positive disease	1.036	0.6-1.78	NS	-	-	-
Visceral metastases	1.727	0.95-3.15	NS	2.177	0.72-6.62	NS
>2 metastatic sites outside CNS	-	-	-	1.369	0.56-3.43	NS
1-3 brain metastases	0.322	0.18-0.58	<0.001	0.152	0.06-0.41	<0.001
Diagnosis of brain metastases <12mths	1.293	0.79-2.46	NS	-	-	-
KPS >70	0.404	0.23-0.72	0.002	1.974	0.8-4.86	NS
HER-targeted therapy after completion of local treatment	0.293	0.16-0.54	<0.001	-	-	-
Lapatinib plus/minus trastuzumab plus/minus chemotherapy	-	-	-	0.279	0.1-0.76	0.012

Abbreviations: HR=hazard ratio, KPS= karnofsky performance status, mths=months, NS=not significant

## Subgroups

One retrospective study was identified which assessed the impact of systemic treatment sequenced after WBRT in immunohistologically defined biological subsets of breast cancer patients with brain metastases.<sup>79</sup>

## Quality

### Study characteristics

Niwinska et al (2010) reported on 399 patients from 4 biological subtypes: luminal A (n=81; 20%), luminal B (n=92; 23%), HER2 (n=120; 30%) and tripe-negative (n=106; 27%). Triple-negative and luminal A subsets were HER2-negative. HER2 and luminal B subsets were HER2-positive.<sup>79</sup>

## Outcomes

### Pattern of metastatic spread

Niwinska et al (2010) reported in patients with HER2-positive breast cancer, metastases in many organs (lung, liver, bone and soft tissues) were detected and brain metastases appeared after metastases to other organs.<sup>79</sup> In patients with luminal A subtype, the bones and lungs were the most common sites of metastasis, while in triple-negative patients, one-third of patients developed brain metastases as a first or only distant event.

## Survival

Median time of prospective observation measured from the detection of brain metastases was 2.9 years in the study by Niwinska et al (2010).<sup>79</sup> Median survival from brain metastases in the whole study was 8 months (luminal A: 10 months, luminal B: 9 months, HER2: 9 months, triple-negative: 4 months;  $p=0.0005$ ). For all patients the median survival from brain metastases in patients without and with systemic treatment after WBRT was 3 months and 10 months respectively ( $p<0.0001$ ). Survival from brain metastases depending on systemic treatment for each subtype is presented in table 24.

**Table 25 Median survival and 1-year survival from brain metastases in 4 biological subgroups depending on systemic treatment after WBRT (Niwinska 2010<sup>79</sup>)**

Biological subtype	No systemic treatment	Chemotherapy/hormonal therapy	Chemotherapy/hormonal therapy with targeted therapy	P value
Luminal A (HER2-negative ER/PgR-positive)				
Median survival, mo	3	12	-	0.003
95% CI	0.01-7.68	8.40-16.44	-	
1-yr survival	10%	51%	-	
Luminal B (HER2-positive ER/PgR-positive)				
Median survival, mo	2	9	15	<0.0001
95% CI	2.04-2.76	6.60-11.52	10.08-19.80	
1-yr survival	0%	33%	58%	
HER 2 (HER2-positive ER/PgR negative)				
Median survival, mo	4	6	13	<0.0001
95% CI	3.36-4.32	4.56-7.92	9.96-16.44	
1-yr survival	5%	33%	55%	
Triple-negative				
Median survival, mo	3	4	-	0.16
95% CI	1.44-4.08	1.32-7.32	-	
1-yr survival	14%	23%	-	

Abbreviations: CI=confidence interval, mo=months

Cox multivariate analysis reported the following factors influenced survival: KPS, number of brain metastases, biological subtype of breast cancer, locoregional disease recurrence, liver metastases, control of extracranial disease and systemic treatment after WBRT. See table 25.<sup>79</sup>

**Table 26 Factors influencing survival from brain metastases (Niwinska 2010<sup>79</sup>)**

Factor	HR	P value	95% CI
KPS ( $\geq 70$ vs. $< 70$ )	0.34	$< 0.001$	0.26-0.44
Biologic subtype (HER2 and luminal B vs. triple negative)	0.6	0.002	0.45-0.83
Biological subtype (luminal A vs. triple negative)	0.6	0.004	0.42-0.84
Locoregional failure (yes vs. no)	1.3	0.025	1.03-1.69
Liver metastases (yes vs. no)	1.3	0.022	1.04-1.72
Systemic disease (controlled vs. uncontrolled)	0.53	$< 0.001$	0.38-0.73
Systemic treatment after WBRT (yes vs. no)	0.35	$< 0.001$	0.26-0.48
No. of brain metastases (multiple vs. 1)	2.2	$< 0.001$	1.56-3.09
No. of brain metastases (1 vs. 2)	1.64	0.60	0.97-2.76
Localisation of brain metastases (infratentorial vs. supratentorial)	1.57	0.065	0.97-2.53

Abbreviations: CI=confidence interval, HR=hazard ratio, KPS= karnofsky performance status, no=number

## Summary

### Chemotherapy

- Eight studies were identified that investigated different chemotherapies for management of CNS metastases, and included trials of the agents: temozolomide alone or in combination, sagopilone, patupilone and methotrexate. All these were phase I or phase II single arm studies and included small patient populations in general. Objective response rates ranged from 4 – 40% and adverse events included fatigue and diarrhoea.

### HER2-directed therapies

- Six retrospective comparative studies of the use of trastuzumab in patients with brain metastases from HER2-positive breast cancer were identified. Increased survival and longer time to progression was reported in HER2-positive patients who were treated with trastuzumab or continued with trastuzumab, after diagnosis of CNS metastases compared to patients who did not receive trastuzumab.
- One single arm phase II study was identified which investigated the use of lapatinib in combination with capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer. Overall survival at 6 months was 90.9% (95% CI 77.6–96.5) and the median overall survival for the 44 patients who were assessable for efficacy outcomes was 17.0 months (13.7–24.9). Objective response rate of 65.9% was reported, all of which were partial responses. At the time of analysis, 36 (82%) patients had received radiotherapy to the brain and median time to radiotherapy was 8.3 months.
- Eight studies investigating the use of lapatinib, or lapatinib in combination with other agents, including capecitabine, for previously treated CNS metastases from HER2 positive metastatic breast cancer were identified. These included two prospective phase II trials and one randomised phase II trial. Objective response rates reported ranged from 2.6% to 6% in patients who received lapatinib alone

and from 20% to 38% in patients who received lapatinib in combination with capecitabine, while no objective responses were observed in patients receiving lapatinib and topotecan. Adverse events reported included diarrhoea, palmarplantar erythrodysesthesia (lapatinib + capecitabine), nausea and fatigue.

- One small study has suggested lapatinib, compared with trastuzumab, may improve overall survival in patients after completion of local therapy.

### Subgroups

- Results from one retrospective study indicated that systemic therapy following WBRT appears to improve survival in patients with luminal A, luminal B and HER2 breast cancer subtypes. Targeted therapy was found to have an additional positive impact on survival. In patients with triple negative breast cancer, the role of systemic therapy after WBRT appears to be less clear and therefore requires further investigation.

## 3.2.4 What is the effectiveness of combinations of the above treatments in the management of CNS metastases from breast cancer?

### Systematic reviews

No systematic reviews on the effectiveness of different combinations of treatments in the management of CNS metastases from breast cancer were identified.

Two systematic reviews<sup>34,80</sup> were identified which assessed the effectiveness of different combinations of treatments in the management of CNS metastases from various primary tumours.

**The systematic review by Linskey et al 2010** addressed different combinations of WBRT, SRS and surgery.<sup>34</sup> The associated clinical practice guideline recommendations included in the paper by Linskey et al, are outlined in appendix F for radiotherapy (note that the comparison SRS alone vs. WBRT alone by Linskey et al is included in section 3.2.2).

- **SRS vs. Surgery + WBRT.** One prospective RCT and two retrospective cohort studies were identified. The RCT found no significant difference in functional performance outcome, neurological death outcomes or median survival for patients with single brain metastases. However this study was closed prematurely with only 25% patient accrual for a study originally designed to detect a 15% difference in survival between the two groups. Of the three retrospective studies, two revealed no significant difference in median survival for patients with 1-3 brain metastases. One suggested a trend favouring single-dose SRS alone for patients with 1-3 tumours, while the other suggested a trend favouring resection + WBRT for patients with single metastatic tumours. The third study demonstrating a significant survival advantage was confounded by poor comparability among patient treatment arms.
- **SRS + WBRT vs. Surgery + WBRT.** No prospective studies were identified. Of the four retrospective cohort trials identified that evaluated this comparison, three

demonstrated no significant survival differences between the two strategies. Of these, two showed a trend favouring single-dose SRS + WBRT and one a trend favouring resection + WBRT. Only one of the studies demonstrated a significant survival advantage for resection + WBRT.

**The systematic review by Kim et al (2012)** compared surgical decompression ± radiation to radiation therapy alone among patients with metastatic spinal cord compression (MESCC).<sup>80</sup> The review included 33 studies addressing: surgery ± radiotherapy (19 studies), radiotherapy only (13 studies) and surgery ± radiotherapy and radiotherapy only (1 study).

Sixty-four per cent of patients who underwent surgical decompression, tumour excision, and stabilization had neurological improvement from non-ambulatory to ambulatory status compared with 29% of the radiation therapy group ( $p < 0.001$ ).<sup>80</sup> Paraplegic patients had a 4-fold greater recovery rate to functional ambulation with surgical intervention than with radiation therapy alone (42% vs. 10%;  $p < 0.001$ ). Surgery resulted in pain relief in 88% of the patients compared with 74% of those treated with radiotherapy ( $p \leq 0.001$ ). For surgery, the overall complication rate was 29% and the rate of mortality was 5% in the acute postoperative period. Complication rates resulting from radiotherapy alone were not available. The median survival of patients when considering all tumours was generally higher for the surgical group relative to radiotherapy (17 vs. 3 months).

The authors concluded that the review suggests that surgical excision of tumour and instrumented stabilization may improve clinical outcomes compared with radiation therapy alone, with regard to neurological function and pain.<sup>80</sup> However, most data are from observational studies, where variations in patient population and treatments cannot be controlled. This compromised the ability to compare the results of both treatments directly.

## **Prospective studies**

Two non-comparative phase II trials were identified which investigated the combination of radiotherapy and chemotherapy in the management of CNS metastases from breast cancer,<sup>81</sup> and breast cancer and lung cancer.<sup>82</sup>

### **Study characteristics**

Addeo et al (2008) conducted a phase II trial to determine the efficacy and safety of a new regimen based on a dose-intensified, protracted course of temozolomide (TMZ) after WBRT.<sup>81</sup> Patients received 30 Gy of WBRT administered with concomitant TMZ (at a dose of 75mg/m<sup>2</sup>/day) for 10 days followed by the administration of TMZ at a dose of 75mg/m<sup>2</sup> per days for 21 days every 4 weeks, for up to 12 cycles. Twenty-seven patients were included in the study, 12 were breast cancer patients and 15 were NSCLC patients.

Cassier et al (2008) undertook a study to assess the efficacy, tolerability and safety of concurrent cisplatin and vinorelbine chemotherapy and radiotherapy in patients with previously untreated brain metastases from breast cancer.<sup>82</sup> Twenty-five patients were treated with cisplatin (20mg/m<sup>2</sup>/day, days 1-5) and vinorelbine (6-mg/m<sup>2</sup> bolus on day 1 and 6mg/m<sup>2</sup>/day continuous infusion on days 1-5) chemotherapy combined with concurrent 30 Gy fractionated external beam radiotherapy.

## Outcomes

### Survival

Addeo et al reported median overall survival was 8.8 months (95% CI 6.8-8.9 months) and the 1-year survival rate was 18.5% (95% CI 8.5-22.8%).<sup>81</sup>

Cassier et al (2008) reported median overall survival was 6.5 months (range 0.5-62.1 months).<sup>82</sup> At 1-year, 28% of patients were alive. In an exploratory analysis, patients were stratified by RPA class. Patients classified as RPA class III had significantly poorer survival compared with RPA class I and II (median overall survival 4.2 months vs. 8.4 months respectively;  $p=0.0026$ ).

### Progression free survival (PFS)

In the study by Addeo et al (2008) the median TTP was 6 months (95% CI 5.1-6.8 months).<sup>81</sup>

Cassier et al (2008) reported median PFS in the brain was 5.2 months (range 0.5-53.3 months).<sup>82</sup> The brain was the first site of disease progression in 16 patients. For responding patients the median duration of response was 8.5 months. Systemic response (cerebral and extracerebral disease) had median PFS of 3.7 months (range 0.2-46.5 months). Four patients (16%) were progression free at 12 months.

### Response rate

Addeo et al (2008) reported response to treatment of brain metastases by primary tumour, see table 26.<sup>81</sup> The overall response rate was 58% (7 of 12 patients) in breast cancer patients and 40% (6 of 15 patients) in the NSCLC patients.

Response rates were also stratified according to RTOG RPA classification. In RPA class I, 9 (82%) objective responses and 2 (8%) stable disease were obtained, while in RPA class III, no objective responses were observed.<sup>81</sup>

**Table 27 Response to treatment of brain metastases (Addeo 2008<sup>81</sup>)**

Responses	Number of patients	%
<b>Complete</b>	<b>2</b>	<b>7.4</b>
Breast cancer	1	
NSCLC	1	
<b>Partial responses</b>	<b>11</b>	<b>40.7</b>
Breast cancer	6	
NSCLC	5	
<b>Objective responses (CR + PR)</b>	<b>13</b>	<b>48.1</b>
<b>Stable disease</b>	<b>6</b>	<b>22.2</b>
Breast cancer	3	
NSCLC	3	
<b>Progressive disease</b>	<b>8</b>	<b>29.7</b>
Breast cancer	2	
NSCLC	6	

Abbreviations: CR=complete response, NSCLC=non-small cell lung cancer, PR=partial response

Response rates were also reported in the study by Cassier et al (2008). An overall response rate of 76% for brain metastases was observed in the study, see table 27.<sup>82</sup>

**Table 28 Response to treatment of brain and systemic metastases (Cassier 2008<sup>82</sup>)**

Site/Response	n	%
<b>Brain</b>		
CR	3	12
PR	16	64
SD	2	8
PD	2	8
Could not be assessed	2	8
ORR(CR+PR), %	76	
<b>Systemic (brain + other sites)</b>		
CR	1	4
PR	10	40
SD	5	20
PD	9	36
ORR(CR+PR), %	44	

Abbreviations: CR=complete response, NSCLC=non-small cell lung cancer, ORR=objective response rate, PR=partial response

### Treatment compliance

In the study by Cassier et al (2008) eleven (44%) patients discontinued treatment early either because of disease progression in 7 (28%) patients or toxicity in 4 (16%) patients.<sup>82</sup>

### Adverse events

Addeo et al (2008) reported that TMZ was generally well tolerated with hematologic toxicities the most commonly observed adverse events.<sup>81</sup> The toxicities were generally between grade 1 or 2 in severity. The most common drug-related non-hematologic toxicities were nausea, vomiting and headache. Further adverse events are presented in table 28. The study found no liver, renal or cardiac toxicities. Treatment interruptions due to toxicity were not observed and no patients required dose reductions.

**Table 29 Adverse events reported in the study (Addeo 2008<sup>81</sup>)**

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	No. of patients (%)
<i>Hematologic</i>					
Neutropenia	7	3	1	-	9 (33)
Anaemia	9	3	1	-	10 (37)
Thrombocytopenia	5	3	-	-	7 (26)
<i>Gastrointestinal</i>					
Nausea	7	5	-	-	9 (33)
Vomiting	5	3	-	-	6 (22)
Constipation	3	-	-	-	2 (7)



Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	No. of patients (%)
Diarrhoea	2	-	-	-	2 (7)
<i>Infection</i>					
Infection without neutropenia	1	1	-	-	1 (4)
<i>Pain</i>					
Headache	5	3	-	-	5 (29)
Myalgia	1	1	-	-	2 (7)
Neuropathic pain	1	-	-	-	-
<i>Haemorrhage</i>					
Epistaxis	2	1	-	-	2 (7)
Petechiae/purpura	1	1	-	-	2 (7)

In the study by Cassier et al (2008) two patients experienced grade 3 toxicity that could be related to WBRT, and there were no grade 4 adverse events during concomitant chemoradiation.<sup>82</sup> Overall, the majority of toxicities from WBRT were mild. However, 23 of 25 patients received prophylaxis for intracranial hypertension with either steroids, mannitol, or both. Further adverse events are displayed in table 29. Grade 3-4 hematologic toxicities was the most common adverse event and were observed in 20 (80%) patients; 5 (20%) patients experienced a grade 3 non-hematologic toxicity.

**Table 30 Toxicities in the study (Cassier 2008<sup>82</sup>)**

Toxicity	Grade	N	%
<b>Main grade 3 toxicities</b>			
Hematologic toxicity >grade 2			
Neutrophils		20	80
Haemoglobin		8	32
Platelets		7	28
Grade 3 asthenia (no grade 4 reported)		6	24
Neurologic (WBRT)		1	4
Nausea/vomiting (WBRT)		1	4
<b>Other toxicities of WBRT</b>			
Cephalalgia	1	4	16
	2	7	28
Nausea	1	2	8
	2	1	4
Confusion	1	1	4
Dizziness	1	1	4
Erythema of the forehead	1	1	4
Photophobia	1	1	4
Mucositis	2	1	4
Ototoxicity	2	1	4
Shaking	2	1	4

## Neurologic function

The effects of treatment on neurologic function were reported by Addeo et al (2008) and are presented in table 30.<sup>81</sup> After 3 cycles of treatment, the percentage of patients in Level I (fully functional) and Level II (fully functional but not able to work) increased from 75% to 85%, whereas the number of patients with Level III status decreased from 25% to 16%. The study also observed a decrease in the requirement for medication to palliate neurologic symptoms, further confirming the clinical benefit of the schedule used in the subset of patients.

**Table 31 Neurologic function assessment performed on evaluable patients (Addeo 2008<sup>81</sup>)**

Time	Level I No. patients (%)	Level II No. patients (%)	Level III No. patients (%)
Baseline	>6 (25)	>12 (50)	>6 (25)
3 cycles	>10 (42.5)	>10 (42.5)	>4 (16)
6 cycles	>6 (32)	>9 (47)	>4 (21)

## Retrospective studies

Three retrospective studies were identified which compared various treatment modalities.<sup>83-85</sup>

### Study characteristics

Ogawa et al (2008) retrospectively analysed the results of treatment for 65 patients with brain metastases from breast cancer, and identified the factors that influence the prognosis of the patients.<sup>84</sup> Eleven (17%) were treated with surgical resection followed by radiotherapy and the remaining 54 patients (83%) were treated with radiotherapy alone. After brain tumour treatment with surgery and radiotherapy or radiotherapy alone, 11 patients received systemic chemotherapy (2 patients in surgery and radiotherapy group, 9 patients in radiotherapy alone group).

Elaimy et al (2011) reported survival outcomes of 275 patients with brain metastases from various primary tumours treated with WBRT, surgery, SRS and combinations of the three modalities.<sup>83</sup> Forty-two patients had breast cancer as primary tumour.

Rades et al (2012) compared surgery + WBRT to surgery + WBRT plus a boost to the site of the resected metastasis.<sup>85</sup> The study included 195 patients with single brain metastases from breast cancer (n=34), NSCLC and other tumours.

## Outcomes

### Survival

Ogawa et al (2008) observed median overall survival of 6.1 months and actuarial survival rates at 12 months and 24 months of 28% and 12% respectively.<sup>84</sup> Longer median survival was reported in the surgery plus radiotherapy group compared with radiotherapy alone (19.3 months vs. 4.8 months respectively).

Surgery plus radiotherapy was found to significantly improve overall survival compared with radiotherapy alone on univariate and multivariate analyses.<sup>84</sup> In univariate analysis one-year overall survival was 73% in the combined group compared with 19% in the radiotherapy alone group ( $p=0.001$ ). For multivariate analysis the relative risk was 5.671 (95% CI 2.094-15.851;  $p=0.001$ ). Administration of systemic chemotherapy after radiotherapy was also associated with longer survival. Univariate analysis reported one-year overall survival 82% in those who received chemotherapy vs. 17% for those who did not receive chemotherapy ( $p=0.015$ ). For multivariate analysis the relative risk was 3.290 (95% CI 1.329-8.148;  $p=0.020$ ).<sup>84</sup>

Eight patients survived for more than 2 years after the diagnosis of brain metastases (median 32.8 months).<sup>84</sup> Seven of eight patients (88%) had a KPS of 0-1 and all 8 patients were treated with surgical resection (4 patients) or systemic chemotherapy (4 patients) in addition to radiotherapy.

Elaimy et al (2011) reported the median survival time was 7.9 months. Median survival times for each treatment modality are presented in table 31.<sup>83</sup>

The study also reported median survival time by tumour type. Median survival for patients with breast cancer was 9.2 months.<sup>83</sup>

For univariate and multivariate survival analyses, patients treated with SRS alone were used as the reference group.<sup>83</sup> Univariate hazard ratio analysis of treatment groups indicated that the survival of the SRS alone treatment group was statistically superior ( $p<0.001$ ) to the survival of the WBRT alone treatment group (95% CI 1.37-2.53). The multivariate analysis also indicated that the survival of the SRS alone treatment group was statistically superior ( $p<0.001$ ) to the survival of the WBRT alone treatment group (95% CI 1.37-2.73) and also that the survival of the surgery + SRS treatment group was statistically superior ( $p=0.020$ ) to the survival of the SRS alone treatment group (95% CI 0.49-0.94).<sup>83</sup>

Multivariate hazard ratio also indicated that the survival of patients in the breast cancer group was statistically superior ( $p<0.001$ ) to the survival of patients in the NSCLC group (95% CI 0.78-0.96).<sup>83</sup>

**Table 32 Median survival times of different treatment modalities (Elaimy 2011<sup>83</sup>)**

Treatment modality	n	Median survival, months, 95% CI
WBRT	117	4.3 (3.30-5.38)
SRS	65	9.4 (6.41-12.45)
WBRT + SRS	48	12 (8.74-15.98)
Surgery + SRS	15	24 (1.73-45.55)
Surgery + WBRT	11	10 (8.17-12.15)
Surgery + WBRT + SRS	19	13 (9.70-16.54)

Abbreviations=SRS=stereotactic radiosurgery, WBRT=whole brain radiotherapy

Rades et al (2012) reported 1 year, 2 year and 3 year survival rates for each of the treatment groups. See table 32.<sup>85</sup> On univariate analysis, treatment regimen was not associated with improved overall survival ( $p=0.11$ ). Breast cancer had longer survival compared with NSCLC and other tumours, however this was borderline significant

( $p=0.06$ ). On multivariate analysis, primary tumour type was significantly associated with improved survival (RR 1.30, 95% CI 1.01-2.25,  $p=0.012$ ).<sup>85</sup>

**Table 33 Overall survival rates of treatment groups\* (Rades 2012<sup>85</sup>)**

Treatment group	n	1 year, %	2 year, %	3 year, %
Surgery + WBRT	105	52	25	19
Surgery + WBRT plus boost	90	60	40	26

Abbreviations= WBRT=whole brain radiotherapy. \* Included various primary tumours

### Cause of death

Ogawa et al (2008) assessed the cause of death by treatment modality: patients undergoing surgery plus radiotherapy, patients undergoing radiotherapy with systemic therapy and patients undergoing radiotherapy without systemic chemotherapy.<sup>84</sup> Patients treated with surgery plus radiotherapy or radiotherapy plus chemotherapy usually died of recurrent progressive brain metastases, while more than half of the patients treated with radiotherapy without chemotherapy usually died of extracranial disease, see table 33.

**Table 34 Causes of death by treatment modality (Ogawa 2008<sup>84</sup>)**

Treatment	No. of patients	No. of patients who died	Cause of death	
			Brain	Extracranial
Surgery plus radiotherapy	11	10	7 (70%)	3 (30%)
Radiotherapy with chemotherapy	9	8	6 (75%)	2 (25%)
Radiotherapy without chemotherapy	45	45	20 (44%)	25 (56%)
Total	65		33	30

### Local control

Rades et al (2012) reported 1 year, 2 year and 3 year local control rates for each of the treatment groups. See table 34.<sup>85</sup> On univariate and multivariate analysis, surgery + WBRT plus boost was significantly associated with improved local control (univariate analysis  $p=0.002$ ; multivariate analysis RR=1.79, 95% CI 1.18-2.77,  $p=0.006$ ).<sup>85</sup>

**Table 35 Local control rates of treatment groups (Rades 2012<sup>85</sup>)**

Treatment group	n	1 year, %	2 year, %	3 year, %
Surgery + WBRT	105	38	20	9
Surgery + WBRT plus boost	90	67	51	33

Abbreviations= WBRT=whole brain radiotherapy

### Brain metastases-progression/recurrence free survival

Ogawa et al reported that surgery plus radiotherapy significantly improved brain metastases-progression/recurrence free survival (BMPRFS) compared with radiotherapy

alone on univariate and multivariate analyses.<sup>84</sup> One-year BMPRFS was 64% in the surgery plus radiotherapy group compared with 11% in the radiotherapy alone group ( $p=0.0008$ ). In multivariate analysis, relative risk was 6.368 (95% CI 2.238-18.120;  $p=0.001$ ).

### Improvement and duration of neurological symptoms

Ogawa et al (2008) assessed improvements of neurological symptoms by treatment modality: patients undergoing surgery plus radiotherapy, patients undergoing radiotherapy with systemic therapy and patients undergoing radiotherapy without systemic chemotherapy.<sup>84</sup> Improvements were observed more often and for longer in patients who received surgery plus radiotherapy, see table 35.

**Table 36 Improvements in neurological symptoms by treatment modality (Ogawa 2008<sup>84</sup>)**

Treatment	No. of patients with improvement in neurological symptoms	Median duration of improvement
Surgery plus radiotherapy	11 (100%)	13.2 months
Radiotherapy with chemotherapy	8 (89%)	12 months
Radiotherapy without chemotherapy	35 (78%)	3.7 months

### Adverse events

Rades et al (2012) reported Grade  $\geq 2$  acute toxicity such as headache, nausea, and fatigue occurred in 12% of patients who received Surgery + WBRT and 13% of patients who received Surgery + WBRT plus boost ( $p=0.95$ ).<sup>85</sup> Grade  $\geq 2$  late toxicity such as neurocognitive deficits and vision or hearing problems occurred in 15% and 17% of patients, respectively ( $p=0.93$ ).

## Summary

- Two non-comparative phase II trials investigated the combination of radiotherapy and chemotherapy. Both combinations of radiotherapy and chemotherapy appeared to be active and well tolerated. In the two studies, 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 two studies, median overall survival was 6.5 months and 8.8 months and 1 year survival was 18.5% and 28%; median PFS was 5.2 months and 6 months.
- One retrospective study reported significantly longer survival for surgery + radiotherapy vs. radiotherapy alone ( $p=0.001$ ) as well as longer survival in patients who receive systemic chemotherapy after radiotherapy ( $p=0.015$ ).
- One retrospective study that included 15% patients with breast cancer primary tumour reported that surgery + 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 ( $p<0.001$ ).

- 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.

### **3.2.5 Are there specific requirements for the management of the sub-group of patients diagnosed with asymptomatic CNS metastases?**

#### **Systematic reviews**

No systematic reviews were identified which addressed specific requirements for the management of breast cancer patients diagnosed with asymptomatic CNS metastases.

#### **Prospective studies**

One study was identified which assessed disease-free survival (DFS), survival from the detection of brain metastases, overall survival, and cause of death in patients with occult brain metastases compared with patients with symptomatic brain metastases.<sup>86</sup>

#### **Study characteristics**

In the study by Niwinska et al (2010) 80 HER2-positive breast cancer patients with distant metastases and/or locoregional failure underwent MRI screening of the brain during the asymptomatic period.<sup>86</sup> Eligible patients either had recently been detected with dissemination of the disease (first brain MRI scan performed at the time of recurrence) or had dissemination develop earlier but without brain metastases on the first MRI scan (screening group). A comparison group of 52 patients with symptomatic brain metastases was matched to the screening group to compare survival.<sup>86</sup>

#### **Outcomes**

##### **Incidence of occult brain metastases**

In the study by Niwinska et al (2010) occult brain metastases were detected in 36% of the screening group during the 20 month follow-up (34% had single brain metastasis and 66% had multiple metastases).<sup>86</sup> The median time between recurrence (distant and/or locoregional) and the diagnosis of occult brain metastases was 9 months (range 0-76 months).

##### **Risk factors of occult brain metastases**

Niwinska et al (2010) reported univariate and multivariate analysis found only visceral metastases (lung and/or liver) to be significant predictors of brain metastases development ( $p=0.0018$  and  $p=0.052$  respectively).<sup>86</sup> Age at initial diagnosis, histopathologic type and grade, estrogen/progesterone receptor status, DFS, and locoregional failure did not reach the level of significance.

##### **Response to treatment**

In the study by Niwinska et al (2010) 26 patients (90%) with occult brain metastases were given WBRT (three patients did not receive WBRT due to poor performance status due to

visceral metastases).<sup>86</sup> Radiological response rate was evaluated in 24 patients as 2 patients died. MRI 3 months after the completion of WBRT found that 29% were in complete remission, 63% were in partial remission, and no change in the brain in 8%. All patients were free from neurologic symptoms. New occult lesions appeared in 11 of 19 patients (58%) 6 months after WBRT. Nine months after WBRT, 90% (17 of 19 patients) had recurrence in the brain, though were still free from clinical symptoms. Among 5 survivors, complete remission has been maintained in 2 patients for 26 and 28 months after WBRT.

## Survival

After a mean of 9 months, 24 patients with occult brain metastases had died, while 5 patients were alive with 8, 12, 23, 26 and 28 months of follow-up, and no clinical symptoms of brain involvement and dementia have occurred through the completion of the study by Niwinska et al (2010).<sup>86</sup> In 90% of patients occult brain metastases occurred during the first 12 months after recurrence of the disease.

When survival of patients with occult vs. symptomatic brain metastases were compared, there was no significant difference in DFS, overall survival, survival from recurrence of the disease, interval between recurrence and brain metastases and survival with brain metastases.<sup>86</sup> The only difference was the cause of death. In the group of patients with occult brain metastases, immediate WBRT decreased the risk of cerebral death from 48% to 16% ( $p=0.009$ ), see table 36.

**Table 37 Survival and cause of death in patients with occult and symptomatic brain metastases (Niwinska 2010<sup>86</sup>)**

Endpoint	Occult brain metastases	Symptomatic brain metastases	P value
<b>Survival [median (range)], months</b>			
Overall Survival	53.1 (10-162)	51.1 (4-172)	0.944
Disease Free Survival	17 (0-117)	19.9 (0-115)	0.588
Survival from recurrence of disease	21 (4-79)	25.6 (4-105)	0.282
Interval between recurrence and BM	9.3 (0.76)	15 (0-91)	0.11
Survival with brain metastases	9 (1.7-28)	8.78 (0.5-32)	0.80
<b>Cause of death (%)</b>			
Brain progression	16%	48%	0.009
Visceral progression	84%	52%	

Abbreviations: BM= brain metastases

## Summary

- One prospective study was identified that investigated asymptomatic compared with symptomatic brain metastases in HER2-positive breast cancer patients. The study concluded that in HER2-positive breast cancer patients with visceral and brain metastases, WBRT performed during the asymptomatic period had no influence on survival but decreased the risk of cerebral death. The study showed visceral (lung/liver) metastases to be a significant predictor (univariate analysis) of brain metastasis development and cause of death in majority of patients.

## 3.3 Other issues

### 3.3.1 The incidence/prevalence of CNS metastases in breast cancer patients, specifically those with HER2-positive and triple negative breast cancer.

Breast cancers are characterised by clinical, pathological and molecular characteristics that determine a number of recognised biological subtypes. Major subtypes identified by gene expression profiles, classify breast cancers into basal, luminal (hormone receptor positive), and HER2/neu-positive/oestrogen receptor (ER)-negative subtypes which have differing prognostic profiles.<sup>87,88</sup>

The HER2 oncogene encodes a trans-membrane tyrosine kinase receptor involved in proliferation, survival and angiogenesis. HER2 is amplified in approximately 25% of primary breast cancers and overexpression of the HER2 protein is an important risk factor for the development of brain metastases.<sup>88,89</sup>

Ten to 15% of breast cancers are of the triple receptor negative subtype (TNBC). These tumours do not express ERs and progesterone receptors (PRs) and do not exhibit overexpression and/or gene amplification of HER2.<sup>87</sup>

Increased risk of developing CNS metastases has been reported for patients with HER2-positive or triple negative breast cancers. Here we summarise 34+ studies that presented incidence data on brain metastases in patients with HER2-positive and/or triple negative breast cancer.HER2-positive breast cancer.

#### **HER2-positive breast cancer**

Twenty-eight papers reported data for CNS or brain metastases in patients with HER2-positive breast cancer. These papers are summarised in table 37. Most were conducted as retrospective single cohort studies. Also included were one meta-analysis<sup>11</sup>, one phase II RCT<sup>90</sup> one large retrospective study pooling data from International Breast Study Group (IBCSG) trials I through IX<sup>91</sup>, one prospective cohort study<sup>92</sup>, one retrospective survival analysis<sup>93</sup>, one retrospective cohort study with concurrent controls<sup>94,95</sup>, and one case series study.<sup>96</sup>

The incidence of brain metastases in all HER2-positive patients with early breast cancer (or stages I-III) was reported as 6% to 9% (see table 37 for details). For all HER2-positive patients with metastatic breast cancer (or stages IIIb-IV) the incidence was reported as 20% to 46% (see table 37 for details). The range in incidence may be due to treatment (e.g. trastuzumab vs. no trastuzumab), variation in median follow up times, or to the way in which incidence was reported (e.g. percentage vs. n vs. cumulative yearly incidence).

For all patients with CNS or brain metastases, 25% to 60% were HER2-positive (see table 35 for details).

Viani et al (2007) presented a meta-analysis of five RCTs comparing adjuvant trastuzumab treatment for HER2-positive early breast cancer to no trastuzumab.<sup>11</sup> Pooled data from three studies reporting CNS or brain metastases incidence (9117 patients;



HERA, N9831, NSABP-31) showed the likelihood of BM was 1.82-fold higher (95% CI 1.16–2.85) in trastuzumab-treated patients (Test for heterogeneity:  $\text{Chi}^2 = 1.39$ ,  $\text{df} = 2$  ( $p=0.50$ ),  $I^2 = 0\%$ ; overall effect  $Z=2.61$ ,  $p=0.009$ ).

**Table 38 Summary of studies reporting CNS or brain metastases for HER2-positive breast cancer patients**

Study	Study type	Patient population (Median follow up)	Incidence of CNS or brain metastases in all HER2-positive patients <sup>1</sup>	Proportion of all CNS or brain metastases that were HER2-positive <sup>2</sup>
<b>Early BC or Stage I-III</b>				
Gabos 2006 <sup>97</sup>	RSC	636 newly diagnosed BC patients (3.9 years/~47 months)	9%	
Heitz 2009 <sup>92</sup>	Prospective cohort	2441 patients with primary invasive BC; of which 245 patients were HER2 positive (47 months)	7.8%	23.8%
Neciosup 2004 <sup>98</sup>	retrospective review	1232 stage I-III BC patients; of which 401 patients were HER2 positive (7.6 years)	7.7%	25.8%
Pestalozzi 2006 <sup>91</sup>	From IBCS clinical trials	9524 women with early BC (n=608 HER2 positive patients, n=3263 HER2 negative patients) (13 years)	6.4% in HER2 positive vs. 3.3% in HER2 negative Cumulative incidence in HER2 positive: 2-yr 1.3%; 5-year 4.2%; 10-year 6.8%; 15-year 6.8%	
Viani Afonso 2007 <sup>11</sup>	Meta-analysis	Data pooled from 3 RCTs comparing adjuvant trastuzumab treatment (n=3365) to no trastuzumab (n=3373) for HER2-positive early BC. Follow up: mean 2 years; median 2.4 years and median 1.5 years respectively for the 3 RCTs.	T: 1.6% No-T: 0.89%	
<b>Metastatic, secondary, advanced, Stage IIIB/IV or stage not defined BC</b>				
Arslan 2011 <sup>99</sup>	RSC	259 patients with BC BM; 178 with HER2 status available (42 months)		59.9%
Bendell 2003 <sup>100</sup>	Retrospective cohort	122 patients with BC (23 months follow up; median 16 months after diagnosis of metastatic breast cancer)	34%	

Berghoff 2012 <sup>101</sup>	RSC	213 patients treated for symptomatic BM from BC (not reported)		58.2%
Burstein 2005 <sup>90</sup>	RCT & Phase II trial	464 (RCT), 54 (Phase II) HER2-overexpressing metastatic BC receiving trastuzumab-based therapy (4.6-7 months)	Phase I: Prevalence in RCT, Traz + chemo=9.8%; Chemo only=7%; Phase II trial: Traz + chemo = 9.3% (combined early + metastatic)	
Clayton 2004 <sup>102</sup>	RSC	93 patients commencing trastuzumab for metastatic BC (HER2 immunohistochemistry: 6 patients 2+ and 87 patients 3+) (10.8 months)	25%	
Dawood 2008 <sup>64</sup>	RSC	598 with invasive breast cancer, CNS metastases and known HER2 status (20 months)		47%
Dawood Uneo 2010 <sup>103</sup>	RSC	203 newly diagnosed stage III/IV Inflammatory BC with known HER2 status (20 months)		37.5%
Dawood Gonzalez 2010 <sup>52</sup>	RSC	223 patients with BC BM (not reported)		45.50%
Dawson 2006 <sup>104</sup>	RSC	28 metastatic HER2-positive over-expressing BC patients treated with trastuzumab and chemotherapy (24 patients confirmed HER2 positive) (31 months)	46%	

Duchnowska 2009 <sup>105</sup>	RSC	264 patients with HER-2-positive metastatic BC (3.1 years/~37 months)	39% symptomatic brain mets and 6% presented with BM at the time of dissemination occurrence. Cumulative risk of brain mets: 1-yr 17%, 3-yr 42%,; 5-yr 55%; 3-yr risk with trastuzumab 20%, without trastuzumab 29%	
Ferreria 2008 <sup>106</sup>		950 BC patients, 38 of which developed CNS metastases (not reported – abstract)		68% (of the 38 patients with CNS metastases)
Gori 2007 <sup>107</sup>	RSC	122 HER2-positive metastatic BC patients treated with chemotherapy and trastuzumab (28 months)	35.2%	
Jang 2011 <sup>108</sup>	Retrospective cohort	7872 patients with BC BM; of which 137 developed brain metastases and had known subtype (99 months)		50.4%
Montagna 2009 <sup>109</sup>	RSC	78 patients with HER2 over-expressing metastatic BC treated with trastuzumab (35.3 months)	46% ( 5 before starting trastuzumab and 31 during trastuzumab treatment)	
Nam 2008 <sup>93</sup>	Retrospective survival analysis	805 patients with metastatic BC (26.2-31.1 months)	25.9%	44%
Niwinska 2010 <sup>110</sup>	Case series	205 consecutive patients with BC BM (not reported)		53%
Ono 2009 <sup>111</sup>	RSC	204 metastatic HER2-overexpressing BC and treated with trastuzumab (53.6 months)	36.3%	
Puente Vazquez 2006 <sup>112</sup>	RSC	86 HER2-positive BC patients treated with trastuzumab (not reported)	19.5%	

Saip 2008 <sup>113</sup>	RSC	86 BC patients with known HER2 status, (73 presented as early BC, 13 as advanced BC) who later developed BM (not reported)		46%
Sanna 2007 <sup>95</sup>	Case control	72 patients with BC BM, 136 controls BC no BM. (55-60 months)		44%
Shmueli 2004 <sup>96</sup>	Case series	41 metastatic HER2-overexpressing BC patients, of which 32 showed an initial response to trastuzumab (43 weeks from start of trastuzumab treatment)	31% (of the 32 patients that responded initially to trastuzumab)	
Souglakos 2006 <sup>114</sup>	Retrospective cohort	4 groups with BM (early and metastatic) two treated with taxane (T), 2 not taxane (n-T): early breast cancer (n = 253), advanced stage breast cancer (n = 239), other solid tumours (n = 336) (not reported)		52.9% (data includes both early and advanced/metastatic breast cancer)
Stemmler 2006 <sup>115</sup>	RSC	136 patients with HER2-positive metastatic BC (not reported)	30.9%	

Abbreviations: BC = breast cancer, BM = brain metastases, cum = cumulative, CI = confidence interval, RSC = retrospective single cohort study, RCT = randomised controlled trial, T=treated, vs. = versus

1. Incidence of patients with HER2-positive BC that developed brain or CNS metastases
2. Proportion of patients with brain or CNS metastases that were found to be HER2-positive

## Triple negative breast cancer

Twelve papers reported data on CNS or brain metastases in patients with Triple Negative Breast cancer.<sup>52,87,92,93,98,101,108,110,116-119</sup> Most papers were retrospective single cohort studies that included BC patients who were diagnosed with brain metastases.

The incidence of brain metastases patients with early breast cancer classified as triple negative was reported as 6% to 7.5% (see table 38 for details). One paper reported the incidence of brain metastases in patients with metastatic breast cancer – the incidence was 46%.<sup>119</sup>

For all patients with breast cancer brain metastases, 17.5% to 37% of tumours were of the triple negative subtype (see table 38 for details).

One paper reported the hazard ratio for developing CNS metastases in patients with triple negative breast cancer (HR 4.0; 95% CI 1.9-8.4).<sup>93</sup>

**Table 39 Summary of studies reporting CNS or brain metastases for triple negative breast cancer patients**

Study	Study type (RSC = retrospective single cohort)	Patient population (median follow up)	Incidence of CNS or brain metastases in all TN patients	Proportion of all CNS or brain metastases that were TN
<b>Early BC</b>				
Dawood 2009 <sup>87</sup>	RSC	679 patients with non-metastatic TNBC (26.9 months)	6.2% Cumulative incidence 2 yrs 5.6% (95% CI 3.8% - 7.9%) 5 yr 9.6% (95% CI 6.8% to 13%)	
Heitz 2009 <sup>92</sup>	Prospective cohort	2441 patients with primary invasive BC; of which 284 patients were triple negative (47 months)	6.7%	23.8%
Neciosup 2004 <sup>98</sup>	Retrospective review	1232 stage I-III BC patients; of which 254 patients were triple negative (7.6 years)	7.5%	30.6%
<b>Metastatic BC</b>				
Anders 2001 <sup>116</sup>	RSC	119 patients with BC BM; 98 patients with confirmed subtype (6.2 years)		31%
Bai 2010 <sup>117</sup>	RSC	89 patients with BC BM; of which		17.5%

Study	Study type (RSC = retrospective single cohort)	Patient population (median follow up)	Incidence of CNS or brain metastases in all TN patients	Proportion of all CNS or brain metastases that were TN
		80 had known subtype (41 months)		
Berghoff 2012 <sup>101</sup>	RSC	213 patients treated for symptomatic BM from BC (not reported)		20.2%
Dawood Gonzalez 2010 <sup>52</sup>	RSC	223 patients with BC BM (not reported)		24.3%
Hines 2008 <sup>118</sup>	RSC	118 patients with BC BM; of which 91 had known receptor status (42 months)		22%
Jang 2011 <sup>108</sup>	RSC	7827 patients who developed BM; of which 137 developed brain metastases and had known subtype (99 months)		32.1%
Lin 2008 <sup>119</sup>	RSC	116 patients treated for metastatic TNBC (34.1 months)	46%	
Nam 2008 <sup>93</sup>	Retrospective survival analysis	805 patients with metastatic BC; of which 126 patients had brain metastases (26.1 months)		37.3%
Niwinska 2010 <sup>110</sup>	Case series	205 consecutive patients with BC BM (not reported)		28%

Abbreviations: BC = breast cancer, BM = brain metastases, T=treated, RSC = retrospective single cohort study, RCT = randomised controlled trial, vs. = versus, cum = cumulative, CI = confidence interval

## Summary

The incidence of brain metastases in all HER2-positive patients with early breast cancer was reported as 6% to 9%. For all HER2-positive patients with metastatic breast cancer the incidence was reported as 20% to 46%. For all patients with breast cancer CNS or brain metastases, 25% to 60% of tumours were HER2-positive.

The incidence of brain metastases in early stage triple negative brain metastases patients was reported as 6% to 7.5%. One paper reported that the incidence for patients with metastatic triple negative brain metastases was 46%. For patients with breast cancer brain metastases, 17.5% to 37% of tumours were of the triple negative subtype.

### **3.3.2 The course, nature and extent of neurocognitive and psychological impairments in CNS metastases in secondary breast cancer, and how these impairments are assessed.**

Two papers discussed neurocognitive function in patients with breast cancer brain metastases.<sup>120,121</sup>

Meyers (2004) presented the results of a randomised phase III trial assessing neurocognitive function (NCF) and progression in 401 patients with brain metastases (75 with breast cancer brain metastases) randomised to receive 30 Gy WBRT given in 10 daily fractions, with or without motexafin gadolinium 5 mg/kg/d, 2 to 5 hours before each fraction of WBRT.<sup>121</sup> NCF scores of memory, fine motor speed, executive function, and global neurocognitive impairment at baseline were correlated with brain tumour volume and survival. Ninety per cent of patients had impairment of one or more neurocognitive tests at baseline. There was no statistically significant difference between treatment arms in time to neurocognitive progression. NCF at baseline was highly correlated with the volume of the indicator lesions at baseline and was predictive of overall survival duration in patients with brain metastases.<sup>121</sup>

Li et al (2008) examined the relationship between NCF and quality of life (QoL) in 208 patients with brain metastases after WBRT (20% breast cancer patients).<sup>120</sup> The study utilised data from the WBRT arm of a Phase III trial (PCIP120-9801). QoL was assessed with two tools: ADL (activities of daily living) and FACT-Br (Functional Assessment of Cancer Therapy–Brain-specific). At baseline and at four months, all NCF tests were significantly correlated with ADL and FACT-Br indicating that NCF and QoL are correlated. The authors concluded that because NCF deterioration precedes QoL decline, delaying NCF deterioration is a worthwhile treatment goal in patients with breast cancer brain metastases.<sup>120</sup>

### **Summary**

The majority of patients with brain metastases have impaired neurocognitive function. Neurocognitive function decline impacts the patient's ability to complete activities of daily living, recognise safe and unsafe behaviour, and comply with medication regimens.<sup>120</sup> One study indicated that neurocognitive function decline precedes QOL decline.<sup>120</sup> Neurocognitive function was highly correlated to tumour volume and predictive of overall survival in one study.<sup>121</sup>



### **3.3.3 The impacts of neurocognitive and psychological impairments on everyday functioning and quality of life of women with CNS metastases from breast cancer.**

One literature review was identified that discussed the use of antiepileptic drugs in patients with cancer.<sup>122</sup> The focus of this review was the pharmacological treatment of epilepsy. The review noted that primary and metastatic brain tumours are frequently complicated by symptomatic epilepsy and that brain tumour patients with seizures account for the 4% of epilepsy patients. The incidence of epilepsy in patients with brain metastases is around 25 to 40%. The author suggests that future clinical trials in patients with cancer and epilepsy should focus on combinations of chemotherapeutic interventions with antiepileptic drugs.

An RCT by Chang et al (2009) assessed whether the benefit of adding WBRT to SRS for the control of brain tumours outweighs the potential neurocognitive effects. Fifty-eight patients with one to three newly diagnosed brain metastases were enrolled and randomly assigned to SRS alone (n=30) or SRS plus WBRT (n=28).

The trial was stopped by the data monitoring committee according to early stopping rules on the basis that there was a high probability (96%) that patients randomly assigned to receive SRS plus WBRT were significantly more likely to show a decline in learning and memory function (mean posterior probability of decline 52%) at 4 months than patients assigned to receive SRS alone (mean posterior probability of decline 24%). At 4 months there were four deaths (13%) in the group that received SRS alone, and eight deaths (29%) in the group that received SRS plus WBRT. 73% of patients in the SRS plus WBRT group were free from CNS recurrence at 1 year, compared with 27% of patients who received SRS alone ( $p=0.0003$ ). In the SRS plus WBRT group, one case of grade 3 toxicity (seizures, motor neuropathy, depressed level of consciousness) was attributed to radiation treatment. In the group that received SRS, one case of grade 3 toxicity (aphasia) was attributed to radiation treatment. Two cases of grade 4 toxicity in the group that received SRS alone were diagnosed as radiation necrosis.

Chang et al concluded that patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone. Initial treatment with a combination of SRS and close clinical monitoring is recommended as the preferred treatment strategy to better preserve learning and memory in patients with newly diagnosed brain metastases.

The Cancer Council has published *Brain tumours and driving: a guide for clinicians*. The guide includes a fit to drive algorithm.

Ausroads published guidelines in March 2012 on assessing fitness to drive for commercial and private vehicle drivers. Brain tumours and other space-occupying lesions (e.g. abscesses, chronic subdural haematomas, cysticercosis) may cause diverse effects depending on their location and type. The guideline includes recommendations presented in table 39.

**Table 40 Medical standards for licensing-neurological conditions**

Condition	Private standards	Commercial standards
Space-occupying lesions (including brain tumours)	<p>A person is not fit to hold an unconditional licence:</p> <ul style="list-style-type: none"> <li>• if the person has had a space-occupying lesion that results in significant impairment of any of the following: visuospatial perception, insight, judgement, attention, reaction time, memory, sensation, muscle power, coordination and vision (including visual fields).</li> </ul> <p>A conditional licence may be considered by the driver licensing authority subject to periodic review, taking into account:</p> <ul style="list-style-type: none"> <li>• the nature of the driving task</li> <li>• information provided by the treating doctor about the likely impact of the neurological impairment on driving ability</li> <li>• the results of a practical driver assessment if required.</li> </ul> <p>If seizures occur, the standards for seizures and epilepsy apply</p> <p>If surgically treated, the advice for intracranial surgery applies</p>	<p>A person is not fit to hold an unconditional licence:</p> <ul style="list-style-type: none"> <li>• if the person has had a space-occupying lesion.</li> </ul> <p>A conditional licence may be considered by the driver licensing authority subject to annual review, taking into account:</p> <ul style="list-style-type: none"> <li>• the nature of the driving task</li> <li>• information provided by an appropriate specialist about the level of impairment of any of the following: visuospatial perception, insight, judgement, attention, reaction time, memory, sensation, muscle power, coordination and vision (including visual fields) and the likely impact on driving ability</li> <li>• the results of a practical driver assessment if required.</li> </ul> <p>If seizures occur, the standards for seizures and epilepsy apply.</p> <p>If surgically treated, the advice for intracranial surgery applies.</p>
Intracranial surgery (advisory only)	<p>A person should not drive for six months following supratentorial surgery or retraction of the cerebral hemispheres.</p> <p>If there are seizures or long-term neurological deficits, refer to Seizures and epilepsy</p>	<p>A person should not drive for 12 months following supratentorial surgery or retraction of the cerebral hemispheres.</p> <p>If there are seizures or long-term neurological deficits, refer to section Seizures and epilepsy</p>
<p>All cases (default standard)</p> <p>Applies to all people who have experienced a seizure.</p> <p>Exceptions may be considered only if the situation matches one of those listed below</p>	<p>A person is not fit to hold an unconditional licence:</p> <ul style="list-style-type: none"> <li>• if the person has experienced a seizure.</li> </ul> <p>A conditional licence may be considered by the driver licensing authority subject to at least annual review, taking into account information provided by the treating doctor as to whether the following criteria are met:</p> <ul style="list-style-type: none"> <li>• there have been no seizures for at least 12 months; and</li> <li>• the person follows medical advice, including adherence to medication if prescribed.</li> </ul> <p>Shorter seizure-free periods may be considered by the driver licensing authority</p>	<p>A person is not fit to hold an unconditional licence:</p> <ul style="list-style-type: none"> <li>• if the person has experienced a seizure.</li> </ul> <p>A conditional licence may be considered by the driver licensing authority subject to at least annual review, taking into account information provided by a specialist in epilepsy as to whether the following criteria are met:</p> <ul style="list-style-type: none"> <li>• there have been no seizures for at least 10 years; and</li> <li>• the EEG shows no epileptiform activity; and</li> <li>• the person follows medical advice, including adherence to medication if prescribed.</li> </ul> <p>Shorter seizure-free periods may be considered by the driver licensing authority</p>

## **Summary**

Up to 40% of patients with BM may experience epilepsy and combination of chemotherapy with antiepileptic treatment is an area of ongoing research.

### **3.3.4 The identification of effective strategies for providing supportive and palliative care to women with CNS metastases from breast cancer**

No papers were identified on this issue.

### **3.3.5 Multidisciplinary care including involvement of allied health.**

One paper was identified that assessed the impact of a multidisciplinary approach for treatment of patients with metastatic epidural spinal cord compression – from primary tumour sites including the lung, breast, and kidney cancers.<sup>27</sup> For this retrospective study, 89 patients were evaluated by a multidisciplinary team including a medical oncologist, radiation oncologist, and neurosurgeon. This paper focussed mostly on details of combining surgery plus radiotherapy, but noted that the discussion of each single case within a multidisciplinary team was of pivotal importance in implementing the most appropriate therapeutic approach.

## **Summary**

Multidisciplinary care is of pivotal importance to drive the most appropriate therapeutic approach and so avoid the aggressive surgery in the treatment of CNS cancers.

### **3.3.6 Measurements of quality of life**

One questionnaire-based study explored the presence of symptom clusters in patients with brain metastases treated with WBRT.<sup>123</sup> One hundred and twenty nine patients with brain metastases were asked to rate their symptoms and QoL using the Spitzer Quality of Life Index (SQLI) and a study-designed 17-item symptom questionnaire. The SQLI assesses QoL based on five domains: activity, daily living, health, support, and outlook. Patients also rated the additional 17 brain metastases-specific symptom items as none, mild, moderate, or severe: headache, weakness, memory loss, confusion, dizziness, trouble concentrating, decreased alertness, imbalance problems, seizures, speech difficulty, vision problems, problems with smell, hearing or tingling, numbness, fatigue, personality change, nausea, and vomiting. Symptom clusters exist in patients with brain metastases. Although the clusters varied over time, they did not weaken or disintegrate following WBRT, suggesting that WBRT may not significantly improve the QoL and symptom distress.<sup>123</sup>

## **Summary**

A 17-item symptom questionnaire has been developed and used together with the Spitzer Quality of Life Index in one study to measure QoL in patients with breast cancer

brain metastases. This study indicated WBRT does not improve QOL measures or symptom distress.<sup>123</sup>

### 3.3.7 Meningeal metastases in women with secondary breast cancer.

Eight papers were identified that reported on breast cancer meningeal metastases (MC).<sup>124-131</sup> These papers consisted of one randomised study<sup>124</sup>, one open-label single-arm multicentre trial<sup>128</sup>, one multicentre cohort study<sup>129</sup>, two retrospective single cohort studies<sup>125,127</sup> one retrospective review<sup>126</sup>, one retrospective cohort study with historical controls<sup>130</sup>, and one case series.<sup>131</sup> See table 40.

**Table 41 Summary of studies considering meningeal metastases in breast cancer patients**

Study	Study type	Patient population	Overview	Conclusions
Boogerdt 2004 <sup>124</sup>	Randomised study	BC patients with leptomeningeal metastasis	Assesses the benefit of intraventricular (IT) chemotherapy compared with non-intrathecal (non-IT) treatment	IT vs. non-IT: OS 18.3 weeks vs. 30.3 weeks (p=0.32) Median TTP: 23 weeks vs. 24 weeks Neurological improvement/stabilisation 59% vs. 67% Neurological complications of treatment 47% vs. 6%
de Azevedo 2011 <sup>126</sup>	Retrospective review	60 BC patients with meningeal carcinomatosis	Describes the treatment and identifies prognostic factors for survival for BC MC patients	OS 3.3 months from diagnosis. High histological grade (HR 9.56, 95%CI 1.88–48.66, p=0.007), poor performance status (HR 8.44, 95% CI 3.07–23.25, p<0.00) associated with poor survival.
Clatot 2009 <sup>125</sup>	RSC	24 successive patients treated for BC leptomeningeal meningitis with high-dose intrathecal methotrexate (MTX)	Analysis of CSF for cytologic response (CSF cytology without neoplastic cells) after MTX	Mean survival 3–4 months with treatment. Cytologic response is predictive of treatment response (p=0.005). Patients should have four cycles of ITC.

Study	Study type	Patient population	Overview	Conclusions
Gauthier 2010 <sup>127</sup>	RSC	91 patients with BC MC treated with MTX	Survival outcomes of patients treated with MTX	1-yr survival rate 25%. In multivariate analysis, adverse prognostic factors at diagnosis are poor performance status, >3 chemotherapy regimens before MC diagnosis, negative hormone receptor status, high Cyfra 21-1 level. Clinical progression after 1 cycle and biological* response after 2 cycles both associated with poor OS.
Jaeckle 2001 <sup>129</sup>	multicentre cohort study	56 patients with BC	To determine the safety and efficacy of DepoCyt for the intrathecal treatment of neoplastic meningitis	DepoCyt demonstrated activity in BC MC comparable to results reported with conventional intrathecal agents but with ¼ as many IT injections. RR 28% (CI 95%: 14–41%); the intent-to-treat RR was 21% (CI 95%: 12–34%)
Jaeckle 2002 <sup>128</sup>	open-label single-arm multicentre trial	110 patients with solid tumour neoplastic meningitis	To define safety, response rate, time to neurologic progression, and survival in patients with solid tumour neoplastic meningitis treated with DepoCyt	Median time to neurologic progression = 55 days; OS = 95 days. DepoCyt injected once every 2 weeks produced a response-rate comparable methotrexate given twice a week.
Kosmas 2002 <sup>130</sup>	retrospective cohort study with historical controls	155 patients with metastatic BC, treated with first-line taxane + anthracyclines or mitoxantrone, 155 historical controls non-taxane treated	To identify the incidence of leptomeningeal carcinomatosis (LMC) as the 1st site of systemic progression after having obtained a major response to first-line taxane based chemotherapy	8.13% (taxane) vs. 1.4% control developed LMC (ns). Median survival after LMC = 3.6 months. LMC after a major response to taxane-based regimens represented a grave disease manifestation.
Orlando 2002 <sup>131</sup>	case series	13 patients with BC MC	Evaluates the efficacy of an ITC regimen for patients presenting with carcinomatous meningitis from BC	ITC failed to provide objective responses or relief in clinical symptoms

Abbreviations: BC = breast cancer, BM = brain metastases, T=treated, RSC = retrospective single cohort study, RCT = randomised controlled trial, vs. = versus, cum = cumulative, MC = meningeal carcinoma/cancer, ITC = intrathecal chemotherapy, IT = intrathecal, MTX = methotrexate, CSF = cerebral spinal fluid, CI = confidence interval, OS = overall survival, RR = response rate, LMC = leptomeningeal carcinomatosis. \* biological response was defined as a normalization of CSF proteins level (without any cancer cell detection).

## Summary

Breast cancer is the most common solid tumour prone to meningeal metastasis.<sup>126</sup> Metastasis to leptomeninges occurs in about 5% of breast cancer patients. Leptomeningeal metastasis develops on the innermost meninges (pia mater) and the middle membrane (arachnoid) or in the subarachnoid space. It can spread via multiple routes, including haematogenic, direct extension, along nerves and through the perineural lymphatics. Once the tumour cells reach the leptomeninges, they are believed to spread via the CSF.

The outlook for patients with meningeal metastases is poor. Survival times are short - up to 3 to 4 months, and survival is associated with poor performance status. Treatment is via intrathecal chemotherapy, however further, prospective studies are needed to clarify the role of intrathecal and systemic chemotherapy, in order to improve survival in breast cancer patients with MC.

### 3.3.8 Use of other medications including steroids and anticonvulsants.

Four systematic reviews, including two Cochrane review were identified that addressed the use of other medications including the use of steroids and prophylactic anticonvulsants.

The **Cochrane review by Tsao et al (2012)** assessed the effectiveness of steroids alone versus WBRT and steroids. One RCT examined the use of WBRT and prednisone vs. prednisone alone and produced inconclusive results.<sup>33</sup>

A second **Cochrane review by Kerrigan et al (2011)** evaluated the relative effectiveness and tolerability of antiepileptic drugs commonly used to treat seizures in adults with brain tumours. The review identified one small, open-label, unblinded, randomised trial of the safety and feasibility of switching from phenytoin to levetiracetam monotherapy or continuing phenytoin for glioma-related seizure control following craniotomy. No significant difference was identified between the effectiveness of the two drugs. The authors concluded that it was safe to switch people from phenytoin to levetiracetam monotherapy following craniotomy for supratentorial glioma. There is a need for larger RCTs to study the effectiveness of different antiepileptic drugs in the treatment of seizures in adults with brain tumours.

**The systematic review by Ryken et al 2010** addressed different combinations of WBRT, SRS and surgery. The associated clinical practice guideline recommendations included in the paper by Ryken et al, are outlined in Section 3.1.<sup>132</sup>

The systematic review addressed the following questions:

1. Do steroids improve neurologic symptoms in patients with metastatic brain tumours compared to no treatment? Only two studies were identified. One study 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.<sup>132</sup>

2. If steroids are given, what dose should be used? Only two studies were identified. One study concluded that a starting dose of 4-8mg/day be considered, unless patients exhibit severe symptoms consistent with increased intracranial pressure.<sup>132</sup>

**The systematic review by Mikkelsen et al (2010)** assessed if prophylactic anticonvulsants decrease the risk of seizures in patients with metastatic brain tumours compared with no treatment.<sup>133</sup> Only a single underpowered RCT of melanoma patients with brain metastases was identified. The study did not detect a difference in seizure occurrence. The study concluded that there is a lack of clear and robust benefit from the routine prophylactic use of anticonvulsants.<sup>133</sup>

### 3.4 Ongoing trials

Clinical trials registries were searched to identify any additional studies investigating CNS metastases in secondary breast cancer

**Table 42 Ongoing trials**

<b>Trial name and location</b>	<b>Study design</b>	<b>Participants</b>	<b>Intervention</b>	<b>Control</b>	<b>Completion Status</b>
<b>NCT01622868</b> Korea	Phase II RCT	Patients with diagnosis of invasive breast cancer/HER2 overexpressing breast cancer and brain metastasis  n = 143 (expected)	Patients receive lapatinib ditosylate orally on days 1 - 42 and undergo WBRT	Patients undergo WBRT once daily 5 days a week for 3 weeks	Ongoing
<b>NCT00875355</b> France	Phase II RCT	Women with brain metastases and Breast Cancer  N = 100 (estimated)	Patients undergo isocentric radiotherapy and oral temozolomide once daily for 2 weeks	Patients undergo isocentric radiotherapy to the brain 5 times a week for 2 weeks	Recruiting
<b>NCT00397501</b> Oregon, US	Phase II, Phase I, Pilot, open-label study	Patients with confirmed breast cancer metastatic to the central nervous system/brain metastasis  n=78 (projected)	Blood-brain barrier disruption (BBBD) followed by Methotrexate and Carboplatin with Trastuzumab	BBBD followed by Methotrexate and Carboplatin without Trastuzumab	Approved – not yet active
<b>NCT01645839</b> France	Phase III, RCT, open-label study	Patients with breast cancer and new diagnosis of leptomeningeal metastases  n = 144 (estimated)	Intrathecal treatment with liposomal cytarabine (DepoCyt®) patient will receive intrathecal treatment	No Intervention: no intrathecal treatment patients will receive standard treatment (chemotherapy)	Recruiting
<b>NCT00875355</b> France	Phase II Randomized Multicentre Study  n=100	In Patients With Brain Metastases From Breast Cancer	Patients undergo radiotherapy and receive oral temozolomide once daily for 2 weeks.	Patients undergo isocentric radiotherapy to the brain 5 times a week for 2 weeks.	Recruiting



<b>Trial name and location</b>	<b>Study design</b>	<b>Participants</b>	<b>Intervention</b>	<b>Control</b>	<b>Completion Status</b>
<b>NCT01494662</b> Massachusetts, United States	Phase II, interventional, open-label study	Confirmed invasive breast cancer, with metastatic disease	HKI-272/Neratinib 240 mg orally, once daily	40 mg orally, once daily + Surgical Resection	Recruiting
<b>NCT00977379</b> France	Phase II, RCT, open-label study n=24	Breast cancer with known HER2 and hormone status and newly diagnosed CNS metastasis	Xeloda (825 mg/sqm orally bid) on days 1-14 of the 1st 3-week cycle together with 10 days standard WBRT	WBRT alone	Completed
<b>NCT00639366</b> France	Phase III, RCT n=390 (estimated)	Brain Metastases and Breast Cancer	Patients receive taxane/trastuzumab therapy for 6 weeks. While continuing taxane/trastuzumab therapy, patients then undergo 10 fractions of concurrent prophylactic cranial radiotherapy in the absence of disease progression or unacceptable toxicity.	Patients receive taxane/trastuzumab therapy without concurrent prophylactic cranial radiotherapy.	Unknown
<b>NCT01480583</b> US	Phase II, intervention, open-label study n=100	Breast Cancer Patients With Brain Metastases	GRN1005 in combination with Trastuzumab for HER2 + metastatic breast cancer patients	GRN1005 alone for HER2 - metastatic breast cancer patients	Recruiting
<b>NCT01372774</b> US	Randomised Phase III	Patients with brain metastases that have been removed by surgery	Post-surgical SRS	WBRT	Active
<b>RTOG 0933</b> USA	Phase II N=92	Brain metastases of a non-hematopoietic malignancy	Hippocampal avoidance during WBRT for BM		Recruiting

## 4 Discussion

In this systematic review of the management of women with CNS metastases from secondary breast cancer, 107 citations and one abstract were identified as eligible from a search of the literature published between January 2001 and April 2012. Fifty-seven citations were included in the review for the primary research questions, and 51 citations addressed other issues. Seven previously published systematic reviews, including two Cochrane reviews, were also used as primary references.

This systematic review focused on evidence for the management of women with CNS metastases from **breast cancer**, rather than CNS metastases from various primary tumours. However, some studies included in this 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.

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

Two systematic reviews, including one Cochrane review, assessed the effectiveness of **surgical resection** in the management of newly diagnosed brain metastases in patients with mixed primary tumours. The Cochrane review by Hart et al of three RCTs including patients with brain metastases from various primary tumours, reported no significant difference in survival between surgery plus whole brain radiotherapy (WBRT) compared with WBRT alone.

One randomised controlled trial (RCT) was identified which assessed the efficacy of **direct decompressive surgery** plus postoperative radiotherapy compared with radiotherapy alone in patients with MESCC caused by metastatic cancer. Patchell et al (2005) reported patients with MESCC treated with direct decompressive surgery plus postoperative radiotherapy had better post treatment ambulatory rates, retained the ability to walk for longer as well as regain the ability to walk more often and had improved survival compared to patients treated with radiotherapy alone.

Five systematic reviews, including a Cochrane review, assessed the effectiveness of **radiotherapy** alone or in combination with other therapies. The Cochrane review by Tsao et al (2012) addressed various radiotherapy comparisons in patients with CNS metastases from various primary tumours. No benefit of altered dose-fractionation schedules as compared to the control fractionation of standard WBRT (30 Gy delivered in 10 fractions daily) for overall survival was reported.

Three retrospective studies evaluated the effectiveness of different doses of WBRT compared to the standard dose in populations that included patients with breast cancer primaries. Shorter course WBRT had similar survival and local control to longer course WBRT, while dose escalation beyond 30 Gy in 10 fractions did not improve survival or local control and increased treatment time and cost of therapy. For each of the three studies, KPS  $\geq 70$  and no extracranial metastases were associated with longer survival in multivariate analyses.

The Tsao 2012 Cochrane review reported that the addition of radiosensitizers (in patients with mixed primary tumours) did not confer additional benefit to WBRT in either the overall survival times or brain tumour response rates. Efaproxiral acts to increase radiation sensitivity by modifying haemoglobin and enhancing tumour oxygenation. Results of the 3 analyses of the REACH randomised study indicated that the addition of efaproxiral to WBRT may improve response rates and survival in patients with brain metastases and particularly in those patients with brain metastases from breast cancer.

The Tsao 2012 Cochrane review included comparisons between WBRT and **radiosurgery** in patients with CNS metastases from various primary tumours. Two RCTs included in the Tsao review reported no difference in overall survival with the use of WBRT and radiosurgery boost as compared to WBRT alone for selected participants with multiple brain metastases (up to four brain metastases). There was a statistically significant improvement in local control in selected patients who received radiosurgery boost compared to WBRT alone.

Two RCTs included in the Tsao review found no difference in overall survival between radiosurgery alone and radiosurgery and WBRT. The addition of WBRT to radiosurgery significantly improved locally treated brain metastases control and distant brain control. Three retrospective studies concluded that SRS alone compared with SRS and WBRT is an effective treatment for patients with one to three brain metastases from breast cancer and as salvage treatment for patients with recurrent brain metastases.

HER2-positive compared to HER2-negative patients had significantly longer survival in two retrospective studies following WBRT and in one retrospective study following gamma knife surgery.

There is a relative paucity of data from prospectively conducted clinical trials investigating the role of **chemotherapy** in the treatment of CNS metastases from breast cancer.<sup>6</sup> A systematic review (Mehta 2010) assessing the addition of chemotherapy to WBRT in patients with newly diagnosed CNS metastases from various primary tumours, reported no survival or neurologic progression benefit compared with WBRT alone.

Eight studies were identified that investigated different chemotherapies for the management of CNS metastases in populations with CNS metastases from breast cancer only (6 studies) and from mixed primary cancer (2 studies). They included trials of the agents: temozolomide alone or in combination, sagopilone, patupilone and methotrexate. All were phase I or phase II single arm studies and included small patient populations in general. General efficacy was suboptimal; objective response rates ranged from 4 – 40% and adverse events included fatigue and diarrhoea. Temozolomide and thalidomide are not appropriate for use in breast cancer or funded through the Pharmaceutical Benefits Scheme; off-label use is not recommended. Sagopilone and patupilone are not appropriate for use in breast cancer or funded through the Pharmaceutical Benefits Scheme and is not commercially available in Australia; off-label use is not recommended.

Systemic therapies can be effective in brain metastases from breast cancer; in particular, effective HER2-directed combination therapies. **Trastuzumab** is a humanised monoclonal antibody against the HER2 receptor and is used in the treatment of HER2-positive breast cancer in both the adjuvant and metastatic setting.<sup>4</sup>

Six retrospective comparative studies of the use of trastuzumab in patients with brain metastases from HER2-positive breast cancer were identified. Increased survival and longer time to progression was reported in HER2-positive patients who were treated with trastuzumab or continued with trastuzumab, after diagnosis of CNS metastases compared to patients who did not receive trastuzumab.

**Lapatinib** is a small-molecule tyrosine kinase inhibitor that targets the cytoplasmic ATP-binding sites of the kinase domains of HER2 and EGFR.<sup>4,5</sup> Because lapatinib is a small molecule, it is able to penetrate the blood brain barrier, particularly if this has been disrupted by the tumour, and it might be active in the treatment and prevention of brain metastases.<sup>4</sup>

Studies support the role for lapatinib plus capecitabine in both first and second line treatment of women with brain metastases from HER2-positive breast cancer. A phase III trial in HER2-positive advanced breast cancer patients who had received prior anthracycline, taxane, and trastuzumab therapy compared capecitabine alone to combination of lapatinib and capecitabine. The study found statistically fewer CNS progression events in patients treated with lapatinib and capecitabine (4 vs. 13 events).<sup>134</sup>

One phase II study investigated the use of lapatinib in combination with capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer. An objective response rate of 65.9% was reported. At the time of analysis, 36 (82%) patients had received radiotherapy to the brain.

Eight studies investigating the use of lapatinib, or lapatinib in combination with other agents, including capecitabine, for previously treated CNS metastases from HER2 positive metastatic breast cancer were identified. These included two prospective phase II trials and one randomised phase II trial. Objective response rates reported ranged from 2.6% to 6% in patients who received lapatinib alone and from 20% to 38% in patients who received lapatinib in combination with capecitabine, while no objective responses were observed in patients receiving lapatinib and topotecan. Adverse events reported included diarrhoea, palmarplantar erythrodysesthesia (lapatinib + capecitabine), nausea and fatigue.

Different **combinations of radiotherapy, surgery and chemotherapy** were also investigated.

Two non-comparative phase II trials investigated the combination of radiotherapy and chemotherapy. Both combinations of radiotherapy and chemotherapy (one study patients received temozolomide and other study patients received concurrent cisplatin and vinorelbine) appeared to be active and well tolerated. Three retrospective studies compared different combinations of treatment modalities and two studies concluded that a combined modality treatment approach was associated with improved outcomes.

This review also addressed if there are specific requirements for the subgroup of **asymptomatic patients**. One prospective study was identified that investigated asymptomatic compared with symptomatic brain metastases in HER2-positive breast cancer patients. The study concluded that in HER2-positive breast cancer patients with visceral and brain metastases, WBRT performed during the asymptomatic period had no

influence on survival but decreased the risk of cerebral death. Of important note, the results of the study showed a failure in the treatment of extracranial disease rather than brain metastases.

This systematic review also addressed several additional issues of interest. The incidence of brain metastases in HER2-positive patients with early breast cancer was reported as 6% to 9%. For HER2-positive patients with metastatic breast cancer the incidence was reported as 20% to 46%. For all patients with breast cancer CNS or brain metastases, 25% to 60% of tumours were HER2-positive.

The incidence of brain metastases in early stage triple negative brain metastases patients was reported as 6% to 7.5%. One paper reported that the incidence for patients with metastatic triple negative brain metastases was 46%. For patients with breast cancer brain metastases, 17.5% to 37% of tumours were of the triple negative subtype.

The majority of patients with brain metastases have impaired neurocognitive function. Decline of neurocognitive function impacts the patient's ability to complete activities of daily living, recognise safe and unsafe behaviour, and comply with medication regimens.<sup>120</sup> One study indicated that neurocognitive function decline precedes QOL decline. Neurocognitive function was highly correlated to tumour volume and predictive of overall survival in one study. Up to 40% of patients with brain metastases may experience epilepsy and combination of chemotherapy with antiepileptic treatment is an area of ongoing research.<sup>122</sup>

Breast cancer is the most common solid tumour prone to meningeal metastasis.<sup>126</sup> Metastasis to the leptomeninges occurs in about 5% of breast cancer patients. Leptomeningeal metastasis develops on the innermost meninges (pia mater) and the middle membrane (arachnoid) or in the subarachnoid space. It can spread via multiple routes, including haematogenic, direct extension, along nerves and through the perineural lymphatics. Once the tumour cells reach the leptomeninges, they are believed to spread via the cerebrospinal fluid.

The prognosis for patients with meningeal metastases is poor. Survival times are short, at up to 3 to 4 months, and survival is associated with poor performance status. Treatment is via intrathecal chemotherapy, however further, prospective studies are needed to clarify the role of intrathecal and systemic chemotherapy, in order to improve survival in breast cancer patients with meningeal metastases.

## 5 Conclusion

This systematic review considered the evidence on the management of women with CNS metastases from breast cancer including the use of systemic therapies, radiotherapy, surgery and multimodality treatment, as well as whether there are any specific requirements for subgroup of patients with asymptomatic CNS metastases.

Improvements in the systemic treatment of breast cancer and in survival have resulted in an increased incidence of CNS metastases.<sup>4</sup> The prognosis for patients diagnosed with CNS metastases from breast cancer is poor, with median survival of 2.3-7.1 months. HER2-positive patients have longer survival with median survival of 5.4-13 months.<sup>4</sup>

Factors that may be considered in the appropriate management of CNS metastases from breast cancer include: number, size and site of lesions, status of systemic metastases, performance status, and expected toxicities of treatment<sup>5,6</sup>

The RTOG-RPA prognostic classes are used to stratify patients into favourable and poor prognosis in order to determine the appropriate therapeutic approach.<sup>6,12</sup>

One Cochrane review by Hart et al (2011) assessed the effectiveness of surgical resection in the management of newly diagnosed single brain metastases in patients with mixed primary tumours.

The authors concluded that the addition of surgery may improve the length of time patients remained independent from others for support and there is a suggestion it may also reduce the risk of death due to neurological causes. Patients undergoing surgery were not reported to have a higher risk of adverse events than patients who only had WBRT. Decisions on the treatment for an individual patient are best made as part of a multidisciplinary team.

One RCT concluded that for patients with MESCC caused by metastatic cancer, direct decompressive surgery plus postoperative radiotherapy is superior to treatment with radiotherapy alone.

A second Cochrane review by Tsao et al (2012) assessed the effectiveness of radiotherapy alone or in combination with other therapies in patients with mixed primary tumours.

The authors concluded that none of the RCTs with altered WBRT dose-fractionation schemes as compared to standard (30 Gy in 10 daily fractions or 20 Gy in 4 or 5 daily fractions) found a benefit in terms of overall survival, neurologic function, or symptom control. The addition of radiosensitisers did not confer additional benefit to WBRT in either overall survival times or brain tumour response rates. Radiosurgery boost with WBRT may improve local disease control in selected participants as compared to WBRT alone, although survival remains unchanged for participants with multiple brain metastases. The addition of WBRT to radiosurgery improves local and distant brain control but there is no difference in overall survival. Patients treated with radiosurgery alone were found to have better neurocognitive outcomes in one trial as compared to patients treated with WBRT and radiosurgery.<sup>33</sup>

Overall, from the systematic review there were few large prospective trials identified that investigated the use of surgery, radiotherapy, systemic therapies or multimodal treatment for the management of women with CNS metastases, specifically from breast cancer. Most of the relevant trial data were limited to small breast cancer patient cohorts or retrospective studies. Systematic reviews identified included two Cochrane reviews that included patients with mixed primary tumours, with 0-68% breast cancer primary tumour patients included in the separate studies. The findings of these reviews are included in this systematic review.

Further evidence, from randomised controlled trials and prospective cohort studies, on the management of women with CNS metastases from secondary breast cancer is required. Areas of further research include:

- The efficacy of WBRT:
  - compared to SRS alone
  - compared to surgery alone
  - for un-resectable disease
  - and efaproxiral
- The efficacy of surgery alone compared to SRS alone
- 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 and palliative care needs for women with CNS metastases from breast cancer.

Based on the evidence from this systematic review, updates to existing clinical practice recommendations are required for the management of CNS metastases in women with secondary breast cancer. Recommendations on the use of surgery, radiotherapy and systemic therapies for the treatment of CNS metastases have been published and are available <link to be provided>

## Appendix A Contributors

### *Working group members*

The management of women with CNS metastases from secondary breast cancer: a systematic review was developed with input from an expert multidisciplinary Working Group with the following members:

- |                                |                           |
|--------------------------------|---------------------------|
| • Professor Fran Boyle (Chair) | Medical Oncologist        |
| • Ms Niki Aravanis (deceased)  | Consumer Representative   |
| • Ms Kim Kerin-Ayres           | Specialist Breast Nurse   |
| • A/Professor Katy Clark       | Palliative Care Physician |
| • Dr Senarath Edirimanne       | Breast Surgeon            |
| • Dr Vanessa Estall            | Radiation Oncologist      |
| • Dr Rosalind Jeffree          | Neurosurgeon              |
| • Dr Mustafa Khasraw           | Medical Oncologist        |
| • Professor Neville Knuckey    | Neurosurgeon              |
| • Ms Jennifer Muller           | Consumer Representative   |
| • Ms Marlene Parsons           | Consumer Representative   |
| • Dr Nitya Patanjali           | Radiation Oncologist      |
| • Professor David Shum         | Neuropsychologist         |

### *Cancer Australia staff*

The following Cancer Australia staff were involved in the development of The management of women with CNS metastases from secondary breast cancer: a systematic review

- |                        |   |
|------------------------|---|
| • Ms Katrina Anderson  | Senior Project Officer, Evidence Review |
| • Ms Phillipa Hastings | Senior Project Officer                  |
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| • Dr Anne Nelson       | Manager, Evidence Review                |
| • Ms Angela Pearce     | Senior Project Officer, Research        |
| • Dr Rebecca Reynolds  | Senior Project Officer, Research        |



- Ms Sue Sinclair General Manager, Service Delivery and Clinical Practice
- Ms Fleur Webster Manager, Breast Cancer
- Ms Tracey Wills Project Officer, Research

## Appendix B Literature databases searched

Source	Results/Retrievals
Medline (OVID)	732
Embase	744
Pubmed	885

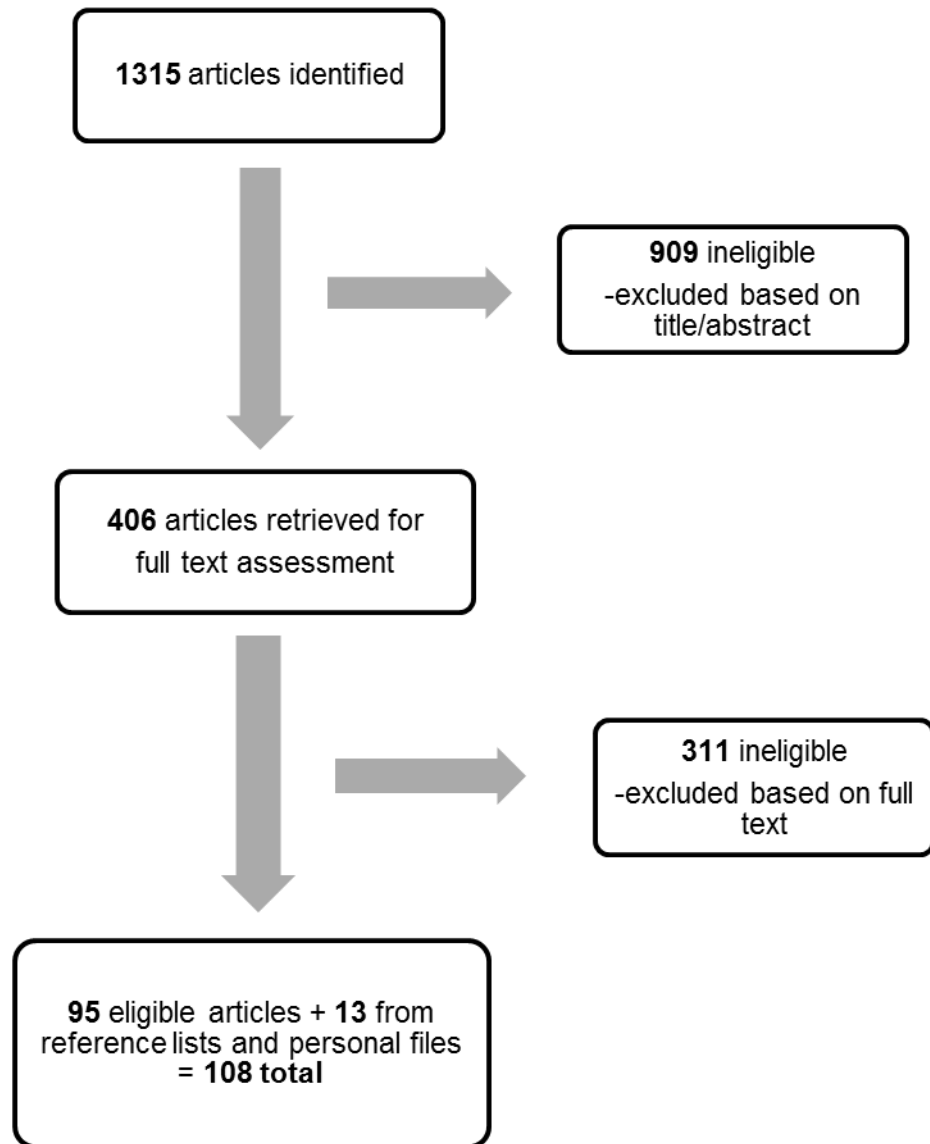
## Appendix C Search strategy

<b>Breast cancer</b>	Breast neoplasms/ "breast cancer" or "breast carcinoma" or "breast neoplasm" or "breast tumour" or "breast tumour"
<b>Central Nervous System (CNS)</b>	Brain neoplasms/ Central nervous system neoplasms/ brain cancer" or "brain neoplasm" or "brain carcinoma" or "brain tumour" or "brain tumour" or "brainstem cancer" or "brainstem neoplasm" or "brainstem carcinoma" or "brainstem tumour" or "brainstem tumour" or "intracranial cancer" or "intracranial neoplasm" or "intracranial carcinoma" or "intracranial tumour" or "intracranial tumour" or "posterior fossa cancer" or "posterior fossa neoplasm" or "posterior fossa carcinoma" or "posterior fossa tumour" or "posterior fossa tumour" or CNS or "central nervous system" OR "spinal cord"
<b>Metastases</b>	Neoplasm metastasis/ Metastatic or metastases or metastasis

## Appendix D Guideline and clinical trials sites searched

Acronym	Organisation	Website
<b>Canada</b>		
CCO	Cancer Care Ontario	<a href="http://www.cancercare.on.ca/">http://www.cancercare.on.ca/</a>
<b>International</b>		
HTAi	Health Technology Assessment International	<a href="http://www.htai.org/">http://www.htai.org/</a>
<b>Scotland</b>		
SIGN	Scottish Intercollegiate Guidelines Network	<a href="http://www.sign.ac.uk/">http://www.sign.ac.uk/</a>
<b>UK</b>		
CCT	Current Controlled Trials	<a href="http://www.controlled-trials.com/">http://www.controlled-trials.com/</a>
NICE	National Institute for Health and Clinical Excellence	<a href="http://www.nice.org.uk/">http://www.nice.org.uk/</a>
NRR	National Research Register	<a href="http://www.nrr.nhs.uk/">http://www.nrr.nhs.uk/</a>
<b>US</b>		
	ClinicalTrials.gov	<a href="http://www.clinicaltrials.gov/">http://www.clinicaltrials.gov/</a>
NCI	National Cancer Institute Clinical Trials	<a href="http://www.cancer.gov/clinicaltrials">http://www.cancer.gov/clinicaltrials</a>
NGC	National Guideline Clearinghouse	<a href="http://www.guideline.gov/">http://www.guideline.gov/</a>

## Appendix E Flowchart inclusion/exclusion



## Appendix F International guidelines and recommendations

### General CNS metastases guidelines (from any primary)

Topic	External guidelines
Surgery	<p>American Society for Radiation Oncology (ASTRO). <i>Radiotherapeutic and surgical management for newly diagnosed brain metastasis/es: An American Society for Radiation Oncology evidence-based guideline (2012)</i>.</p> <ul style="list-style-type: none"> <li>For selected patients with good performance status (e.g., KPS <math>\geq 70</math>), limited extracranial disease, and a resectable brain metastasis, complete resection of the single brain metastasis improves the probability of extended survival.</li> </ul> <p>European Federation Of Neurological Societies (EFNS). <i>Brain metastases: EFNS guidelines on brain metastases (2011)</i>.</p> <ul style="list-style-type: none"> <li>Surgical resection should be considered in patients with single brain metastasis in an accessible location when the size is large, the mass effect is considerable, and an obstructive hydrocephalus is present. Surgery is recommended when the systemic disease is absent/controlled and the Karnofsky performance score is 70 or more</li> </ul> <p>German Society Of Radiation Oncology (DEGRO). <i>DEGRO Practical Guidelines for palliative radiotherapy of breast cancer patients: brain metastases and leptomeningeal carcinomatosis (2010)</i>.</p> <ul style="list-style-type: none"> <li>KPS determines whether excision is feasible and if exclusive or additional WBRT is indicated.</li> </ul> <p>American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS). <i>The role of surgical resection in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline (2010)</i>.</p> <ul style="list-style-type: none"> <li>Level 1: Class I evidence supports the use of surgical resection plus postoperative WBRT, as compared to WBRT alone, in patients with good performance status and limited extra-cranial disease. There is insufficient evidence to make a recommendation for patients with poor performance scores, advanced systemic disease, or multiple brain metastases.</li> <li>Level 2: Surgical resection plus WBRT, versus stereotactic radiosurgery (SRS) plus WBRT, both represent effective treatment strategies, resulting in relatively equal survival rates. SRS has not been assessed from an evidence-based standpoint for larger lesions (<math>&gt;3</math> cm) or for those causing significant mass effect (<math>&gt;1</math> cm midline shift).</li> <li>Level 3: Underpowered class I evidence along with the preponderance of conflicting class II evidence suggests that SRS alone may provide equivalent functional and survival outcomes compared with resection + WBRT for patients with single brain metastases, so long as ready detection of distant site failure and salvage SRS are possible.</li> </ul>

	<p>National Institute of Clinical Excellence (NICE). <i>Advanced breast cancer: diagnosis and treatment (2009)</i>.</p> <ul style="list-style-type: none"> <li>• Offer surgery followed by WBRT to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well-controlled other metastatic disease.</li> </ul> <p>International RadioSurgery Association (IRSA). <i>Stereotactic radiosurgery for patients with metastatic brain tumours (2008)</i>.</p> <ul style="list-style-type: none"> <li>• Patients with large tumours causing symptomatic mass effect may need surgical decompression of the tumour. Residual tumour or tumour bed can be treated by SRS or radiation therapy.</li> </ul> <p>Cancer Care Ontario (CCO). <i>Management of single brain metastases: A clinical practice guideline (2006)</i>.</p> <ul style="list-style-type: none"> <li>• Should be considered for patients with good performance status, minimal or no evidence of extracranial disease, and a surgically accessible single brain metastasis amenable to complete excision.</li> </ul>
Radiotherapy	<p>ASTRO. <i>Radiotherapeutic and surgical management for newly diagnosed brain metastasis/es: An American Society for Radiation Oncology evidence-based guideline (2012)</i>.</p> <ul style="list-style-type: none"> <li>• For good prognosis patients with single brain metastases (less than 4 cm in size, in patients with good performance status and controlled extracranial disease), the use of radiosurgery added to WBRT improves survival, treated brain lesion control, and overall brain control as compared with WBRT alone.</li> <li>• In good prognosis patients with multiple brain metastases (all less than 4 cm in size and up to 4 brain metastases in number), radiosurgery boost when added to WBRT improves treated brain lesion and overall brain control as compared with WBRT alone.</li> <li>• As there is no survival advantage with radiosurgery added to WBRT in patients with multiple brain metastases, WBRT alone may be considered.</li> </ul> <p>EFNS. <i>Brain metastases: EFNS guidelines on brain metastases (2011)</i>.</p> <ul style="list-style-type: none"> <li>• SRS should be considered in patients with metastases of a diameter of <math>\leq 3 - 3.5</math> cm and/or located in eloquent cortical areas, basal ganglia, brainstem, or with comorbidities precluding surgery. SRS may be effective at recurrence after prior radiation.</li> <li>• WBRT alone is the therapy of choice for patients with active systemic disease and/or poor performance status.</li> <li>• Following surgery or radiosurgery, in case of absent/ controlled systemic disease and Karnofsky Performance score of 70 or more, one can either withhold adjuvant WBRT if close follow - up with MRI (every 3 – 4 months) is performed or deliver early WBRT.</li> <li>• In patients with up to three brain metastases, good performance status (KPS of 70 or more) and controlled systemic disease, SRS is an alternative to WBRT, while surgical resection is an option in selected patients.</li> <li>• In patients with more than three brain metastases WBRT with</li> </ul>

	<p>hypofractionated regimens is the treatment of choice.</p> <p>American College of Radiology (ACR). <i>ACR Appropriateness Criteria® multiple brain metastases (2011)</i>; ACR. <i>ACR Appropriateness Criteria® single brain metastases (2010)</i>.</p> <ul style="list-style-type: none"> <li>• WBRT is an effective palliative treatment for patients with multiple brain metastases.</li> <li>• If patients have no evidence of progressive extracranial disease, surgical resection or SRS is appropriate therapy. The addition of WBRT does not add to survival or duration of functional independence, it does reduce the risk of further intracranial failure and delays neurocognitive decline, particularly for those patients whose tumours have responded to WBRT.</li> </ul> <p>DEGRO. <i>DEGRO Practical Guidelines for palliative radiotherapy of breast cancer patients: brain metastases and leptomeningeal carcinomatosis (2010)</i>.</p> <ul style="list-style-type: none"> <li>• Radiotherapy (WBRT and involved-field irradiation of bulky spinal lesions).</li> </ul> <p>AANS/CNS. <i>The role of whole-brain radiation therapy in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline (2010)</i>; AANS/CNS. <i>The role of stereotactic radiosurgery in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline (2010)</i>.</p> <ul style="list-style-type: none"> <li>• Level I: Surgical resection followed by WBRT represents a superior treatment modality when compared to surgical resection alone, in terms of improving tumour control at the original site of the metastasis and in the brain overall when compared to surgical resection alone.</li> <li>• Level I: Class I evidence suggested that altered dose/fractionation schedules of WBRT do not result in significant differences in median survival, local control or neurocognitive outcomes when compared with "standard" WBRT dose/fractionation.</li> <li>• Level 1: Single-dose SRS along with WBRT leads to significantly longer patient survival compared with WBRT alone for patients with single metastatic brain tumours who have a Karnofsky performance status (KPS) <math>\geq 70</math>.</li> <li>• Level 2: Single-dose SRS along with WBRT is superior in terms of local tumour control and maintaining functional status when compared to WBRT alone for patients with 1–4 metastatic brain tumours who have a KPS <math>\geq 70</math>.</li> <li>• Level 3: Single-dose SRS along with WBRT may lead to significantly longer patient survival than WBRT alone for patients with 2–3 metastatic brain tumours.</li> <li>• Level 4: there is class III evidence demonstrating that single-dose SRS along with WBRT is superior to WBRT alone for improving patient survival for patients with single or multiple brain metastases and a KPS <math>&lt; 70</math>.</li> <li>• Level 3: While single-dose SRS and WBRT are effective for treating patients with brain metastases, single-dose SRS alone appears to be</li> </ul>
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	<p>superior to WBRT alone for patients with up to 3 metastatic brain tumours in terms of patient survival advantage.</p> <p>CCO. <i>Management of Brain Metastases: Role of radiotherapy alone or in combination with other treatment modalities</i>(2004).</p> <ul style="list-style-type: none"> <li>• Postoperative WBRT should be considered to reduce the risk of tumour recurrence for patients who have undergone resection of a single brain metastasis.</li> </ul> <p>CCO. <i>Management of single brain metastases: A clinical practice guideline</i> (2006).</p> <ul style="list-style-type: none"> <li>• SRS boost should be considered following WBRT for patients with single metastases. There is insufficient evidence to recommend SRS alone as single modality therapy.</li> </ul> <p>NICE. <i>Advanced breast cancer: diagnosis and treatment</i> (2009).</p> <ul style="list-style-type: none"> <li>• Offer WBRT to patients for whom surgery is not appropriate, unless they have a very poor prognosis.</li> </ul> <p>IRSA. <i>Stereotactic radiosurgery for patients with metastatic brain tumours</i> (2008).</p> <ul style="list-style-type: none"> <li>• SRS may be especially suitable for patients who have limited metastatic brain disease and have controlled systemic disease with good functional status.</li> <li>• SRS is typically employed alone or as a boost after WBRT for patients with metastatic brain tumours.</li> <li>• The optimal dose range for volumetric conformal stereotactic brain metastases radiosurgery has been largely established based on tumour anatomy, tumour volume, prior radiation therapy and estimated adverse radiation risks.</li> </ul>
Systemic therapy	<p>ASTRO. <i>Radiotherapeutic and surgical management for newly diagnosed brain metastasis/es: An American Society for Radiation Oncology evidence-based guideline</i> (2012).</p> <ul style="list-style-type: none"> <li>• Although chemotherapy trials reported improved brain response rates with the use of combined chemotherapy and WBRT, this was at the cost of toxicity and no overall survival advantage was found with the addition of chemotherapy. There currently is no high quality evidence to support the routine use of chemotherapy in the management of brain metastases.</li> </ul> <p>EFNS. <i>Brain metastases: EFNS guidelines on brain metastases</i> (2011).</p> <ul style="list-style-type: none"> <li>• Chemotherapy may be the initial treatment for patients with brain metastases from chemosensitive tumours, especially if asymptomatic, chemo – naïve, or an effective chemotherapy schedule for the primary is still available (GPP).</li> </ul> <p>National Comprehensive Cancer Network (NCCN). <i>Central nervous system cancers guidelines cover metastatic disease with separate recommendations for limited (1-3) metastatic lesions, multiple (&gt;3) metastatic lesions, leptomeningeal metastases, and metastatic spine tumours</i> (2012).</p>

	<ul style="list-style-type: none"> <li>• LC: High dose methotrexate (if breast or lymphoma); or craniospinal irradiation (CSI) (If breast or lymphoma.)</li> <li>• Limited meets: High dose methotrexate, cyclophosphamide (breast and lymphoma). Capecitabine, cisplatin, etoposide (breast).</li> </ul> <p>AANS/CNS. <i>The role of chemotherapy in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline (2010).</i></p> <ul style="list-style-type: none"> <li>• Level I: Routine use of chemotherapy following WBRT for brain metastases has not been shown to increase survival and is not recommended.</li> <li>• Chemotherapy- Depending on individual circumstances there may be patients who benefit from the use of temozolomide or fotemustine in the therapy of their brain metastases.</li> </ul> <p>DEGRO. <i>DEGRO Practical Guidelines for palliative radiotherapy of breast cancer patients: brain metastases and leptomeningeal carcinomatosis (2010).</i></p> <ul style="list-style-type: none"> <li>• Chemotherapy (systemically or intrathecally applied methotrexate, thiotepa and cytarabine) is effective.</li> </ul>
Other drug therapies	<p>AANS/CNS. <i>The role of prophylactic anticonvulsants in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline (2010)</i>; AANS/CNS. <i>The role of steroids in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline (2010).</i></p> <ul style="list-style-type: none"> <li>• For adults with brain metastases who have not experienced a seizure due to their metastatic brain disease, routine prophylactic use of anticonvulsants is not recommended.</li> <li>• Brain Metastases Patients with Mild Symptoms Related to Mass Effect - Corticosteroids are recommended to provide temporary symptomatic relief.</li> <li>• Brain Metastases Patients with Moderate to Severe Symptoms Related to Mass Effect - Corticosteroids are recommended to provide temporary symptomatic relief of. If patients exhibit severe symptoms consistent with increased intracranial pressure, it is recommended that higher doses be considered.</li> <li>• Choice of Steroid- Dexamethasone is the best drug choice given the available evidence.</li> <li>• Duration of Corticosteroid Administration-Corticosteroids, if given, should be tapered slowly over a 2 week time period, or longer in symptomatic patients, based upon an individualized treatment regimen and a full understanding of the long-term sequelae of corticosteroid therapy.</li> </ul> <p>IRSA. <i>Stereotactic radiosurgery for patients with metastatic brain tumours (2008).</i></p> <ul style="list-style-type: none"> <li>• Patients may receive a single stress dose of corticosteroids at the conclusion of the radiosurgery procedure. Patients can continue to take other medications (antiseizure or antiedema drugs) as recommended by their physicians.</li> </ul>

	<ul style="list-style-type: none"> <li>• Patients with hydrocephalus or impending brain herniation should be started on high doses of corticosteroids and evaluated for possible neurosurgical intervention.</li> <li>• The routine use of corticosteroids in patients without neurological symptoms is not necessary.</li> <li>• There is no proven benefit of anticonvulsants in the patient who has not experienced seizures.</li> </ul> <p>CCO. <i>The use of prophylactic anticonvulsants in patients with brain tumours: A clinical practice guideline (2006).</i></p> <ul style="list-style-type: none"> <li>• The routine use of postoperative anticonvulsants is not recommended in seizure-naïve patients with newly diagnosed primary or secondary brain tumours.</li> </ul>
Recurrent disease	<p>AANS/CNS. <i>The role of retreatment in the in the management of recurrent/progressive brain metastases: A systematic review and evidence-based clinical practice guideline (2010).</i></p> <ul style="list-style-type: none"> <li>• Level 3: There is insufficient evidence to make definitive treatment recommendations in patients with recurrent/progressive brain metastases, treatment should be individualized based on a patient's functional status, extent of disease, volume/number of metastases, recurrence or progression at original versus non-original site, previous treatment and type of primary cancer and enrolment in clinical trials is encouraged. In this context, the following can be recommended depending on a patient's specific condition: no further treatment (supportive care), reirradiation (either WBRT and/or SRS), surgical excision or, to a lesser extent chemotherapy.</li> </ul>
Other (rehabilitation, palliation)	<p>AANS/CNS. <i>The role of emerging and investigational therapies for metastatic brain tumours: a systematic review and evidence-based clinical practice guideline of selected topics (2010).</i></p> <ul style="list-style-type: none"> <li>• New Radiation Sensitizers- A subgroup analysis of a large prospective randomized RCT suggested a prolongation of time to neurological progression with the early use of motexafin-gadolinium (MGd).</li> <li>• Interstitial Modalities- There is no evidence to support the routine use of new or existing interstitial radiation, interstitial chemotherapy and or other interstitial modalities outside of approved clinical trials.</li> </ul> <p>NICE. <i>Advanced breast cancer: diagnosis and treatment (2009).</i></p> <ul style="list-style-type: none"> <li>• Offer active rehabilitation to patients who have surgery and/or whole brain radiotherapy.</li> <li>• Offer referral to specialist palliative care to patients for whom active treatment for brain metastases would be inappropriate.</li> </ul> <p>CCO. <i>Management of Brain Metastases: Role of radiotherapy alone or in combination with other treatment modalities (2004).</i></p> <ul style="list-style-type: none"> <li>• The use of radiosensitizers is not recommended outside research studies.</li> </ul> <p>ASTRO. <i>Radiotherapeutic and surgical management for newly diagnosed brain metastasis/es: An American Society for Radiation Oncology evidence-based guideline (2012)</i></p>

	<ul style="list-style-type: none"> <li>• There is no evidence of survival benefit with the use of radiosensitizers and whole brain radiotherapy.</li> </ul>
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Abbreviations: AANS/CNS=American Association of Neurological Surgeons/Congress of Neurological Surgeons; ACR=American College of Radiology; ASTRO=American Society for Radiation Oncology; CCO=Cancer Care Ontario; CSI=Craniospinal Irradiation; DEGRO=German Society of Radiation Oncology; EFNS=European Federation of Neurological Societies; IRSA=International RadioSurgery Association; KPS=Karnofsky Performance Status; LC= Leptomeningeal Carcinomatosis; MGd=Motexafin-Gadolinium; NCCN=National Comprehensive Cancer Network (NCCN); NICE=National Institute for Health and Care Excellence; RCT=Randomised Controlled Trial (RCT); SRS=Stereotactic Radiosurgery; WBRT=Whole Brain Radiotherapy

## Appendix G Patient numbers in trials included in Cochrane reviews and systematic reviews

Tsao 2012. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases.<sup>33</sup>

Studies included in review	Total patients in study	Breast cancer patients in study
<i>Altered WBRT dose-fractionation schedules versus conventional WBRT fractionation schedules</i>		
Borgelt 1980	1812	312 (17%)
Borgelt 1981	202	138 (68%)
Chatani 1985	69	0 (0)
Chatani 1994	162	0 (0)
Harwood 1977	101	27 (27%)
Kurtz 1981	255	18 (7%)
Murray 1997	429	43 (10%)
Priestman 1996	533	101 (19%)
<i>WBRT plus radiosensitizers versus WBRT</i>		
DeAngelis 1989	58	8 (14%)
Eyre 1984	111	13 (12%)
Komarnicky 1991	779	91 (12%)
Mehta 2003	401	75 (19%)
Phillips 1995	70	2 (3%)
Suh 2006	515	109 (21%)
<i>WBRT plus radiosurgery versus WBRT</i>		
Andrews 2004	331	34 (10%)
Chougule 2000	96	12 (13%)
Kondziolka 1999	27	4 (15%)
<i>Radiosurgery plus WBRT versus radiosurgery</i>		
Aoyama 2006	132	9 (7%)
Chang 2009	58	8 (14%)
Kocher 2011	359	42 (12%)

**Hart 2011. Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases.<sup>22</sup>**

Studies included in review	Total patients in study	Breast cancer patients in study
Mintz 1996	84	10 (12%)
Patchell 1990	48	3 (6%)
Vecht 1993	63	12 (19%)

**Mehta 2010. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline.<sup>53</sup>**

Studies included in review	Total patients in study	Breast cancer patients in study
Antonadou 2002	48	5 (10%)
Guerrieri 2004	42	0 (0%)-lung cancer only
Kim 2010	63	0 (0%)-lung cancer only
Ushio 1991	88	0 (0%)-lung cancer only
Verger 2005	82	13 (16%)

**Tsao 2012 Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases.<sup>33</sup> Recurrence of brain metastases after WBRT-studies**

Study	Outcome	SRS + WBRT	SRS alone	P value
Aoyama 2006	12-month actuarial brain tumour recurrence rate	46.8% (95% CI 29.7%-63.9%)	76.4% (95% CI 63.3%-89.5%)	<0.001
	12-month actuarial rate of developing new brain metastases	41.5% (95% CI 24.4%-58.6%)	63.7% (95% CI 49%-78.4%)	0.003
Chang 2009	1-year freedom from CNS recurrence	73% (95% CI 46-100)	27% (95% CI 14-51)	0.0003
Study	Outcome	SRS or Surgery then WBRT	SRS or Surgery then Observation	P value
Kocher 2011	Extracranial progressions	66%	64%	
	Cumulative incidence rates of extracranial progression (6 months)	38% (95% CI 31%-45%)	37% (95% CI 30%-44%)	
	Cumulative	65%	63%	0.73

	incidence rates of extracranial progression (2 years)	(95% CI 58%-72%)	(95% CI 56%-70%)	
	Intracranial progression	48%	78%	<0.001

## Abbreviations

AANS/CNS	American Association of Neurological Surgeons/Congress of Neurological Surgeons
ADL	Activities Of Daily Living
ACR	American College of Radiology
ASCO	American Society Of Clinical Oncology
AST/ALT	Aspartate Aminotransferase/Alanine Aminotransferase
ASTRO	American Society for Radiation Oncology
BC	Breast Cancer
BM	Brain Metastases
BMPRFS	Brain Metastases Progression/Recurrence Free Survival
CCO	Cancer Care Ontario
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CSF	Cerebral Spinal Fluid
DEGRO	German Society Of Radiation Oncology
DLT	Dose Limiting Toxicity
EFNS	European Federation Of Neurological Societies
ER	Estrogen Receptor
E-RBC	Efaproxiral Red Blood Cell
ESMO	European Society Of Medical Oncology
FACT-Br	Functional Assessment Of Cancer Therapy-Breast
FIS	Functionally Independent Survival
GIN	Guidelines International Network
GKS	Gamma Knife Surgery
Gy	Gray
HER	Human Epidermal Growth Factor Receptor
HR	Hazard Ratio
IBCSG	Internal Breast Cancer Study Group
IRSA	International RadioSurgery Association
IT	Intrathecal
ITC	Intrathecal Chemotherapy
KPS	Karnofsky Performance Status
LC	Leptomeningeal Metastases/Carcinomatosis
LMC	Leptomeningeal Carcinomatosis
MDSAI	M.D. Anderson Symptom Inventory
MESCC	Metastatic Epidural Spinal Cord Compression
MRI	Magnetic Resonance Imaging
MSCC	Metastatic Spinal Cord Compression
MTX	Methotrexate
NCCN	National Comprehensive Cancer Network
NCF	Neurocognitive Function



NICE	National Institute for Health and Care Excellence
NR	Not Reported
NS	Not Significant
NSCLC	Non-Small Cell Lung Cancer
NSS	Neurological Signs And Symptoms
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Pulmonary Embolus
PFS	Progression Free Survival
PFS	Progression Free Survival
PPE	Palmar-Plantar Erythrodysesthesia
PR	Partial Response
QAS	Quality Adjusted Survival
QoL	Quality Of Life
RCT	Randomized Controlled Trial
REACH	Radiation Enhancing Allosteric Compound for Hypoxic Brain Metastases
RECIST	Response Evaluation Criteria In Solid Tumours
RPA	Recursive Partitioning
RR	Relative Risk
RTOG	Radiation Therapy Oncology Group
SABCS	San Antonio Breast Cancer Symposium
SD	Stable Disease
SEER	Surveillance Epidemiology And End Results
SIR	Score Index For Radiosurgery
SQLI	Spitzer Quality Of Life Index
SRS	Stereotactic Radiosurgery
TMZ	Temozolomide
TNBC	Triple Negative Breast Cancer
TTF	Time To Failure
TTP	Time To Progression
UK	United Kingdom
USA	United States Of America
Vs.	Versus
WBRT	Whole Brain Radiotherapy

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