# Topic proposal

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| I understand that this proposal will be retained by the SIGN Programme Lead and be made available on the SIGN website for time period that the proposal is being considered. **Only proposals with a completed Declaration of Interests for the principal proposer will be considered** | |
| | |
| **1.** | **What is the problem/need for a guideline/clinical scenario?** |
| | Breast cancer is the most common cancer in women in Scotland and the second commonest cancer overall after lung cancer. Although the five year relative survival has been improving over the last decade, from 61% for those diagnosed and treated in 1983-1987 to 81% in 2003-2007, there is still evidence of variations in the treatment of patients with breast cancer.[2, 3]<br><br>A uniform approach to the management of secondary breast cancer would be useful and in particular benefits would be largely to inform patients, carers and indeed the medical profession of an evidential base to their ongoing clinical decisions. |
| **2.** | **Burden of the condition** |
| | Mortality<br><br>A NICE literature review from 2008 found that up to 40% of those diagnosed with breast cancer in the UK will develop advanced disease within 10 years.[4] Variation in outcomes was not geographical. Mortality from breast cancer is highest in those from higher socioeconomic groups, but survival is poorest at every disease stage in those from lower socioeconomic groups.[4] |
| | Incidence<br><br>The incidence has been increasing and over the last 10 years has risen by approximately 12%.[1] In Scotland in 2010 there were 4,457 newly diagnosed cases in women and 23 cases in men.[1] |
| | Prevalence<br><br>In Scotland in 2010 there were 4,457 newly diagnosed cases in women and 23 cases in men.[1] |
| **3.** | **Variations** |
| | In practice in Scotland<br><br>Development of clinical management guidelines is largely driven on a regional basis thus there is the potential for variation in practice in the management of this condition across Scotland. |
| | In health outcomes in Scotland<br><br>While treatable, metastatic breast cancer is rarely curable. Some women with metastatic breast cancer live for many years; however, the median survival ranges from 18 to 24 months. As a consequence women with advanced breast cancer, and their families, are not only living with uncertainty about the future, the burden of treatment, and the threat of dying, but also with the emotional, social and psychological difficulties their situation brings. |
| **4.** | **Areas of uncertainty to be covered** |
| | Key question 1 |

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| | Key question 2 |
| | Key question 3 |
| **5.** | **Areas that will not be covered** |
| | |
| **6.** | **Aspects of the proposed clinical topic that are key areas of concern for patients, carers and/or the organisations that represent them** |
| | Key areas of concern to patients are predominantly around dying, quality of life issues, ability to cope and care for family, medication side-effects, the condition being overshadowed by early-stage breast cancer and end of life care which lead to feelings of fear, low mood, anger and isolation. These issues were presented in the results of an international patient survey calling for a change in attitude to metastatic breast cancer (Mayer et al 2010 [living with mbc a global survey]). The survey results highlight the need for patient support and information, raising awareness of the disease and a focus on the whole person, not just the cancer. |
| **7.** | **Population** |
| | Included |
| | Not included |
| **8.** | **Healthcare setting** |
| | Included |
| | Not included |
| **9.** | **Potential** |
| | Potential to improve current practice |
| | Potential impact on important health outcomes<br>(name measureable indicators) |

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| | Potential impact on resources<br>(name measureable indicators) |
| **10.** | **What evidence based guidance is currently available?** |
| | None |
| | Out-of-date (list) |
| | Current (list)<br><br>Five meta-analysis compared different imaging modalities for the detection of breast cancer recurrence<br><br>Eleven HTAs were identified providing clinical and cost effectiveness data on a wide range of chemotherapy and biological interventions for advanced and metastatic breast cancer. There are a further nine Cochrane reviews and 18 other systematic reviews of chemotherapy and biologics. One Cochrane review covered whole brain radiotherapy for brain metastasis and there was a further systematic review of hepatic resection for metastatic breast cancer.<br><br>In addition 4,516 RCTs were identified.<br><br>Dent R, Haynes AE, Enright K, Hamm C, Trudeau M, Eisen A. **The use of bevacizumab in metastatic breast cancer.** Toronto (ON): Cancer Care Ontario (CCO); 2009 Apr 17. 24 p.(CED-CCO special advice report; no. 12). [24 references]<br><br>Flemming J, Madarnas Y, Franek J, Breast Cancer Disease Site Group. **Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women: guideline recommendations.** Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2008 Sep 25. 42 p.(Evidence-based series; no. 1-13).<br><br>Madarnas Y, Haynes AE, Eisen A. **The continued use of trastuzumab beyond disease progression in patients with metastatic breast cancer.** Toronto (ON): Cancer Care Ontario (CCO); 2009 Aug 17. 26 p.(CED-CCO special advice report; no. 13). [21 references]<br><br>National Collaborating Centre for Cancer. **Advanced breast cancer: diagnosis and treatment.** NICE Clinical Guideline 81. March 2009.<br><br>http://www.nice.org.uk/nicemedia/live/11778/43414/43414.pdf<br><br>Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, Bosserman LD, Geoghegan C, Hillner BE, Theriault RL, Zuckerman DS, Von Roenn JH. **American Society of Clinical Oncology clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer.** Alexandria (VA): American Society of Clinical Oncology (ASCO); 2011. 17 p. [77 references] |

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| | NICE published a Breast Cancer quality standard (QS12) in September 2011 which Includes an advanced breast cancer pathway. |
| **11.** | **Relevance to current Scottish Government policies** |
| | Breast Cancer Clinical Quality Performance Indicators were published by the Scottish Government and Healthcare Improvement Scotland in March 2012 Cancer Quality Performance Indicators (QPIs) |
| **12.** | **Who is this guidance for?** |
| | This guideline would be of interest to all members of the multidisciplinary team (MDT) treating patients with breast cancer, including surgeons, oncologists, pathologists, radiologists, therapy and diagnostic radiographers, nurses and palliative care specialists, as well as to patients and carers, managers and policy makers. |
| **13.** | **Implementation** |
| | Links with existing audit programmes |
| | Existing educational initiatives |
| | Strategies for monitoring implementation |
| **14.** | **Primary contact for topic proposal** |
| | *Group members from SIGN 134* |
| **15.** | **Group(s) or institution(s) supporting the proposal** |
| | Representatives from the major cancer voluntary organisations: Breast Cancer Care, Breakthrough Breast Cancer, Macmillan, Maggie's Centres Scotland, Marie Curie Cancer Care would be essential. |


1. Information Services Division (ISD). Cancer in Scotland (October 2011). NHS National Services Scotland; 2012. Available from url: http://www.isdscotland.org/Health-Topics/Cancer/Publications/2012-04-24/2012-04-24-Cancer-Incidence-report.pdf?49042910338
2. van Nes JG SC, Jones S, Markopoulos C, Putter H, van de Velde CJ et al. Variations in locoregional therapy in postmenopausal patients with early breast cancer treated in different countries Br J Surg 2010;97(5):671-9.
3. Bates T, Kearins O, Monypenny I, Lagord C, Lawrence G. . Clinical outcome data for symptomatic breast cancer: the Breast Cancer Clinical Outcome Measures (BCCOM) Project. Br J Cancer 2009;101(3):395-402.
4. National Collaborating Centre for Cancer. **Advanced breast cancer: diagnosis and treatment.** NICE Clinical Guideline 81. March 2009. http://www.nice.org.uk/nicemedia/live/11778/43414/43414.pdf

# Declaration of Interests

*Please complete all sections and if you have nothing to declare please put 'N/A*

| Having read the attached SIGN Policy on Declaration of Competing Interests I declare the following competing interests for the previous year, and the following year. I understand that this declaration will be retained by the SIGN Programme Lead and be made available on the SIGN website for time period that the proposal is being considered. | |
|---|---|
| **Signature:** | |
| **Name:** | |
| **Relationship to SIGN:** | Topic proposal primary contact |
| **Date:** | |
| **Date received at SIGN:** | |

## Personal Interests

**Remuneration from employment**

| | **Name of Employer and Post held** | **Nature of Business** | **Self or partner/ relative** | **Specific?** |
|---|---|---|---|---|
| **Details of employment held which may be significant to, or relevant to, or bear upon the work of SIGN** | | | | |

**Remuneration from self employment**

| | **Name of Business** | **Nature of Business** | **Self or partner/ relative** | **Specific?** |
|---|---|---|---|---|
| **Details of self employment held which may be significant to, or relevant to, or bear upon the work of SIGN** | | | | |

**Remuneration as holder of paid office**

| | **Nature of Office held** | **Organisation** | **Self or partner/ relative** | **Specific?** |
|---|---|---|---|---|
| **Details of office held which may be significant to, or relevant to, or bear upon the work of SIGN** | | | | |

**Remuneration as a director of an undertaking**

| | Name of Undertaking | Nature of Business | Self or partner/ relative | Specific? |
|---|---|---|---|---|
| **Details of directorship held which may be significant to, or relevant to, or bear upon the work of SIGN** | | | | |

**Remuneration as a partner in a firm**

| | Name of Partnership | Nature of Business | Self or partner/ relative | Specific? |
|---|---|---|---|---|
| **Details of Partnership held which may be significant to, or relevant to, or bear upon the work of SIGN** | | | | |

**Shares and securities**

| | Description of organisation | Description of nature of holding (value need not be disclosed) | Self or partner/ relative | Specific? |
|---|---|---|---|---|
| **Details of interests in shares and securities in commercial healthcare companies, organisations and undertakings** | | | | |

**Remuneration from consultancy or other fee paid work commissioned by, or gifts from, commercial healthcare companies, organisations and undertakings**

| | Nature of work | For whom undertaken and frequency | Self or partner/ relative | Specific? |
|---|---|---|---|---|
| **Details of consultancy or other fee paid work which may be significant of to, or relevant to, or bear upon the work of SIGN** | | | | |

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| **Details of gifts which may be significant to, or relevant to, or bear upon the work of SIGN** | | | | |

**Non-financial interests**

| | Description of interest | Self or partner/ relative | Specific? |
|---|---|---|---|
| **Details of non-financial interests which may be significant to, or relevant to, or bear upon the work of SIGN** | | | |

## Non-personal interests

| | Name of company, organisation or undertaking | Nature of interest |
|---|---|---|
| **Details of non-personal support from commercial healthcare companies, organisations or undertakings** | | |

*Signature* _____ *Date:* _____

*Thank you for completing this form.*

**Please return to**
**Roberta James**
**SIGN Programme Lead**
**SIGN Executive, Healthcare Improvement Scotland,**
**Gyle Square | 1 South Gyle Crescent | Edinburgh | EH12 9EB**

t: **0131 623 4735**
e:**roberta.james@nhs.net**

**Data Protection**

Your details will be stored on a database for the purposes of managing this guideline topic proposal. We may retain your details so that we can contact you about future Healthcare Improvement Scotland activities. We will not pass these details on to any third parties. Please indicate if you do not want your details to be stored after the proposal is published.

## Initial screen

**Purpose**: initial screening by SIGN Senior Management Team to exclude proposals that are neither clinical, nor multi-professional, nor appropriate for the SIGN process.

| | | |
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| **1.** | **Is this an appropriate clinical topic for a SIGN guideline?**<br>Is it a clinical topic, what is the breadth of the topic and is there a need for the guideline as identified in the proposal? | |
| | This is a clinical topic with a narrow focus. It covers patients not included on SIGN 134: Treatment of primary breast cancer and would stand alongside this guideline. | |
| **2.** | **Is there a suitable alternative product which would address this topic?**<br>Would another Healthcare Improvement Scotland product better address the topic? | |
| | No, indicators already exist from HIS and this potential guideline would dovetail with these | |
| **3.** | **Has this topic been considered before and rejected?**<br>What were the reasons for rejection and are they still applicable. | |
| | No | |
| **4.** | **Outcome** | |
| | Go forward to the next stage of topic selection | **YES** |
| | Reject | |

## Suitability screen

**Purpose**: screening by the Guideline Programme Advisory Board to select applications suitable for inclusion in the SIGN topic selection process.

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| **1.** | **Is there an owner for the project?** (preferably an individual) |
| | No, the topic was proposed by the guideline development group for SIGN 134: Treatment of primary breast cancer. |
| **2.** | **Is this a clinical priority area for NHSScotland?** |
| | This is an important topic as the area is neglected with respect to both research and processes. Most focus on treatment rather than palliation. |
| **3.** | **Is there a gap between current and optimal practice? OR Is there wide variation in current practice?** (is this an area of clinical uncertainty) |
| | People want more advice on psychosocial aspects of the conditions and on palliative care. This is done well by some GPs but there is probably variation. Although breast cancer services are well processed there may be variation. |
| **4.** | **Is there a suitable guideline already available that could be adapted?** (not necessarily by SIGN) |
| | There are some focused guidelines from Canada and one from NICE which will inform the evidence base. |
| **5.** | **Is there adequate literature to make an evidence-based decision about appropriate practice?** (is effective treatment proven and would it reduce mortality or morbidity) |
| | Yes, there is a body of literature. |
| **6.** | **Would the proposed practice change result in sufficient change in outcomes** (health status, provider and consumer satisfaction and cost) **to justify the effort?** |
| | Not possible to say from available information. Psychosocial care could probably be improved. |
| | How big is the gap? |
| | |
| | How much effort will it take to close the gap? |
| | |
| **7.** | **Is there a perceived need for the guideline, as indicated by a network of relevant stakeholders?** |
| | There is a need as this topic was omitted from SIGN 134. There is interest from the voluntary sector. |
| **8.** | **Is there a reasonable likelihood that NHSScotland could implement the change?** |
| | Probably evidence that would support a potential guideline on this topic is already being implemented. Many of the newer drugs are expensive and have not been approved by SMC which could impact on the guideline. There could be a political aspect. |

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| **9.** | **Does the proposer have any conflicts of interest? If so how will these be managed?** | |
| | The proposal was first received prior to the policy of requesting declarations. The initial proposer has now retired. | |
| **10.** | **Outcome** | |
| | Go forward to the next stage of topic selection | **YES** |
| | Reject | |
| **11.** | **Decision** | |
| | Ratified by SIGN Council for inclusion on the SIGN guideline development programme | **Date** |
| | *Comment*<br>SIGN Executive will identify an owner of the proposal | **10/02/2016** |

## Scope of recent evidence

**Topic: Management of women with metastatic breast cancer**

**Resources searched:**

GIN

National Guidelines Clearinghouse

NICE

Cochrane Library

DARE

INAHTA

UKHTA

MEDLINE

Dates searched: 2003 to April 2013

**Guidelines (5)**

Dent R, Haynes AE, Enright K, Hamm C, Trudeau M, Eisen A. **The use of bevacizumab in metastatic breast cancer.** Toronto (ON): Cancer Care Ontario (CCO); 2009 Apr 17. 24 p.(CED-CCO special advice report; no. 12). [24 references]

Flemming J, Madarnas Y, Franek J, Breast Cancer Disease Site Group. **Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women: guideline recommendations.** Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2008 Sep 25. 42 p.(Evidence-based series; no. 1-13).

Madarnas Y, Haynes AE, Eisen A. **The continued use of trastuzumab beyond disease progression in patients with metastatic breast cancer.** Toronto (ON): Cancer Care Ontario (CCO); 2009 Aug 17. 26 p.(CED-CCO special advice report; no. 13). [21 references]

National Collaborating Centre for Cancer. **Advanced breast cancer: diagnosis and treatment.** NICE Clinical Guideline 81. March 2009.

http://www.nice.org.uk/nicemedia/live/11778/43414/43414.pdf

Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, Bosserman LD, Geoghegan C, Hillner BE, Theriault RL, Zuckerman DS, Von Roenn JH. **American Society of Clinical Oncology clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer.** Alexandria (VA): American Society of Clinical Oncology (ASCO); 2011. 17 p. [77 references]

**Health Technology Assessments (11)**

Fleeman N, Bagust A, Boland A, Dickson R, Dundar Y, *et al*. **Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis.** *Health Technol Assess* 2011;**15**(42).

http://www.hta.ac.uk/2228

Authors' conclusions: Study found lapatinib combined with an aromatase inhibitor (AI) and trastuzumab combined with an AI to be clinically more effective than AI monotherapy for the first-line treatment of patients who have hormone receptor-positive/human epidermal growth factor 2-positive metastatic breast cancer. However, neither of these treatments are cost-effective compared with AIs alone.

Jones L, Hawkins N, Westwood M, Wright K, Richardson G, *et al*. **Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.** *Health Technol Assess* 2004;**8**(5).

http://www.hta.ac.uk/fullmono/mon805.pdf

National Institute for Health and Clinical Excellence. **Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer.** NICE Technology Appraisal guidance 263. August 2012

http://www.nice.org.uk/nicemedia/live/13869/60678/60678.pdf

Conclusions:

1.1 Bevacizumab in combination with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months.

1.2 People currently receiving bevacizumab in combination with capecitabine that is not recommended according to 1.1 should have the option to continue treatment until they and their clinician consider it appropriate to stop.

National Institute for Health and Clinical Excellence. **Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer.** NICE Technology Appraisal guidance 214. February 2011

http://www.nice.org.uk/nicemedia/live/13342/53167/53167.pdf

Authors' conclusions: NICE does not recommend bevacizumab in combination with a taxane as first treatment for people with metastatic breast cancer.

National Institute for Health and Clinical Excellence. **Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours.** NICE Technology Appraisal guidance 265. October 2012

http://www.nice.org.uk/nicemedia/live/13939/61129/61129.pdf

1.1 Denosumab is recommended as an option for preventing skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from breast cancer and from solid tumours other than prostate if: bisphosphonates would otherwise be prescribed **and** the manufacturer provides denosumab with the discount agreed in the patient access scheme.

1.2 Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer.

1.3 Adults with bone metastases from solid tumours currently receiving denosumab for the prevention of skeletal-related events that is not recommended according to 1.1 and 1.2 should be able to continue treatment until they and their clinician consider it appropriate to stop.

National Institute for Health and Clinical Excellence. **Eribulin for the treatment of locally advanced or metastatic breast cancer.** NICE Technology Appraisal guidance 250. April 2012

http://www.nice.org.uk/nicemedia/live/13710/58769/58769.pdf

Conclusions:

1.1 Eribulin is not recommended, within its licensed indication, for the treatment of

locally advanced or metastatic breast cancer that has progressed after at least

two chemotherapy regimens for advanced disease.

1.2 People currently receiving eribulin, within its licensed indication, for the

treatment of locally advanced or metastatic breast cancer that has progressed

after at least two chemotherapy regimens should have the option to continue

therapy until they and their clinicians consider it appropriate to stop.

National Institute for Health and Clinical Excellence. **Fulvestrant for the treatment of locally advanced or metastatic breast cancer.** NICE Technology Appraisal guidance 239. December 2011

http://www.nice.org.uk/nicemedia/live/13631/57558/57558.pdf

Conclusions:

1.1 Fulvestrant is not recommended, within its licensed indication, as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy.

1.2 Post-menopausal women currently receiving fulvestrant within its licensed indication as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

National Institute for Health and Clinical Excellence. ***Gemcitabine for the treatment of metastatic breast cancer***. NICE Technology Appraisal guidance 116. January 2007

**http://www.nice.org.uk/nicemedia/live/11610/33875/33875.pdf**

Authors' conclusions: Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.

National Institute for Health and Clinical Excellence. **Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormonereceptor- positive breast cancer that overexpresses HER2.** NICE Technology Appraisal guidance 257. June 2012

http://www.nice.org.uk/nicemedia/live/13777/59707/59707.pdf

Conclusions:

1.1 Lapatinib in combination with an aromatase inhibitor is not recommended for

first-line treatment in postmenopausal women with metastatic hormonereceptor-

positive breast cancer that overexpresses human epidermal growth

factor receptor 2 (HER2).

1.2 Trastuzumab in combination with an aromatase inhibitor is not recommended

for first-line treatment in postmenopausal women with metastatic hormonereceptor-

positive breast cancer that overexpresses HER2.

1.3 Postmenopausal women currently receiving lapatinib or trastuzumab in

combination with an aromatase inhibitor that is not recommended according to

1.1 or 1.2 should have the option to continue treatment until they and their

clinicians consider it appropriate to stop.

Ross J, Saunders Y, Edmonds P, Patel S, Wonderling D, *et al*. **A systematic review of the role of bisphosphonates in metastatic disease.** *Health Technol Assess* 2004;**8**(4).

http://www.hta.ac.uk/fullmono/mon804.pdf

Takeda A, Jones J, Loveman E, Tan S, Clegg A. **The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.** *Health Technol Assess* 2007;**11**(19).

http://www.hta.ac.uk/fullmono/mon1119.pdf

Conclusions: The evidence from this review may indicate that treatment with gemcitabine and paclitaxel confers an improved outcome for breast cancer patients in terms of survival and disease progression, but at the cost of increased toxicity and at an expense higher than would usually be considered cost-effective.

**NICE TAs in Development (4)**

Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) [ID523]. NICE. Expected publication date: November 2013.

Breast cancer (metastatic hormone-receptor) - lapatinib and trastuzumab (with aromatase inhibitor) [ID344]. NICE. Expected publication date: June 2012?

Breast cancer (HER2 negative, oestrogen receptor positive, locally advanced or metastatic) - everolimus (with an aromatase inhibitor) [ID538]. NICE. Expected publication date: July 2013

Breast cancer (HER2 positive, unresectable) - trastuzumab emtansine (after trastuzumab & taxane) [ID603] NICE. Expected publication date: August 2014

NICE Quality Standards (1)

NICE. Breast Cancer (QS12). September 2011 (Includes an Advanced breast cancer pathway)

**Cochrane reviews (12)**

Butters DJ, Ghersi D, Wilcken N, Kirk SJ, Mallon PT. **Addition of drug/s to a chemotherapy regimen for metastatic breast cancer.** Cochrane Database of Systematic Reviews 2010, Issue 11.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003368.pub3/pdf

Authors' conclusions: The addition of one or more drugs to the regimen shows a statistically significant advantage for tumour response in women with metastatic breast cancer but the results suggest no difference in survival time or time to progression. The positive effect on tumour

response was also associated with increased toxicity.

Carrick S, Ghersi D, Wilcken N, Simes J. **Platinum containing regimens for metastatic breast cancer.** Cochrane Database of Systematic Reviews 2004, Issue 2.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003374.pub3/pdf

Authors' conclusions: In view of the significant excess toxicity, lack of progression or survival benefit and the availability of less toxic active agents it is difficult to justify the use of platinum-containing regimens, particularly as first line treatment for women with metastatic breast cancer in routine clinical practice. Ongoing trials are examining the possibility of synergy between platins and trastuzamab, a monoclonal

antibody treatment. No randomised trials containing oxalplatin were identified for the present review.

Carrick S, Parker S, Thornton CE, Ghersi D, Simes J, Wilcken N. **Single agent versus combination chemotherapy for metastatic breast cancer.** Cochrane Database of Systematic Reviews 2009, Issue 2

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003372.pub3/pdf

Authors' conclusions: Combination chemotherapy regimens show a statistically significant advantage for survival, tumor response and time to progression in women with metastatic breast cancer but they also produce more toxicity. An unresolved question is whether combination regimens are more effective than single agents given sequentially.

Edwards AGK, Hulbert-Williams N, Neal RD. **Psychological interventions for women with metastatic breast cancer.** Cochrane Database of Systematic Reviews 2008, Issue 3.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004253.pub3/pdf

Authors' conclusions: There is insufficient evidence to advocate that group psychological therapies (either cognitive behavioural or supportive-expressive) should be made available to all women diagnosed with metastatic breast cancer. Any benefits of the interventions are only evident for some of the psychological outcomes and in the short term. The possibility of the interventions causing harm is not ruled out by the available data.

Farquhar C, Marjoribanks J, Basser R, Hetrick SE, Lethaby A. **High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer.** Cochrane Database of Systematic Reviews 2005, Issue 3.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003142.pub2/pdf

Authors' conclusions: Although there is evidence that high dose chemotherapy and autograft significantly improves event-free survival compared to conventional chemotherapy in women with metastatic breast cancer there is no significant evidence of benefit in overall survival. High dose

chemotherapy with bone marrow or stem cell transplantation should not be given to women with metastatic breast cancer outside of clinical trials.

Ghersi D, Wilcken N, Simes J, Donoghue E. **Taxane containing regimens for metastatic breast cancer**. Cochrane Database of Systematic Reviews 2005, Issue 2.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003366.pub2/pdf

Authors' conclusions: When all trials are considered, taxane-containing regimens appear to improve overall survival, time to progression and overall response in women with metastatic breast cancer. The degree of heterogeneity encountered indicates that taxane-containing regimens are more effective than some, but not all non-taxane-containing regimens.

Gibson L, Lawrence D, Dawson C, Bliss J. **Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women.** Cochrane Database of Systematic Reviews 2009, Issue 4.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003370.pub3/pdf

Authors' conclusions: In women with advanced (metastatic) breast cancer, aromatase inhibitors including those in current clinical use show a survival benefit when compared to other endocrine therapy.

Lord S, Ghersi D, Gattellari M, Wortley S, Wilcken N, Thornton CE, Simes J. **Antitumour antibiotic containing regimens for metastatic breast cancer.** Cochrane Database of Systematic Reviews 2004, Issue 4.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003367.pub2/pdf

Authors' conclusions: Compared to regimens without antitumour antibiotics, regimens that contained these agents showed a statistically significant advantage for tumour response and time to progression in women with metastatic breast cancer but were not associated with an improvement in overall survival. The favourable effect on tumour response and time to progression observed in anthracycline containing regimens was also associated with greater toxicity.

Tsao MN, Lloyd N, Wong RKS, Chow E, Rakovitch E, Laperriere N, Xu W, Sahgal A. **Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases.** Cochrane Database of Systematic Reviews 2012, Issue 4.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003869.pub3/pdf

Authors' conclusions: 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. The use of radiosensitizers or chemotherapy in conjunction with WBRT remains experimental. 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.

This updated review now includes a total of three RCTs examining the use of radiosurgery alone versus WBRT and radiosurgery. 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. The benefit of WBRT as compared to supportive care alone has not been studied in RCTs. It may be that supportive care alone, without WBRT, is appropriate for some participants, particularly those with advanced disease and poor performance status.

Wagner AD, Thomssen C, Haerting J, Unverzagt S. **Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer.** Cochrane Database of Systematic Reviews 2012, Issue 7.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008941.pub2/pdf

Authors' conclusions: The overall patient benefit from adding bevacizumab to first- and second-line chemotherapy in metastatic breast cancer can at best be considered as modest. It is dependent on the type of chemotherapy used and limited to a prolongation of PFS and response rates in both first- and second-line therapy, both surrogate parameters. In contrast, bevacizumab has no significant impact on the patient related secondary outcomes of OS or QoL, which indicate a direct patient benefit. For this reason, the clinical value of bevacizumab for metastatic breast cancer remains controversial.

Wilcken N, Hornbuckle J, Ghersi D. **Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer.** Cochrane Database of Systematic Reviews 2003, Issue 2.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002747/pdf

Authors' conclusions: In women with metastatic breast cancer and where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease.

Wong MHF, Stockler MR, Pavlakis N. **Bisphosphonates and other bone agents for breast cancer.** Cochrane Database of Systematic Reviews 2012, Issue 2.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003474.pub3/pdf

Authors' conclusions: In women with clinically evident BCBM, bisphosphonates (oral and i.v.) and denosumab (s.c.) reduced the risk of developing SREs, as well as delaying the time to SREs. Some bisphosphonates may also reduce bone pain and may improve QoL. The optimal timing and duration of treatment for patients with BCBM remains uncertain. There is currently insufficient evidence to support the routine use of bisphosphonates as adjuvant treatment for patients with EBC. However, a number of large clinical trials investigating bisphosphonates in EBC have completed accrual and are awaiting results.

**Other Systematic reviews (28)**

Al-Batran SE, Guntner M, Pauligk C, Scholz M, Chen R, Beiss B, Stopatschinskaja S, Lerbs W, Harbeck N, Jager E. **Anthracycline rechallenge using pegylated liposomal doxorubicin in patients with metastatic breast cancer: a pooled analysis using individual data from four prospective trials.** *British Journal of Cancer*.2010;103(10):1518-1523

http://www.nature.com/bjc/journal/v103/n10/full/6605961a.html

Authors' conclusions: Anthracycline rechallenge using PLD is effective in patients with MBC who have a favourable performance status, regardless of setting, resistance, cumulative dose or time since prior conventional anthracycline therapy.

Amir E, Ocana A, Seruga B, Freedman O, Clemons M. **Lapatinib and HER2 status: results of a meta-analysis of randomized phase III trials in metastatic breast cancer.** *Cancer Treatment Reviews*.2010;36(5):410-415

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12010006038/frame.html

**Authors' conclusions:** Clinical benefits from treatment with lapatinib were limited to women with human epidermal growth factor receptor 2-positive breast cancer. Women with human epidermal growth factor receptor 2-negative breast cancer should not be treated with lapatinib outside of a clinical trial setting, because of the increased toxicity and lack of benefit in disease outcome.

**CRD summary:** This review found that clinical benefits from treatment with lapatinib were limited to women with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. Lack of information about included populations, interventions and trial quality means that the reliability of the authors' conclusions is unclear and the results of the review should be interpreted with a substantial degree of caution.

Belfiglio M, Fanizza C, Tinari N, Ficorella C, Iacobelli S, Natoli C, Consorzio Interuniversitario Nazionale per la Bio-Oncologia. **Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in metastatic breast cancer.** *Journal of Cancer Research and Clinical Oncology*.2012;138(2):221-229

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12012013301/frame.html

Authors' conclusions: Combined chemotherapy with docetaxel produced a longer time to tumour progression, but had no effect on overall survival and the overall response rate for women with metastatic

breast cancer. More patients on combined therapy had diarrhoea and stomatitis. It was unlikely that any single agent or combination chemotherapy would be superior due to the varied nature of the disease.

CRD summary: This review concluded that chemotherapy combined with docetaxel versus docetaxel alone prolonged the time to tumour progression, but had no effect on overall survival and the overall response rate for women with metastatic breast cancer. The lack of good data and omissions in reporting limit interpretation, making the reliability of the authors' conclusion unclear.

Beresford M, Tumur I, Chakrabarti J, Barden J, Rao N, Makris A. **A qualitative systematic review of the evidence base for non-cross-resistance between steroidal and non-steroidal aromatase inhibitors in metastatic breast cancer.** *Clinical Oncology*.2011;23(3):209-215.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12011002024/frame.html

Authors' conclusions: This review suggested that switching from a NSAI to a SAI in patients with metastatic breast cancer was a reasonable option.

CRD summary: This review concluded that switching to the steroidal aromatase inhibitor exemestane after failure of the non-steroidal aromatase inhibitors anastrozole, letrozole and aminoglutethimide in patients with metastatic breast cancer was a reasonable option. Potential limitations in the review process, limited evidence and uncertainties about study quality mean the authors' conclusions should be treated with caution.

Berry DA, Ueno NT, Johnson MM, Lei X, Caputo J, Smith DA, Yancey LJ, Crump M, Stadtmauer EA, Biron P, Crown JP, Schmid P, Lotz JP, Rosti G, Bregni M, Demirer T. **High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: overview of six randomized trials.** *Journal of Clinical Oncology* 2011;**29**(24):3224-3231.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12011005648/frame.html

Authors' conclusions: Overall survival of patients with metastatic breast cancer in the six randomized trials was not significantly improved by high-dose chemotherapy; any benefit from high doses was small. No identifiable subset of patients seems to benefit from high-dose chemotherapy.

Bria E, Giannarelli D, Felici A, Peters W P, Nistico C, Vanni B, Cuppone F, Cognetti F, Terzoli E. **Taxanes with anthracyclines as first-line chemotherapy for metastatic breast carcinoma: pooled analysis of 2805 patients.** *Cancer*.2005;103(4):672-679.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12005004913/frame.html

Authors' conclusions: The adjunction of taxanes to anthracyclines in first-line chemotherapy for metastatic breast carcinoma yielded a significant benefit in activity (ORR, CR), a slight advantage in TTP, and a trend in OS, although with a significant cost in hematologic toxicity.

Carlini P, Bria E, Giannarelli D, Ferretti G, Felici A, Papaldo P, Fabi A, Nistico C, Di Cosimo S, Ruggeri E M, Milella M, Mottolese M, Terzoli E, Cognetti F**. New aromatase inhibitors as second-line endocrine**

**therapy in postmenopausal patients with metastatic breast carcinoma: a pooled analysis of the randomized trials.** *Cancer*.2005;104(7):1335-1342.

http://www.ncbi.nlm.nih.gov/pubmed/16088965

Authors' conclusions: This pooled analysis suggested that AIs in second-line ET for patients with MBC do not seem to add any significant benefit to MEG in terms of ORR and TTP. With regard to toxicity, the findings in the current study showed that weight gain, dyspnea, and peripheral edema are more frequent with the use of MEG, whereas hot flashes were more represented using AI.

Chua TC, Saxena A, Liauw W, Chu F, Morris DL. **Hepatic resection for metastatic breast cancer: a systematic review.** *European Journal of Cancer*.2011;47(15):2282-2290.

http://www.ejcancer.com/article/S0959-8049(11)00428-X/abstract

Authors: conclusions: Hepatectomy is rarely performed for BCLM but the studies described in this review indicate consistent results with superior 5-year survival for selected patients with isolated liver metastases and in those with well controlled minimal extrahepatic disease. To evaluate its efficacy and control for selection bias, a randomised trial of standard chemotherapy with or without hepatectomy for BCLM is warranted.

Dent S, Messersmith H, Trudeau M. **Gemcitabine in the management of metastatic breast cancer: a systematic review.** *Breast Cancer Research and Treatment*.2008;108(3):319-331.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12008104277/frame.html

Authors' conclusions: There was insufficient evidence to support the use of of gemcitabine as a routine first-line therapeutic alternative in women who are anthracycline naive and as an option in women in the third-line or greater setting. The findings suggested that gemcitabine was most beneficial in combination with a taxane as a first- or second-line treatment.

CRD summary: This study looked at the role of gemcitabine as a first-line or greater chemotherapy in women with metastatic breast cancer. The authors concluded that gemcitabine administered in combination with a taxane could be used in practice as an alternative to taxane combinations for first- or second-line treatment. Despite methodological limitations the authors' conclusions were likely to be reliable.

Ferretti G, Bria E, Giannarelli D, Felici A, Papaldo P, Fabi A, Di Cosimo S, Ruggeri E M, Milella M, Ciccarese M, Cecere F L, Gelibter A, Nuzzo C, Cognetti F, Terzoli E, Carlini P. **Second- and third-generation aromatase inhibitors as first-line endocrine therapy in postmenopausal metastatic breast cancer patients: a pooled analysis of the randomised trials**. *British Journal of Cancer*.2006;94(12):1789-1796.

http://www.ncbi.nlm.nih.gov/pubmed/16736002

Gennari A, Stockler M, Puntoni M, Sormani M, Nanni O, Amadori D, Wilcken N, D'Amico M, DeCensi A, Bruzzi P. **Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials.** *Journal of Clinical Oncology*. 2011;29(16):2144-2149.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12011003825/frame.html

Authors' conclusions: Longer duration of first-line chemotherapy was associated with clinically modest but statistically significant improvements in overall survival, and clinically meaningful and statistically significant improvements in progression-free survival in patients with metastatic breast cancer.

CRD summary: This review concluded that there were significant benefits in overall survival and progression-free survival with longer duration regimens of chemotherapy compared with shorter duration regimens in patients with metastatic breast cancer. The unknown quality of the included trials and comparisons between different treatments in the trials mean that the authors' conclusions should be interpreted with caution.

Isasi C R, Moadel R M, Blaufox M D. **A meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases.** *Breast Cancer Research and Treatment*. 2005;90(2):105-112.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12005000225/frame.html

Authors' conclusions: FDG-PET has a high diagnostic accuracy for the detection of breast cancer recurrence and can be considered a valuable tool for detecting recurrence and metastases.

CRD summary: This was a well-conducted review (with the exception of a limited search) assessing the diagnostic accuracy of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography (FDG-PET) in evaluating breast cancer recurrence and metastases. The authors reported good diagnostic accuracy, and recommend that clinicians consider using the technique and that further research be undertaken. The authors' conclusions are supported by the results presented.

Jassem J, Carroll C, Ward SE, Simpson E, Hind D. **The clinical efficacy of cytotoxic agents in locally advanced or metastatic breast cancer patients pretreated with an anthracycline and a taxane: a systematic review.** *European Journal of Cancer*.2009;45(16):2749-2758.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12009110351/frame.html

Authors' conclusions: Evidence was extremely limited on the efficacy of chemotherapy regimens currently available in Europe for treating women with locally advanced or metastatic breast cancer previously treated with a taxane and anthracycline.

CRD summary: The review found that evidence was extremely limited on the efficacy of chemotherapy regimens currently available in Europe for women with locally advanced or metastatic breast cancer previously treated with a taxane and anthracycline. Although there was some possibility that foreign language studies were missed, the review was well conducted in most respects and the authors' cautious conclusions appear reliable.

Li L, Li J, Yang K, Tian J, Sun T, Jia W, Zhang P, Yi K. **Ixabepilone plus capecitabine with capecitabine alone for metastatic breast cancer.** *Future Oncology*.2010;6(2):201-207

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12010003759/frame.html

Authors' conclusions: Compared with capecitabine alone, ixabepilone plus capecitabine demonstrated clinical activity with an acceptable safety profile in patients with locally-advanced breast cancer.

CRD summary: The authors concluded that compared with capecitabine alone, ixabepilone plus capecitabine demonstrated a clinical activity with an acceptable safety profile in patients with locally-advanced breast cancer. There were concerns with trial quality and comparability, so caution is warranted when interpreting the authors' conclusions.

Li Y L, Xiao J L, Yang K H, Ma B. **Capecitabine plus docetaxel for metastatic breast cancer: a systematic review.** *Chinese Journal of Evidence-Based Medicine*.2009;9(8):893-898.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12009108212/frame.html

Li YZ, Ma B, Yang KH, Zhou HQ. **Diagnostic value of MRI versus bone scan for osseous metastasis in breast cancer: a meta-analysis.** *Chinese Journal of Evidence-Based Medicine*.2010;10(10):1159-1163.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12010007820/frame.html

Liu T, Cheng T, Xu W, Yan WL, Liu J, Yang HL. **A meta-analysis of 18FDG-PET, MRI and bone scintigraphy for diagnosis of bone metastases in patients with breast cancer.** *Skeletal Radiology*.2011;40(5):523-531.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12011002797/frame.html

Authors' conclusions: Magnetic resonance imaging was found to be better than 18FDG-PET and bone scintigraphy for diagnosis of bone metastases in patients with breast cancer on a per-patient basis. On a per-lesion basis, 18FDG-PET had lower sensitivity and higher specificity than bone scintigraphy.

CRD summary: This review concluded that magnetic resonance imaging was better than 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) and bone scintigraphy for diagnosis of bone metastases in breast cancer (per-patient basis). 18FDG-PET had lower sensitivity and higher specificity than bone scintigraphy (per-lesion basis). Caution is needed in interpretation due to the small number and size of included studies.

Loibl S, Skacel T, Nekljudova V, Luck HJ, Schwenkglenks M, Brodowicz T, Zielinski C, von Minckwitz G. **Evaluating the impact of Relative Total Dose Intensity (RTDI) on patients' short and long-term outcome in taxane- and anthracycline-based chemotherapy of metastatic breast cancer: a pooled analysis.** *BMC Cancer*.2011;11:131

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12011003465/frame.html

Authors' conclusions: RTDI above 85% appeared to improve long term outcomes in patients with metastatic breast cancer who received taxane or anthracycline based chemotherapy regimens.

CRD summary: This meta-analysis examined the impact of dose reductions and delays in patients with metastatic breast cancer who received taxane or anthracycline based chemotherapy. The authors concluded that reductions or delays should only be undertaken for important reasons as relative total dose intensity (actual dose/planned dose) above 85% improved outcomes. Methodological limitations indicate that these conclusions are not reliable.

Mannocci A, De Feo E, de Waure C, Specchia ML, Gualano MR, Barone C, Ricciardi W, La Torre G. **Use of trastuzumab in HER2-positive metastatic breast cancer beyond disease progression: a systematic review of published studies.** *Tumori*.2010;96(3):385-391

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12010006028/frame.html

Authors' conclusions: Trastuzumab-based regimens might have activity in HER2+ metastatic breast cancer beyond progression, but only well-designed phase III studies would possibly identify patients who would progress after trastuzumab by keeping in mind other drugs that potentially targeted the same biological pathway.

CRD summary: This review investigated the efficacy of trastuzumab-based treatments beyond progression in HER2-positive metastatic breast cancer and found that trastuzumab-based regimens might have a role and well-designed phase III trials were needed. The authors' conclusions are cautious, but given the limitations (particularly the inclusion of observational studies and only one RCT) these conclusions may not be reliable.

Members of the Breast Cancer Disease Site Group. **The role of the taxanes in the management of metastatic breast cancer.** Hamm C, Tey R, reviewers. Toronto (ON): Cancer Care Ontario; 2011 Sep 15 [Archived 2010 Jun 11]. Program in Evidence-based Care Evidence-Based Series No.: 1-3 Archived 2010.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12004008011/frame.html

https://www.cancercare.on.ca/common/pages/UserFile.aspx?serverId=6&path=/File%20Database/CCO%20Files/PEBC/pebc1-3f.pdf

Authors' conclusions: In patients without previous anthracycline exposure there is little evidence that single-agent paclitaxel is superior to doxorubicin. For patients who have already been treated with anthracycline, there is only weak evidence for paclitaxel but some evidence that docetaxel is an effective treatment in anthracycline-resistant metastatic breast cancer. There is a lack of evidence from direct comparisons, which makes it difficult to recommend one drug over the other.

CRD summary: The authors recommended the use of docetaxel with or without doxorubicin for women who have never previously received anthracyclines, and docetaxel or paclitaxel treatment for those with prior anthracycline use. The poor reporting of review methods and lack of a quality assessment make it difficult to assess the reliability of the authors' conclusions.

Pan L, Han Y, Sun X, Liu J, Gang H. **FDG-PET and other imaging modalities for the evaluation of breast cancer recurrence and metastases: a meta-analysis.** *Journal of Cancer Research and Clinical Oncology*.2010;136(7):1007-1022.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12010004592/frame.html

Authors' conclusions: MRI appeared to be a more useful supplement to surveillance techniques to assess patients with suspected recurrent and/or metastatic breast cancer. If MRI showed an indeterminate or benign lesion or MRI was not applicable, PET could be performed in addition.

CRD summary: The authors concluded that magnetic resonance imaging appeared to be a more useful supplement to surveillance techniques to assess patients with suspected recurrent and/or metastatic breast

cancer. These conclusions should be interpreted with some caution due to the possibility of missed studies, lack of analysis based on direct comparisons and small size and methodological limitations of the included studies

Riemsma R, Forbes CA, Kessels A, Lykopoulos K, Amonkar MM, Rea DW, Kleijnen J. **Systematic review of aromatase inhibitors in the first-line treatment for hormone sensitive advanced or metastatic breast cancer.** *Breast Cancer Research and Treatment*.2010;123(1):9-24.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12010006377/frame.html

Authors' conclusions: There were no significant differences between aromatase inhibitors in the outcomes overall survival and progression-free survival; therefore, a class effect for all aromatase inhibitors was possible. These results were based on indirect comparisons and a network analysis for which the assumptions of homogeneity, similarity and consistency were not fulfilled; therefore, the results must be interpreted with caution.

CRD summary: This well-conducted review reliably concluded that although there were no significant differences between letrozole, anastrozole and exemestane in overall survival and progression-free survival for hormone-sensitive advanced or metastatic breast cancer in postmenopausal women, basic assumptions were not fulfilled for the indirect comparisons and network analysis and so the results must be interpreted with caution.

Shen JJ, Hu SL, Shen G, Xu TJ, Chen Y, Wu L, Xu WP. **Lapatinib plus adjuvant chemotherapy for metastatic and HER-2 positive advanced breast cancer patients: a meta-analysis.** *Chinese Journal of Cancer Prevention and Treatment*.2010;17(24):2038-2041.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12011003497/frame.html

Shie P, Cardarelli R, Brandon D, Erdman W, Rahim N A**. Meta-analysis: comparison of F-18 fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastases in patients with breast cancer.** *Clinical Nuclear Medicine*.2008;33(2):97-101.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12008103056/frame.html

Authors' conclusions: Whether FDG-PET or BS is superior in detecting osseous metastases from breast cancer remained inconclusive. However, FDG-PET had a higher specificity than BS and may be a better confirmatory test. FDG-PET could potentially be used to monitor response to therapy.

CRD summary: This review evaluated F-18 Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) and bone scintigraphy (BS). The authors concluded that it was unclear which was superior, although FDG-PET had greater specificity and may be a better confirmatory test. The reliability of the conclusion is unclear due to poor reporting of the analysis and the quality of the evidence available.

Valachis A, Polyzos NP, Patsopoulos NA, Georgoulias V, Mavroudis D, Mauri D. **Bevacizumab in metastatic breast cancer: a meta-analysis of randomized controlled trials.** *Breast Cancer Research and Treatment*.2010;122(1):1-7.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12010007816/frame.html

Authors' conclusions: The addition of bevacizumab to chemotherapy was associated with improvement in progression free survival and objective response rate in patients with metastatic breast cancer.

CRD summary: The authors concluded that the addition of bevacizumab to chemotherapy was associated with improvement in progression free survival and objective response rate in patients with metastatic breast cancer. The conclusions appear reliable, but small sample sizes and incomplete reporting of review processes suggest a need for some caution.

van Wely BJ, Teerenstra S, Schinagl DA, Aufenacker TJ, de Wilt JH, Strobbe LJ. **Systematic review of the effect of external beam radiation therapy to the breast on axillary recurrence after negative sentinel lymph node biopsy.** *British Journal of Surgery*.2011;98(3):326-333.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12011001501/frame.html

Authors' conclusions: External beam radiation therapy to the breast was associated with a significantly lower axillary recurrence rate after negative sentinel lymph node biopsy.

CRD summary: The review concluded that external beam radiation therapy to the breast was associated with a statistically significantly lower axillary recurrence rate after negative sentinel lymph node biopsy. The review was based on observational studies of uncertain quality, which makes the reliability of the authors' conclusion unclear.

Wang Y, Yao HR, Su FX. **Meta-analysis of continuing trastuzumab therapy in pretreated metastatic breast cancer progressing after trastuzumab therapy.** *Chinese Journal of Cancer Prevention and Treatment*.2011;18(17):1321-1324.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12012010009/frame.html

Wilcken N, Dear R. **Chemotherapy in metastatic breast cancer: a summary of all randomised trials reported 2000-2007.** *European Journal of Cancer*.2008;44(15):2218-2225.

http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12009101123/frame.html

Authors' conclusions: There was little evidence from trials that reported between 2000 and 2007 that there were major survival differences between many commonly employed chemotherapy regimens for metastatic breast cancer.

CRD summary: This review concluded that there was little evidence from trials that reported between 2000 and 2007 that there were major survival differences between many commonly employed chemotherapy regimens for metastatic breast cancer. This conclusion reflects the results of the review, but the comprehensiveness of the review and reliability of the included trials are unclear.

## Medline search for RCTs

Medline search strategy

29/04/13

1. exp Neoplasm Metastasis/

2. exp Breast Neoplasms/

3. (metasta* adj6 breast).tw.

4. (advanced adj6 breast).tw.

5. (recurr* adj6 breast).tw.

6. 1 and 2

7. or/3-6

Combined with SIGN RCT search filter; limits: English language, date range 2003-2013

Results retrieved = 4516