Evidence Based Clinical Practice Guidelines on the Diagnosis and Management of Breast Cancer.
Part II.Locally Advanced Breast Cancer, Locally Recurrent Breast Cancer, and Metastatic Breast Cancer

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STARTER STATEMENT

This information, based on the Philippine College of Surgeons (PCS) Clinical Practice Guidelines, is intended to assist doctors and patients in the management of breast cancer. The PCS Clinical Practice Guidelines were developed by a diverse panel of experts. The guidelines are a statement of the Philippine College of Surgeons regarding the scientific evidence and its views of currently accepted approaches to treatment.

These guidelines are not intended to replace, but to assist the expertise and clinical judgment of physicians on the management of individual patients. Each patient's situation must be evaluated individually. It is important to discuss the guidelines and all information regarding treatment options with the patient.

EXECUTIVE SUMMARY

The clinical area identified by the Philippine College of Surgeons (PCS) for the third evidence – based clinical practice guidelines (EBCPGs) was on the management of breast cancer. Funding for the research project was provided by the Philippine Council for Health Research and Development (PCHRD). A Technical Working Group (TWG) was formed, composed of 6 general surgeons and 1 medical oncologist. The TWG was tasked to identify the clinical questions and to adhere to the PCS approved method of developing EBCPGs. The TWG divided the report into two parts: Part I. Early Breast Cancer, Part II. Locally Advanced Breast Cancer, Locally Recurrent Breast Cancer, and Metastatic Breast Cancer. The report on Part I. Early Breast Cancer has been published (Philipp J Surg Spec 2001; 56 (1) : 7-30) .

The TWG began work on part II of the EBCPG on breast cancer in January 2001. Electronic search of the Medline, Cochrane (Issue 2, 2001), and Herdin (version I, 1997) databases were done using the search (MeSH) terms locally advanced breast cancer, local recurrence in breast cancer, and metastatic breast cancer and treatment.

For locally advanced breast cancer, the search was limited to English publications, reviews, randomized controlled trials (RCTs), and clinical trials. There were no meta-analyses or systematic overviews found. A manual search was also done using the reference lists of the relevant articles. For locally recurrent breast cancer, the search was limited to RCTs, cohort studies,case series reports and review articles in the English language. There were also no meta-analyses or systematic overviews found. Reference lists of the relevant articles were likewise manually searched. For metastatic breast cancer, the search was limited to RCTs and meta analyses in the English language.Manual searching of the reference list of the meta-analyses and important RCTs were also done.

The primary outcome of interest for the treatment options was survival (overall and disease free). Complications of treatment and morbidity rates were also included for aggressive chest wall resection for local recurrence because it was deemed important to discourage its practice as standard treatment. Impact on survival was also the main outcome of interest on the question regarding metastatic work-up in locally advanced breast cancer. For the clinical questions on detection and diagnosis of locoregional recurrence, test characteristics of the various procedures were reported as secondary outcomes of interest. However, and more importantly, studies which showed their impact on survival were also reported.

The TWG classified the evidence according to three levels and proposed a first draft of recommendations according to three categories:

LEVELS OF EVIDENCE

I. Evidence from at least one properly designed randomized controlled trial or meta-analysis.

II. Evidence from at least one well – designed clinical trial without proper randomization, from prospective cohort or case – control analytic studies (preferably from one center), from multiple time – series studies, or from dramatic results in uncontrolled experiments.

III. Evidence from opinions of respected authorities on the basis of clinical experiences, descriptive studies, or reports of expert committees.

CATEGORIES OF RECOMMENDATIONS

Category A : Recommendations that were approved by consensus (75 % of the multisectoral expert panel)

Category B : Recommendations that were somewhat controversial and did not meet consensus.

Category C : Recommendations that caused real disagreements among members of the panel.

The following clinical questions were formulated:

A. Locally Advanced Breast Cancer

1. What is the operational definition of the term "locally advanced breast cancer "?

2. Is it necessary to perform intensive metastatic work-up for asymptomatic patients with locally advanced breast cancer? What is the magnitude of the survival benefit, if any?

3. What are the benefits in terms of disease free survival (DFS) and overall survival of locoregional treatment /s (surgery, radiotherapy, or surgery plus radiotherapy) in locally advanced breast cancer?

4. What are the benefits in terms of disease free survival (DFS) and overall survival of systemic treatments (hormonal and / or chemotherapy) in locally advanced breast cancer?

B. Locally Recurrent Breast Cancer

1. What are the methods currently used for the early detection of locoregional recurrence (LRR) and what are their test characteristics?

2. What is the impact on survival of early detection of LRR?

3. What are the methods currently used for the diagnosis of LRR and what are their test characteristics?

4. What are the benefits in terms of disease free survival (DFS) and overall survival of locoregional treatments (surgery and/or radiotherapy) in locally recurrent breast cancer?

5. Will adding systemic treatment (chemotherapy, hormonal therapy, or combination of both) improve recurrence free and overall survival after potentially curative local treatment of isolated LRR?

C. Metastatic Breast Cancer

1. Does systemic chemotherapy or hormonal therapy confer a survival benefit for patients with metastatic breast cancer ? If so, what is the magnitude of the survival benefit?

2. Which is the better initial treatment modality for metastatic breast cancer: systemic chemotherapy or hormonal therapy?

3. What are the survival benefits of the different hormonal therapies in metastatic breast cancer?

4. What are the survival benefits of the different chemotherapy regimens in metastatic breast cancer?

5. Will the addition of chemotherapy to hormonal therapy or the addition of hormonal therapy to chemotherapy confer a survival benefit for patients with metastatic breast cancer?

6. Are there other treatments which have shown survival or palliative benefits in metastatic breast cancer? If so, what are these modalities and what are their survival or palliative benefits, if any?

The TWG prepared a first draft of the manuscript which consisted of a summary of the strongest evidence associated with the clinical questions and suggested recommendations. The first draft was discussed and modified by a Panel of Experts convened by the PCS on September 22, 2001 at the PCS building. A second draft was prepared by the TWG and this was discussed in a Public Forum on December 5, 2001 during the 57th Clinical Congress of the PCS held at the EDSA Shangrila Hotel. The guidelines were then approved by the PCS Board of Regents on January 5, 2002.

Recommendations

A. Locally Advanced Breast Cancer

1. *Breast cancer cases which are included in the definition of the Early Breast Cancer Trialists Collaborative Group (EBCTCG), namely cases wherein cancer is restricted to the breast and, in the case of node positive patients, the local lymph nodes can be removed surgically, should be managed according to the PCS evidence based clinical practice guidelines on early breast cancer (Philipp J Surg Spec 2001; 56(1):7-36). (Level I, Category A)*

2. *The term "locally advanced breast cancer" shall from now on be used for cases that are not considered early breast cancer and have no evidence of distant metastasis. This will comprise T4 tumors or stage IIIB cases. (Level II, Category A)*

3. *Diagnostic tests for detection of distant metastases in patients with locally advanced breast cancer should be individualized and symptom-directed; and not done routinely. Physicians should do exhaustive search for clinical evidence of distant metastases by doing thorough history and physical examination.(Level II, Category B)*

4. *There seems to be some evidence that for locally advanced breast cancer, the use of systemic therapy and radiotherapy may increase survival, but the size and duration of the benefit is unclear.(Level II, Category A)*

5. *In some cases, neoadjuvant systemic therapy may reduce primary tumor size to such an extent that may permit mastectomy or even breast conserving surgery. (Level II, Category A)*

B. Locally Recurrent Breast Cancer

1. *Physical examination alone adequately detects locoregional recurrence due to breast cancer in most cases. (Level II, Category A)*

2. *Periodic follow-up aimed at early detection of local recurrences of breast cancer may be recommended, although the prognostic impact of such a policy is probably limited. (Level II, Category A)*

3. *Cytologic or histologic documentation of recurrent disease should be obtained whenever possible, prior to active treatment. (Level III, Category A)*

4. *Core needle biopsy (CNB) is the initial diagnostic procedure in breast cancer patients with a palpable locoregional recurrence. (Level III, Category A)*

5. *Open biopsy, whenever possible, may be done for histologic documentation of recurrent disease when the initial CNB yields unsatisfactory results.(Level III, Category A)*

6. *The determination of estrogen receptor (ER) status of the local recurrence is encouraged. However, women with locally recurrent breast cancer with unknown estrogen receptor status are managed as estrogen receptor positive tumors. (Level III, Category A)*

7. *Metastatic work up to evaluate extent of disease is recommended prior to treatment for recurrent breast cancer. (Level III, Category A)*

8. *Salvage mastectomy is the standard treatment for locoregional control of recurrence after breast conservation treatment. (Level II, Category A)*

9. *Radiotherapy is given for locoregional control of locally recurrent breast cancer appearing after initial treatment with mastectomy. (Level II, Category A)*

10. *Surgical resection of local soft tissue recurrence after initial treatment with mastectomy may be done prior to radiotherapy, for local recurrences measuring 3 centimeters or less, which could be excised completely and safely, recurring 2 years or more after primary treatment. (Level II, Category A)*

11. *Aggressive chest wall resection of locally recurrent breast cancer is not recommended because it carries a high morbidity rate and there is no proven survival benefit. (Level II, Category A)*

12. *For patients with locally recurrent breast cancers which are estrogen receptor positive, hormonal therapy is the initial systemic treatment given. (Level I, Category A)*

13. *Tamoxifen is the preferred first-line hormonal therapy for patients with locally recurrent breast cancers which are estrogen receptor positive.(Level I, Category A) Tamoxifen is given at a dose of 20 mg daily and is given continuously even if there is complete response, until disease progression. (Level III, Category A)*

14. *For elderly postmenopausal women with long disease free interval (≥ 2 years between primary treatment and local recurrence) whose recurrence is confined to skin and soft tissue, locoregional treatment may not be done and tamoxifen alone may be given. (Level III, Category A)*

15. *For patients with locally recurrent breast cancers which are estrogen receptor negative, chemotherapy may increase survival but the size and duration of the benefit is unclear. (Level II, Category A)*

C. Metastatic Breast Cancer

1. *The primary goal of therapy for patients with metastatic breast cancer is palliation. Palliative care is the active total care of patients whose disease is no longer responsive to curative treatment. The goal of palliative care is achievement of the best possible quality of life for patients and their families. Control of pain and of other symptoms, and alleviation of psychological, social, and spiritual problems are paramount. (Level III , Category A)*

2. *The WHO method of cancer pain relief should be immediately started for all patients with metastatic breast cancer who complain of pain. (Level III , Category A)*

3. *In general, for patients with metastatic breast cancer, systemic chemotherapy may be offered because it has been shown to confer a modest survival benefit of 6-9 months. (Level II, Category A)*

4. *The determination of estrogen receptor (ER) status of the metastatic lesion is encouraged. However, patients with metastatic breast cancer with unknown estrogen receptor status are managed as estrogen receptor positive tumors. (Level III, Category A)*

5. *For patients with metastatic breast cancer which are estrogen receptor positive, hormonal therapy is the initial systemic treatment given. (Level II, Category A)*

6. *Tamoxifen is the preferred first-line hormonal therapy for patients with metastatic breast cancer which are estrogen receptor positive. (Level I, Category A) Tamoxifen is given at a dose of 20 mg daily and is given continuously, even if there is complete response, until disease progression.(Level I, Category A)*

7. *Patients with metastatic breast cancer who responded to tamoxifen initially are offered second line hormonal therapies at the time of disease progression. (Level I, Category A)*

8. *For patients with metastatic breast cancer which are estrogen receptor negative, chemotherapy may increase survival but the size and duration of the benefit is unclear. (Level II, Category A)*

9. *There is no survival benefit among the different polychemotherapy regimens. Continued therapy until disease progression is better compared to limited therapy. However, drug toxicity and complications of chemotherapy should be given serious consideration bearing in mind that palliation of symptoms and not tumor response is the main goal of therapy. (Level I, Category A)*

10. *The addition of chemotherapy to hormonal therapy does not confer a survival benefit for patients with metastatic breast cancer who are already responding to hormonal therapy. Likewise, the addition of hormonal therapy to chemotherapy does not confer a survival benefit for patients with metastatic breast cancer who are already responding to chemotherapy. (Level I, Category A)*

11. *Radiotherapy may be given to symptomatic patients with bone metastases for relief of symptoms. (Level I, Category A)*

12. *For patients with bone metastases, bisphosphonates may be given because they reduce the incidence of skeletal complications and decrease pain medication requirements; however, no survival benefit has been observed. (Level I, Category A)*

Technical Working Group

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3. Ray B. Malilay (general surgeon, PCS Board of Regents, Philippine Society of General Surgeons)
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BACKGROUND

The Philippine College of Surgeons (PCS) had identified the development, dissemination and implementation of evidenced - based clinical practice guidelines (EBCPG), as an important strategy in improving surgical care, training and research. The Philippine Council for Health Research and Development (PCHRD) of the Department of Science and Technology (DOST) had also identified the development of EBCPGs as one of the top priorities in the national research agenda, and in 1999 the DOST – PCHRD, PCS and the Department of Surgery of the University of the Philippines Manila College of Medicine signed a trilateral Memorandum of Agreement on the development of EBCPGs on certain areas of surgical care in the Philippines. These areas of surgical care should be those wherein current practice may not be truly evidence- based, which have a large potential of improving major outcomes and even decreasing costs; furthermore, the EBCPGs should be implementable nationwide in both government and private health facilities. The first PCS-EBCPG was on seeking referral for perioperative cardiac evaluation for noncardiac surgery and when the intraoperative presence of a cardiologist / internist would be beneficial.[1] The second PCS – EBCPG was on some important aspects in the care of critically ill surgical patients. [2]

This project is the third PCS EBCPG and aims to produce guidelines on the diagnosis and management of breast cancer.

Breast cancer had consistently been the most common cancer among Filipino women. With an age – standardized incidence rate (ASR) of 47.7 per 100,000 women (1998), it was second only to lung cancer when both male and female cancers were considered. ASRs had increased (1980-1992), and ASRs of female residents in highly urbanized cities in Metro Manila were already similar to some populations in Europe, South America and Oceania. One out of 28 Filipinos who live up to 64 years, and one of 19 who live up to 74 years will have breast cancer.[3] In 1998, an estimated 9,325 new cases would have occured in the country.[4]

In the absence of evidence – based clinical practice guidelines, there exists wide variations regarding important aspects in the diagnosis and management of breast cancer. These "controversies" continue to have a serious impact on the quality of care, as well as on the judicious utilization of resources. Furthermore, owing to the large number of publications on breast cancer in the medical literature, in lay periodicals, as well as on the internet, incomplete or even erroneous information may be provided to physicians and patients leading to wrong perceptions that seriously affect the management of breast cancer.

METHODS

The PCS appointed a Technical Working Group (TWG) composed of 6 general surgeons and 1 medical oncologist. The group was instructed to adhere to the methods used in the development of the guidelines used on the first two PCS EBCPGs (Roxas 1999, Laudico 2000) . The group was also given a free hand to formulate the specific clinical questions on areas considered important in the diagnosis and management of breast cancer. The TWG decided to divide the report into 2 parts: Part I. Early Breast Cancer and Part II. Locally Advanced Breast Cancer, Locally Recurrent Breast Cancer and Metastatic Breast Cancer. The report on Part I. Early Breast Cancer has been published (Philipp J Surg Spec 2001; 56(1):7-30).

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For locally advanced breast cancer, the search was limited to reviews, randomized controlled trials (RCTs), and clinical trials in the English language. There were no meta-analyses or systematic overviews found. A manual search was also done using the reference lists of the relevant articles. There were 299 titles obtained, out of which 206 were chosen for review of abstracts. Only 43 full text articles were retrieved and appraised, and 10 articles were chosen for the final paper.

For locally recurrent breast cancer the search was limited to RCTs, cohort studies,case series reports and review articles in the English language. There were also no meta-analyses or systematic overviews found. A manual search was also done using the reference lists of the relevant articles. There were 288 titles obtained from the Medline and 28 articles in the Cochrane Library, out of which 173 were chosen for review of abstracts. Seventy one full text articles were retrieved and appraised, 31 articles were chosen as the evidence in the formulation of the recommendations.

For metastatic breast cancer the search was limited to RCTs and meta analyses in the English language.The search yielded 504 titles from the Cochrane Library and 6,326 titles from Pubmed. There were 12 meta analyses and 470 RCTs. Sixty seven titles were chosen for review of abstracts, 33 full text articles were retrieved and appraised and 20 articles were chosen for the final paper.

The primary outcome of interest for the treatment options was survival (overall and disease free). Complications of treatment and morbidity rates were also included for aggressive chest wall resection for local recurrence because it was deemed important as to discourage its practice as standard treatment. Impact on survival was also the main outcome of interest on the question regarding metastatic work-up in locally advanced breast cancer. For the clinical questions on detection and diagnosis of locoregional recurrence, test characteristics of the various procedures were reported as secondary outcomes of interest. However, and more importantly, studies which showed their impact on survival were also reported.

The TWG then compiled, summarized and classified the evidence according to 3 levels and proposed a first draft of recommendations according to 3 categories:

LEVELS OF EVIDENCE

I. Evidence from at least one properly designed randomized controlled trial or meta-analysis.

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III. Evidence from opinions of respected authorities on the basis of clinical experiences, descriptive studies, or reports of expert committees.

CATEGORIES OF RECOMMENDATIONS

Category A : Recommendations that were approved by consensus (75 % of the multisectoral expert panel)

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Category C : Recommendations that caused real disagreements among members of the panel.

The following clinical questions were formulated:

A. Locally Advanced Breast Cancer

1. What is the operational definition of the term "locally advanced breast cancer "?

2. Is it necessary to perform intensive metastatic work-up for asymptomatic patients with locally advanced breast cancer? What is the magnitude of the survival benefit, if any?

3. What are the benefits in terms of disease free survival (DFS) and overall survival of locoregional treatment /s (surgery, radiotherapy, or surgery plus radiotherapy) in locally advanced breast cancer?

4. What are the benefits in terms of disease free survival (DFS) and overall survival of systemic treatments (hormonal and / or chemotherapy) in locally advanced breast cancer?

B. Locally Recurrent Breast Cancer

1. What are the methods currently used for the early detection of locoregional recurrence (LRR) and what are their test characteristics?

2. What is the impact on survival of early detection of LRR?

3. What are the methods currently used for the diagnosis of LRR and what are their test characteristics?

4. What are the benefits in terms of disease free survival (DFS) and overall survival of the following locoregional treatments (surgery and/or radiotherapy) in locally recurrent breast cancer?

5. Will adding systemic treatment (chemotherapy, hormonal therapy, or combination of both) improve recurrence- free and overall survival after potentially curative local treatment of isolated LRR?

C. Metastatic Breast Cancer

1. Does systemic chemotherapy or hormonal therapy confer a survival benefit for patients with metastatic breast cancer ? If so, what is the magnitude of the survival benefit?

2. Which is the better initial treatment modality for metastatic breast cancer: systemic chemotherapy or hormonal therapy?

3. What are the survival benefits of the different hormonal therapies in metastatic breast cancer?

4. What are the survival benefits of the different chemotherapy regimens in metastatic breast cancer?

5. Will the addition of chemotherapy to hormonal therapy or the addition of hormonal therapy to chemotherapy confer a survival benefit for patients with metastatic breast cancer?

6. Are there other treatments which have shown survival or palliative benefits in metastatic breast cancer? If so, what are these modalities and what are their survival or palliative benefits, if any?

Results

A. Locally Advanced Breast Cancer

1. What is the operational definition of the term "locally advanced breast cancer "?

Locally advanced breast cancer (LABC) has been defined by many investigators as T3-4 primary cancer or N2-3 lymph node metastases. This includes Stages IIB, IIIA and IIIB of the UICC/AJCC Staging System and overlaps with the definition of early breast cancer by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) which includes Stages I – IIIA. This definition of early breast cancer has been adopted by the PCS, and used in Part I of the PCS Clinical Practice Guidelines on Breast Cancer. The lack of a globally standardized definition of LABC is a major cause of controversy regarding its treatment. It also supports the EBCTCG definition of early breast cancer which will include most stage IIIA cases whose relative 5-year survival probability was 56 per cent. In contrast, stage IIIB cases, many of which will be excluded from the EBCTCG definition of early breast cancer had a lower 5-year relative survival probability of 49 per cent. Table 1 shows American registry data on relative 5-year survival by stage.[5] These data show the broad range of survival rates among patients who are included in the many definitions of locally advanced breast cancer.

Breast cancer cases which are neither covered by the EBCTCG definition of "early breast cancer", nor satisfy the criteria for metastatic breast cancer, will now be labeled "locally advanced breast cancer". Essentially, this will comprise T4 tumors or Stage III B cases .

Recommendations:

1. *Breast cancer cases which are included in the definition of the Early Breast Cancer Trialists Collaborative Group (EBCTCG), namely cases wherein cancer is restricted to the breast and, in the case of node positive patients, the local lymph nodes can be removed surgically, should be managed according to the PCS evidence based clinical practice guidelines on early breast cancer (Philipp J Surg Spec 2001; 56(1):7-36). (Level I, Category A)*

2. *The term "locally advanced breast cancer" shall from now on be used for cases that are not considered early breast cancer and have no evidence of distant metastasis. This will comprise T4 tumors or stage IIIB cases.(Level II, Category A)*

2. Is it necessary to perform intensive metastatic work-up for asymptomatic patients with locally advanced breast cancer? What is the magnitude of the survival benefit, if any?

A retrospective study by Ciatto[6] in 1985 reported on a consecutive series of 3,627 histologically confirmed breast cancer patients who underwent preoperative staging examinations in 11 Italian centers from 1973-1985. Of the 3,627 cases, there were 265 Stage IIIA and 417 Stage III B patients who underwent tests consisting of chest x-ray, bone x-ray, bone scan , and liver echography. The detection rate of asymptomatic distant

metastases on these examinations are shown in Table 2. Detection rates were around 1 to 2 per cent.

It was also shown that to detect one case of asymptomatic distant metastasis, a large number of examinations had to be done. Table 3 shows that for Stage IIIB cases, it will take 83 chest x-rays and 75 bone scans to detect one metastasis.

After searching the literature, no study was found which addressed the issue of, or which provided evidence that early detection of distant metastases resulted in an improvement in survival. However, since detection of distant metastases in a patient with locally advanced breast cancer could change management, and since most reviews [7, 8] would still conclude that majority of breast cancer patients with distant metastases have some clinical sign or symptom; physicians are advised to do exhaustive search for clinical evidence of distant metastases by doing thorough history and physical examination. Requesting for metastatic work-up for patients with locally advanced breast cancers should be individualized and done on a case to case basis.

Recommendation:

3. *Diagnostic tests for detection of distant metastases in patients with locally advanced breast cancer should be individualized and symptom-directed; and not done routinely. Physicians should do exhaustive search for clinical evidence of distant metastases by doing thorough history and physical examination. (Level II, Category B)*

3. What are the benefits in terms of disease free survival (DFS) and overall survival of locoregional treatment /s (surgery, radiotherapy, or surgery plus radiotherapy) in locally advanced breast cancer?

The management of LABC has evolved from no treatment to locoregional therapies to the multimodal therapy that is favored by most breast centers today. There are only few clinical trials that compare purely locoregional with a combination of locoregional and systemic therapies and they have small sample sizes. There are also a number of reported case series on multimodal therapy which are uncontrolled. A review of studies before the advent of systemic therapies may allow some indirect comparisons.

It would seem worthwhile to look at data from untreated cases of locally advanced breast cancer to realize the impact of present treatment. Bloom et al[9] examined the natural history of 250 untreated breast cancer patients who were admitted to Middlesex Hospital from 1805-1933. Two hundred forty four (97.6%) of these patients were either Stage III (58) or Stage IV (186) based on the Manchester classification. Stage III was defined as tumor invading the skin or underlying muscle with or without movable axillary nodes and Stage IV as tumor fixed to chest wall, matted axillary nodes, deposits in supraclavicular nodes or distant metastases. All patients died in the hospital and were subjected to necropsy. Survival, measured from time of onset of symptoms was 18 per cent at 5 years, 4 per cent at 10 years and 0.8 per cent at 15 years with a median survival of 2.7 years.[9]

Hortobagyi and Buzdar[10] summarized the data from more than 30 studies of LABC that were treated by locoregional therapy alone. No significant difference was noted between the mean survival at 5 and 10 years for patients treated by surgery, radiotherapy or surgery plus radiotherapy. Five year and 10 year survival rates for all treatments were approximately 32 per cent and 20 per cent , respectively. There were however, wide ranges in survival statistics which may be due to variations in number of patients and staging accuracy. Survival ranged from 3 to 61 per cent for surgery alone, 1 to 66 per cent for radiotherapy alone and 12 to 53 per cent for combined surgery and radiotherapy. Median disease-free survival was 8-12 months and median survival approximately 24 months or 2 years.

Indirect comparison with natural history data suggests that locoregional treatment does not produce improvement in survival. It must be emphasized however, that there are numerous limitations to using historical controls, particularly those that are based on retrospective data. Furthermore, Bloom's survival data was measured from onset of symptoms, and not from date of diagnosis.

4. What are the benefits in terms of disease free survival (DFS) and overall survival of systemic treatments (hormonal and / or chemotherapy) in locally advanced breast cancer?

The results of three randomized controlled trials on combined locoregional and systemic therapies are summarized in Table 4. Olson et al for the Eastern Cooperative Oncology Group (ECOG)[11] reported on the role of radiotherapy in the management of "operable locally advanced breast cancer". After undergoing mastectomy, 383 patients were treated with 6 courses of chemohormonal therapy. Fifty three per cent were Stage IIIA and 40 per cent Stage IIIB. Three hundred twelve patients who remained without recurrence after mastectomy and chemohormonal therapy were then randomized to receive radiotherapy of 46 gray over 4 ½ weeks to the chest wall and regional lymph node areas or to observation alone. One hundred sixty four patients were randomized to radiotherapy and 148 to observation. Patients in the observation arm who developed locoregional recurrence with no distant metastases were offered radiotherapy but were analyzed according to their original randomization. After 9.1 years of median follow up, median survival was 8.3 years for radiotherapy and 8.1 years for observation. There were virtually identical relapse and survival rates in the two treatment arms. There were more locoregional recurrences as sites of first relapse in the observation group while there were more distant metastases in the radiotherapy arm. Twenty nine patients (20%) had locoregional recurrence and 45 (30%)had distant metastases as site of first relapse in the observation arm, while 14 patients (9%) had locoregional recurrence and 72 (44%) had distant metastases in the radiotherapy arm.

Koning and Hart[12] reported a randomized trial in the Netherlands conducted from 1977 to 1980. They reported on a 14-year follow up of 118 patients who were randomized between radiotherapy alone; radiotherapy(RT), 12 courses of CMF and tamoxifen(RT/CMFT); and adriamycin, vincristine (AV) alternated with CMF, then radiotherapy, followed by four cycles of AV/CMF and tamoxifen during the entire treatment period. Aside from the usual signs of locally advanced breast cancer, patients

must have had a positive axillary apex biopsy which was considered a sign of advanced locoregional disease. The survival curves for the three treatment arms were almost identical for the first 6 years. Thereafter, the survival curves grew apart, resulting in differences in 10-year survival rates, up to 15 per cent between arms III and I, but not reaching statistical significance (p=0.38, 95% confidence interval = -3 to 33%). Disease free survival data are shown in Table 5. This study was discontinued so as to take part in the EORTC trial. Owing to the small number of patients, the relative value of the various treatments cannot be established.

Bartelink[13] reported an 8-year follow up of a European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group trial which randomly allocated 410 patients from 1979-1985 to receive radiotherapy (RT) alone, RT with chemotherapy(CT), RT with hormonotherapy (HT), or RT with CT and HT. Of the 374 evaluable patients, 29.7 per cent were Stage IIIA, 43 per cent Stage IIIB, 24.3 per cent not Stage III, and 3 per cent unknown stage. Results of treatment were not reported according to specific stage. Analysis of results performed 8 years after trial closure showed a significantly improved survival in patients treated with HT(p=0.04) but not with CT(p=0.21). The median duration of survival in patients who received adjuvant HT was 4.3 years, as opposed to 3.3 years in those who did not receive HT. For CT, the medians were 3.8 years and 3.6 years, respectively. The combined treatment with HT and CT provided the greatest therapeutic effect(p=0.02), with median survival of about 5 years.

In this EORTC trial, both CT (p=0.0002) and HT (p=0.0007) significantly delayed the time to locoregional recurrence with the combined treatment group experiencing the greatest therapeutic effect (p=0.0001). The locoregional recurrence rate was reduced from 59 per cent to 48 per cent at 6 years in patients who received CT, and from 61 per cent to 47 per cent in patients who received HT.

There were also a number of case series reports on combined locoregional and systemic therapy for LABC. Hortobagyi[14] reported on the M.D. Anderson experience with 174 patients who received 3 cycles of cyclophosphamide, doxorubicin and 5-fluorouracil followed by local treatment in the form of mastectomy with axillary dissection, or radiotherapy or both, then continuation of the chemotherapy. There were 48 patients with Stage IIIA and 126 patients with Stage IIIB. The 5-year disease free survival rates were 84 per cent for Stage IIIA and 33 per cent for Stage IIIB. The 5-year overall survival rates were 84 per cent for Stage IIIA and 44 per cent for Stage IIIB. These figures highlight the big difference between these two Stage III subgroups. In this series, Stage IIIB patients with good responses to induction chemotherapy had statistically better prognosis.

Pierce[15] et al reported on 107 patients who received chemohormonotherapy to maximal response followed by local treatment and maintenance therapy. Patients with a clinical partial response underwent mastectomy and radiotherapy while patients with a clinical complete response were biopsied. Those with residual disease received mastectomy/RT while those with pathologic complete response received RT only. There were 48 Stage IIIA, 46 Stage IIIB-inflammatory (IBC), 13 Stage IIIB-non

inflammatory (non – IBC) patients. The 5-year actuarial locoregional failure rate as first site of failure was 3 per cent for IIIA, 21 per cent for IIIB IBC and 33 per cent for IIIB non-IBC. The 5-year actuarial locoregional failure rate at first site of failure was 23 per cent for radiation only versus 5 per cent for mastectomy and post operative radiotherapy. Five-year survival data are shown in Table 6.

Jacquillat et al[16] reported on the results of neoadjuvant chemotherapy and radiation therapy in a breast conserving treatment of 250 patients. This series included 36 Stage IIIA and 58 Stage IIIB patients. At 5 years, the rate of breast preservation for the entire group was 94 per cent. The 5-year disease free survival rates were 46 per cent for Stage IIIA and 52 per cent for Stage IIIB.

Analysis of the data of Olson will show that the survival rates of his patients were comparable to survival of patients reported by the EBCTCG[17] (Table 7), which leads us to surmise that this population of "operable locally advanced breast cancer" may be included in the EBCTCG's definition of early breast cancer. The survival rates in the two other randomized trials more closely approximated the data reported by the American College of Surgeons. The patients in these two other trials were a more heterogeneous mix of "operable" and "inoperable" locally advanced breast cancer. We believe that Stage IIIA has a different prognosis compared to Stage IIIB and it would seem that within the Stage IIIB group, treatment of operable and inoperable tumors would also have differing outcomes.

There is evidence that combined locoregional and systemic therapies improved survival in these heterogeneous groups of "locally advanced breast cancer". However, the benefit to the "inoperable" cases is unclear because the participation of many patients with operable breast cancers improved the entire survival picture. Several clinical trials had also demonstrated good response rates of locally advanced breast cancer to systemic therapies but whether these responses translated to an improvement in survival is more difficult to establish.

Recommendations:

4. *There seems to be some evidence that for locally advanced breast cancer, the use of systemic therapy and radiotherapy may increase survival, but the size and duration of the benefit is unclear. (Level II, Category A)*

5. *In some cases, neoadjuvant systemic therapy may reduce primary tumor size to such an extent that may permit mastectomy or even breast conserving surgery.*
(Level II, Category A)

Recommendations for Research

1. There are important unresolved issues in the treatment of "inoperable" locally advanced breast cancer. This subset still comprises a big number of breast cancer cases in developing countries and underscores the urgent need for clinical trials.

2. A comprehensive review of data on locally advanced breast cancer may allow subset analysis and elucidate differences among patients in this group.

B. Locally Recurrent Breast Cancer

The majority of women with primary breast cancer have apparently operable disease, and are treated with surgery, and in many cases, with radiotherapy and / or some form of systemic therapy (such as chemotherapy or tamoxifen). However, depending on the stage of the disease, and the treatment given, between 10 per cent and 35 per cent of women experience an isolated locoregional recurrence (LRR).[18-20] About 80 per cent of these recurrences occur during the first two years after primary treatment.[21]

Regardless of whether the primary treatment is mastectomy or breast conservation therapy, locoregional recurrence in breast cancer comprises any reappearance of the disease in the area of the primary (local) treatment and / or the regional lymph nodes (axillary, clavicular and parasternal, or internal mammary). It may be preceded or accompanied by distant metastases. As previously mentioned, isolated LRR (ie. no overt evidence of distant metastases) accounts for 10-35 per cent of first breast cancer relapses.

1. What are the methods currently used for the early detection of LRR and what are their test characteristics?

Early detection and diagnosis of LRR of breast cancer is possible with a variety of diagnostic methods. A combination of palpation, sonography, and biopsy, eg. aspiration cytology; and mammography for patients who underwent breast conservation treatment, is probably as accurate and certainly simpler, faster, and cheaper compared to other more complicated and costly tests like computerized sonogarphy (CT) and magnetic resonance imaging (MRI).[22]

Most LRR are detected by physical examination. Palpation is highly sensitive (70 - 96% sensitivity) for detecting superficial recurrences in the surgical scar or chest wall. Retrospective studies showed that as the site of LRR deepened, the sensitivity of palpation decreased progressively according to site, from supraclavicular to axillary (especially in the apex) to internal mammary nodes, the latter being palpable only when they were very large and grew anteriorly through the intercostal spaces.[22] The diagnostic limits of palpation have justified the attempt to improve its accuracy by supplementing it with other tests.

Sonography is currently used as an adjunct to palpation for the detection of local recurrences. Retrospective studies showed that the sensitivity of sonography was not higher when compared to palpation; its accuracy was poor as it often failed to differentiate between local recurrences and fibrous surgical scarring. However, sonography was very sensitive for detecting lymph nodes (even of small size) and was particularly useful to confirm the presence of nodes in the supraclavicular area and the axilla.[23] Unfortunately, differentiating between reactive and metastatic nodes was

difficult. Metastatic nodes tended to be more intensely hypoechoic, rounded, and the hyperechoic hilum was absent.[22]

Retrospective studies showed that other imaging techniques such as CT and MRI might detect local recurrences but had no power to distinguish between benign and malignant masses. [22] Such techniques may be helpful in the internal mammary region where both palpation and sonography may fail to detect small recurrences, but their use is generally aimed at staging the extent of disease in the presence of otherwise evident local recurrences. The routine use of CT scan and MRI in otherwise negative subjects is not recommended.

Recommendation:

1. *Physical examination alone adequately detects locoregional recurrence due to breast cancer in most cases.(Level II, Category A)*

2. What is the impact on survival of early detection of LRR?

Retrospective studies had estimated that periodic observation may detect asymptomatic local recurrences about 3 months before onset of symptoms.[24-25] After correcting for lead and length time, this presymptomatic detection had a moderate to null effect on survival from primary treatment. Table 8 shows the results of two retrospective studies on the prognostic impact of early detection of local recurrences from breast cancer. The 1985 study shows that the median survival was basically the same for those women with local recurrences detected "earlier" even in the asymptomatic stage (45 months) and those whose recurrences were detected already in the symptomatic stage (46 months). The limited improvement in median survival among those whose recurrences were detected "earlier" in the asymptomatic stage, as reported in the 1984 study could be possibly explained by length based sampling; that is by selective concentration of slow growing lesions (long presymptomatic phase) among asymptomatic recurrences, and of fast growing (short presymptomatic phase) among symptomatic recurrences.

Because there was no controlled study available to confirm whether such a diagnostic anticipation has any impact on prognosis, Ciatto in 1995 concluded that "Periodic control aimed at the early detection of these local recurrences might be recommended, although the prognostic impact (if any) of such a policy is probably limited, and extremely large controlled studies would be necessary to demonstrate impact at a significant level.[22]

Recommendation:

2. *Periodic follow up aimed at early detection of local recurrences of breast cancer may be recommended, although the prognostic impact of such a policy is probably limited. (Level II, Category A)*

3. What are the methods currently used for the diagnosis of LRR and what are their test characteristics?

Cytologic or histologic documentation of recurrent disease should be obtained whenever possible. Retrospective studies showed that fine needle aspiration cytology (FNAC) had high accuracy in the diagnosis of local recurrences.[22] Table 9 shows the test characteristics of FNAC in the diagnosis of suspected LRR.

No studies evaluating core needle biopsy (CNB) in diagnosing locally recurrent breast cancer were found. However, it may be inferred that the high sensitivity and specificity reported with FNAC can also be obtained, if not surpassed, using larger CNB. Moreover, CNB will yield more tissue resulting in a lower inadequacy rate. Therefore, CNB is the initial diagnostic procedure recommended in patients with a palpable LRR because more tissue will be made available not only for tissue diagnosis, but also for estrogen receptor status determination.

Open biopsy may be done if CNB yields unsatisfactory results.

Recommendations:

3. Cytologic or histologic documentation of recurrent disease should be obtained whenever possible, prior to active treatment. (Level III, Category A)

4. Core needle biopsy (CNB) is the initial diagnostic procedure in breast cancer patients with a palpable locoregional recurrence. (Level III, Category A)

5. Open biopsy, whenever possible, may be done for histologic documentation of recurrent disease when the initial CNB done yields unsatisfactory results. (Level III, Category A)

Recurrent breast cancer is often responsive to therapy, although treatment is rarely curative at this stage of disease. However, patients with localized breast or chest wall recurrences may be long term survivors with appropriate therapy. Prior to treatment for recurrent cancer, restaging to evaluate extent of disease is indicated. As previously mentioned, cytologic or histologic documentation of recurrent disease should be obtained whenever possible. The estrogen receptor status (at the time of recurrence, or during previous primary treatment) should be considered when selecting therapy. ER status may change at the time of recurrence. In a single small study, 36 per cent of previously hormone receptor – positive tumors were found to be receptor – negative in biopsy specimens of recurrent lesions.[26] Patients in this study had no interval treatment. If ER status is unknown, then the site(s) of recurrence, disease free interval, response to previous treatment, and menopausal status are useful in selecting between hormone therapy or chemotherapy as initial systemic treatment.[27]

Recommendations:

6. *The determination of estrogen receptor (ER) status of the local recurrence is encouraged. However, women with locally recurrent breast cancer with unknown estrogen receptor status are managed as estrogen receptor positive tumors. (Level III, Category A)*

7. *Metastatic work up to evaluate extent of disease is recommended prior to treatment for recurrent breast cancer. (Level III, Category A)*

4. What are the benefits in terms of disease free survival (DFS) and overall survival of locoregional treatments (surgery and /or radiotherapy) in locally recurrent breast cancer ?

Salvage mastectomy is recognized as the standard treatment for breast relapses after primary treatment with breast conservation. Several retrospective studies showed that at 5 years, the DFS ranged from 51 to 63 per cent, with an overall survival rate of 48 to 84 per cent. At 10 years, the DFS was 50 to 57 per cent.[28-31] It is notable that many of these women received systemic therapy (hormonal or chemotherapy).

A second breast conserving surgery had been proposed as an alternative to salvage mastectomy for small recurrent tumors. If the breast had been irradiated after the initial surgery, additional irradiation is not possible. Two retrospective studies showed a DFS of 62 to 69 per cent, similar to salvage mastectomy. [30,32] However, this should be interpreted with caution because of the small patient numbers involved, the retrospective nature of the studies, and the fact that these were done in highly selected patients with small recurrences.

Multivariate analysis of the study by Kurtz et al showed that positive or unknown margins and a short disease free interval (DFI) were predictive of additional local relapse. For patients who had a relapse in the breast more than 5 years after initial breast sparing treatment, the subsequent 5- year local control rate was 92 per cent, but only 49 per cent for patients with shorter DFI . The local control rate after 5 years was 73 per cent in patients with clear margins at the time of resection of the recurrence, but only 36 per cent for those with positive or unknown margins.[32] In short, as Kennedy pointed out in 1992, "Negative margins are essential if additional breast- sparing surgery is to be considered after initial relapse, and this approach should be considered only as an alternative to mastectomy in the context of carefully designed and monitored clinical trials".[33]

Recommendation:

8. *Salvage mastectomy is the standard treatment for locoregional control of recurrence after breast conservation treatment. (Level II, Category A)*

In contrast to recurrence in the breast, local chest wall recurrence following mastectomy is usually the harbinger of widespread disease, but in a subset of patients it

may be the only site of recurrence. For patients in this subset, surgery and/ or radiation therapy may be curative.

Halverson et al found that the 5-year locoregional control rate was highest in patients with isolated chest wall rather than isolated regional nodal or combined chest wall and nodal recurrences. In addition, the ability to secure and maintain local control was related directly to the extent of local disease. Tumors that were larger than 3 cm and could not be excised completely were controlled only 53 per cent of the time, compared with 85 per cent and 75 per cent for smaller or excisable soft tissue lesions, respectively.[34] Schwaibold et al identified a subgroup of "good – prognosis" patients with a DFI greater than 2 years, completely excised soft tissue recurrence, and good locoregional control after radiation therapy, who had a 5-year over all survival rate of 61 per cent.[35]

In summary, patients with local soft tissue recurrences of less than 3 cm, axillary and internal mammary node recurrence (as opposed to para-clavicular), and greater than a 2-year DFI prior to recurrence have the best chance for prolonged survival. The 5-year DFS rate in one series of such patients was 25 per cent, with a 10-year DFS rate of 15 per cent; while locoregional control rate was 57 per cent at 10 years.[36]

Most chest wall tumors can be theoretically resected aggressively, knowing that stabilization of the chest wall and resurfacing of the defect is possible with current reconstructive techniques using musculocutaneous flaps, with or without prosthetic materials. However, aggressive chest wall resection is not commonly done because of the realization that systemic failure from metastases is the principal limitation in improving survival. Retrospective studies showed that distant metastases eventually developed in about 80 per cent of patients after treatment of locoregional recurrence of breast cancer.[37] Moreover there was a repeat local failure rate of 40-50 per cent after surgical treatment for locally recurrent breast cancer.[38] In addition, aggressive chest wall resections carried high morbidity rates.

One case series done at the M.D. Anderson Cancer Center involved 93 chest wall resections in 85 patients with a variety of chest wall tumors (excluding T_3 lung carcinomas). There were 47 women and 38 men. The mean and median ages were 46 and 47 years, respectively (range 11 to 81 years). The operative mortality rate was 3.2 per cent, with major complications in 12.9 per cent. [38] Table 10 shows the complications in this case series.Two of the four major pulmonary complications resulted in mortality; one from pneumonia with adult respiratory distress syndrome, and another from pneumonia with multiple organ failure. One nonpulmonary major complication also led to death due to ventricular arrhythmias. Preoperative chemotherapy was given to 43 patients (43.8 per cent) and preoperative irradiation was used in 7 patients (8.0 per cent).[38]

Nineteen per cent (16/85) of the patients in the M.D. Anderson series underwent chest wall resection for breast cancer. Of these, 94 per cent (15/16) had locoregional recurrence. Eleven patients had chest wall recurrence, three had internal mammary node metastases, and one had an isolated sternal recurrence. Most of the patients had received

irradiation either after a primary mastectomy or breast-conserving surgery; or for a prior local recurrence. The only disease free survivor was a woman still alive 40 months after resection of a sternal metastasis. All patients surviving beyond 3 years and all but one of the 8 patients still alive had a disease-free survival of greater than 2 years between primary treatment and recurrence. Thirty eight per cent (6/16) suffered additional local recurrences, including the two patients who received radiation before and after chest wall resection. The repeat local failures occurred 3 to 30 months after the resection.[38]

From the data presented, it seems that surgical resection should only be considered for patients with isolated soft tissue recurrence measuring 3 centimeters or less, and/or which could be excised completely and safely, recurring 2 years or more after primary treatment. Postoperative radiotherapy is also given after the surgical resection if it has not been given previously.

Recommendations:

9. *Radiotherapy is given for locoregional control of locally recurrent breast cancer appearing after initial treatment with mastectomy. (Level II, Category A)*

10. *Surgical resection of local soft tissue recurrence after initial treatment with mastectomy may be done prior to radiotherapy, for recurrences measuring 3 centimeters or less, which could be excised completely and safely, recurring 2 years or more after primary treatment. (Level II, Category A)*

11. *Aggressive chest wall resection of locally recurrent breast cancer is not recommended because it carries a high morbidity rate and there is no proven survival benefit. (Level II, Category A)*

Isolated LRR may be resectable without (this is categorized as RO), or with (RI) microscopic disease remaining in situ.[39] In these cases, the biological significance of LRR is still not clear. There is an ongoing debate as to whether LRR is generally an indication of poor prognosis [40-41] or whether resectable LRR is strictly locally confined reappearance of the disease.[42] If the latter is true, complete removal of the LRR should, like a complete resection of the primary breast cancer, make definitive cure a possibility. However, when women with resected primary breast cancer who have had LRR are compared with similar women who have not had LRR, an increased rate of further progress of the disease is found in the former. The 10-year survival for women with LRR is less than 50 per cent. [39] After potentially curative resection of the primary cancer, adjuvant systemic treatment has been shown to prolong recurrence-free and overall survival. [17,43] Consequently, it might seem advisable to also use systemic adjuvant therapy after "potentially curative" local treatment of LRR.

5. Will additional systemic treatment (chemotherapy, hormonal therapy, or combination of both) improve recurrence free and overall survival in breast cancer patients, after potentially curative local treatment of isolated LRR ?

Currently, there is paucity of evidence to recommend routine use of systemic therapy in patients with locoregional relapse of breast cancer. To date, there is only one randomized trial published on this topic and this 1994 study of the Swiss Group for Clinical Cancer Research investigated the role of tamoxifen (TAM) after complete excision and radiotherapy for isolated LRR in patients with breast cancer.[44] One hundred sixty seven "good-risk" patients with an estrogen receptor positive (ER+) recurrence or, in case of unknown receptor status, a DFI greater than 12 months and ≤ three recurrent tumor nodules each ≤ 3 cm in diameter, were randomized to observation subsequent to local treatment or to receive TAM until disease progression. Seventy nine per cent of the patients were postmenopausal.

The median observation period for the entire study population was 6.3 years. The median DFS duration was 26 months for observation and 82 months for TAM patients (p=0.007). This was mainly due to the reduction of further local recurrences, whereas the occurrence of early distant metastases was delayed. Multivariate analysis identified DFI and treatment with tamoxifen as significant prognostic factors for DFS. Systemic therapy with TAM after isolated LRR of breast cancer significantly increased 5-year DFS rates from 36 to 59 per cent compared with observation alone. It also prolonged median DFS by more than 4.5 years in patients with ER positive tumors and unknown ER status, with DFI greater than 12 months and minimal tumor burden. However, the 5 year overall survival rate of 76% for those given TAM was not significantly different from the 74% rate who were treated with observation alone (p=0.77).Hence the authors concluded that "TAM currently has no significant impact on overall survival, but the median survival duration of the study population has not yet been reached."[44]

Recommendations:

12. *For patients with locally recurrent breast cancers which are estrogen receptor positive, hormonal therapy is the initial systemic treatment given. (Level I, Category A)*

13. *Tamoxifen is the preferred first-line hormonal therapy for patients with locally recurrent breast cancers which are estrogen receptor positive.(Level I, Category A) Tamoxifen is given at a dose of 20 mg daily and is given continuously even if there is complete response, until disease progression. (Level III, Category A)*

14. *For elderly postmenopausal women with long disease- free interval (≥ 2 years between primary treatment and local recurrence) whose recurrence is confined to skin and soft tissue, locoregional treatment may not be done and tamoxifen alone may be given. (Level III, Category A)*

The randomized study done by the Swiss Group [44] failed to accrue large enough number of patients to evaluate cytotoxic chemotherapy for estrogen receptor negative,

"high risk" patients with chest wall relapses. To date, there are no published randomized studies comparing cytotoxic chemotherapy to no treatment following or simultaneously with local treatment for LRR. What the literature contains are some retrospective studies which had prognostic factor analysis at first relapse, to identify subsets of patients who could be considered for systemic cytotoxic chemotherapy at the time of local relapse.

A brief disease-free interval (DFI) emerged as a consistent prognostic factor which predicted patients who were at high risk for distant metastases, and who would therefore possibly benefit from systemic treatment at time of local relapse. The definition of "brief" DFI varied with a range of 1 year [40] to 4 years [45]. However, majority of the studies used 2 years as the cut-off to define "brief " DFI or early relapse [35,42,45,46] . Data from these studies showed that patients who experienced LRR within the first few years following original diagnosis had a relatively poor prognosis, with 50 per cent developing distant metastases compared to only 17 per cent in one series[47] among those who developed the LRR later in the course of the disease. The relatively high distant metastasis rate of 50 per cent in patients who experienced early LRR may justify consideration of some form of systemic therapy at the time of local relapse .

Other factors to consider are extent of LRR, hormone receptor status, menopausal status, histologic grade, and prior systemic therapy. In a retrospective study of 433 patients with first relapse (both local and systemic relapse were considered), Vogel *et al* found that the median survival time from first relapse (MSFR) ranged from 15 months for poor risk patients with negative ER, DFI of less than 2 years, and visceral dominant sites, to more than 90 months for good risk patients with positive ER, DFI of more than 2 years , and soft tissue dominant sites. Although menopausal status alone was not a significant prognostic variable in regression analysis, 66 per cent of premenopausal patients had a constellation of "poor" prognostic variables.[45]

Based on the data presented, various investigators had concluded that systemic polychemotherapy should be considered on a case to case basis for patients in this situation, particularly in the context of a clinical trial.

On the other extreme, Schaibold et al [35] and Kurtz et al[48] identified a subgroup of patients with a DFI greater than 2 years, completely excised recurrence, and good locoregional control after RT who had a 5-year overall survival rate of 61 per cent, who would presumably do well without systemic chemotherapy.

Recommendation:

15. *For patients with locally recurrent breast cancer which are estrogen receptor negative, chemotherapy may increase survival but the size and duration of the benefit is unclear. (Level II, Category A)*

C. Metastatic Breast Cancer

Metastatic breast cancer is defined as breast cancer occurring anywhere in the body outside the breast and regional lymph nodes. Common sites of distant spread of breast cancer are the bones, skin and soft tissues, lungs / pleura, liver and brain. Disease in the supraclavicular lymph nodes is also considered "distant" metastases and as such is also included in Stage IV or metastatic disease.[5] In general, when cancer has spread to distant sites, cure is no longer possible. However,palliation of symptoms can be achieved in most patients and in some cases the length of survival can be increased.

Before attempting to answer the specific clinical questions formulated in the treatment of metastatic breast cancer, the TWG first outlined the primary goal of therapy to serve as a guiding principle and to set the spirit in intervention in the setting of metastatic breast cancer. This primary goal of PALLIATION, particularly cancer pain relief, is embodied in the first two recommendations.

Recommendations:

1. *The primary goal of therapy for patients with metastatic breast cancer is palliation. Palliative care is the active total care of patients whose disease is no longer responsive to curative treatment. The goal of palliative care is achievement of the best possible quality of life for patients and their families. Control of pain and of other symptoms, and alleviation of psychological, social, and spiritual problems are paramount. (Level III , Category A)*

2. *The WHO method of cancer pain relief should be immediately started for all patients with metastatic breast cancer who complain of pain. (Level III , Category A)*

1. Does systemic chemotherapy or hormonal therapy confer a survival benefit for patients with metastatic breast cancer ? If so, what is the magnitude of the survival benefit?

No studies were found that compared prognosis between patients who were not given treatment versus those given either chemotherapy or hormonal therapy for metastatic breast cancer. All the systematic reviews were in agreement that such studies would have been unethical due to the significant number of tumor responses with treatment. Data from retrospective studies, a population cohort study from Denmark [49] and several studies based on hospital registries [50,51] indicated that the use of non-anthracycline containing chemotherapy compared with no chemotherapy might add a survival gain of six to nine months. Hern et al[52] analyzed the results from 50 trials involving 6056 patients to test the hypothesis that if chemotherapy improved survival in advanced breast cancer, there should be a tendency for the treatment arm demonstrating higher response rate to also demonstrate a longer survival. A statistically significant relationship was demonstrated between the relative response rate and median survival ($p < 0.001$). It was claimed that effective chemotherapy might prolong the median survival time by around six months.

Recommendation:

3. *In general, for patients with metastatic breast cancer, systemic chemotherapy may be offered because it has been shown to confer a modest survival benefit of 6-9 months. (Level II, Category A)*

2. Which is better: systemic chemotherapy or hormonal therapy as initial treatment modality for metastatic breast cancer?

There was no convincing evidence to prove the superiority of chemotherapy over hormonal therapy or vice versa as initial treatment for metastatic breast cancer. Based on a two-study analysis, the systematic review of Stockler et al for the National Health and Medical Research Council (NHMRC) Clinical Trials Centre and the Cochrane Collaboration Collaborative Review Group in Breast Cancer in Australia[53] found no significant difference in median survival (18 months each) using either of these modalities (p=0.73, 95% CI=0.02-60.3), as shown in Table 11 and Figure 1.

Since there was level II evidence which showed that treatment of systemic recurrence of breast cancer did prolong survival and enhanced quality of life but was not curative, treatments associated with minimal toxicity are preferred. As such, hormonal therapy is generally preferred to cytotoxic chemotherapy. Johnston and Stebbing[54] summarized clinical factors that may be used to predict response to hormonal therapy in metastatic breast cancer based on the Piedmont Oncology Association Trials[55]and 4 reviews[56-59]. These are shown in Table 12.

Recommendations:

4. *The determination of estrogen receptor status of the metastatic lesion is encouraged. However, patients with metastatic breast cancer with unknown estrogen receptor status are managed as estrogen receptor positive tumors. (Level III, Category A)*

5. *For patients with metastatic breast cancer which are estrogen receptor positive, hormonal therapy is the initial systemic treatment given. (Level II, Category A)*

3. What are the survival benefits of the different hormonal therapies in metastatic breast cancer?

For patients in whom hormonal therapy is deemed appropriate, tamoxifen is the preferred first-line hormonal therapy for women who have not received it previously. The systemic reviews of RCTs from NHMRC Clinical Trials Centre and the Cochrane systematic review done in Australia[53] found no additional survival benefit with the use of ovarian ablation, progestins or combination hormonal therapy as compared to Tamoxifen alone (median survival 26 months each, p=0.83, 95% CI 0.82-1.10). These are shown in table 13 and figure 2.

Recommendation:

6. *Tamoxifen is the preferred first-line hormonal therapy for patients with metastatic breast cancer which are estrogen receptor positive. Tamoxifen is given at a dose of 20 mg daily and is given continuously, even if there is complete response, until disease progression. (Level I, Category A)*

In women who had received prior tamoxifen therapy, progestins, aromatase inhibitors, androgens or oophorectomy in premenopausal women, can be offered.

Women who responded to a hormonal therapy with either shrinkage of tumor or long term stabilization are usually offered second line hormonal treatment at the time of disease progression.

Buzdar et al[60] evaluated anastrozole, an aromatase inhibitor versus megestrol acetate in postmenopausal women with advanced breast cancer which were predominantly (70%) ER positive and 30% ER unknown. They found an improvement in median survival of 4 months (26.7 months versus 22.5 months) for patients on anastrozole compared to progestins. Gershanovich et al [61] also evaluated letrozole, another aromatase inhibitor versus aminogluthetimide in postmenopausal women with advanced breast cancer. Results showed that letrozole had better overall survival (H.R. 0.64; 95% C.I.=0.49-0.85; p = 0.002). Dombernowsky et al.[62] also did an RCT comparing letrozole with megestrol acetate for advanced breast cancer. Results showed that letrozole had longer time to treatment failure (H.R. 0.77; 95% C.I.=0.61-0.99; p=0.04).

The analysis of 10 other studies (12 comparisons with 3349 patients) [53] also showed that aromatase inhibitors seemed to perform better than other second-line hormonal therapies with a 12 percent decrease in the risk of death.

Recommendation:

7. *Patients with metastatic breast cancer who responded to tamoxifen initially are offered second line hormonal therapies at the time of disease progression. (Level I, Category A)*

4. What are the survival benefits of the different chemotherapy regimens in metastatic breast cancer?

For patients who are not candidates for hormonal treatment, chemotherapy may be offered.

Systematic review done by the Italian Cochrane Center[63] showed no solid evidence of a survival benefit using chemotherapy regimens in the metastatic setting as illustrated in table 14 and figure 3.

A Cochrane systematic review done in Australia[53] showed evidence that continued therapy until disease progression was better than limited therapy as illustrated in table 15 and figure 4. The median survival was 17 months for more cycles

versus 13 months for less cycles, p=0.01, 95 % CI 1.01-1.49. However, in keeping with the primary goal of palliation in the setting of metastatic breast cancer, it is emphasized that toxicities and complications of chemotherapy be given serious consideration. Palliation of symptoms should be the primary goal.

Recommendations:

8. *For patients with metastatic breast cancer which are estrogen receptor negative, chemotherapy may increase survival but the size and duration of the benefit is unclear.(Level II, Category A)*

9. *There is no survival benefit among the different polychemotherapy regimens. Continued therapy until disease progression is better compared to limited therapy. However, toxicities and complications of chemotherapy should be given serious consideration bearing in mind that palliation of symptoms and not tumor response is the main goal of therapy.*
   (Level I, Category A)

5. Will the addition of chemotherapy to hormonal therapy or the addition of hormonal therapy to chemotherapy confer a survival benefit for patients with metastatic breast cancer?

There was level I evidence that chemotherapy did not add any survival benefit to patients already responding to hormonal therapy.The NHRMC Clinical Trials Centre and the Cochrane systematic review done in Australia [53] included nine treatment comparisons from seven trials which assessed the effect of the addition of chemotherapy in patients who were already receiving endocrine therapy. The combined analysis did not show a survival benefit for the addition of chemotherapy to endocrine therapy (median survival 28 months for additional chemotherapy versus 25 months without additional chemotherapy, p=0.85, 95 % CI 0.85 - 1.32). While the proportions of good responses were higher in the additional chemotherapy group (62.3 % versus 33.1 %) this did not result in significant increase in the duration of survival. These are shown in table 16 and figure 5. The overview by Bergh et al for the Swedish Council of Technology Assessment in Health Care (SBU) [64] arrived at the same conclusion.

There was also level I evidence that hormonal therapy did not add any survival benefit to patients already responding to chemotherapy. Eleven comparisons from 10 trials included in the same systematic review[53] assessed the addition of hormonal therapy to chemotherapy. Table 17 and Figure 6 show that the combined analysis did not show a survival benefit for the addition of hormonal therapy to chemotherapy (median survival 22 months for additional hormone therapy versus 20 months without additional hormone therapy, p=0.14, 95 % CI 0.97-1.25). Again the higher response rates seen without the addition of hormone therapy (65.5 % versus 46.3 %) did not result in longer survival. The systematic review done by the Italian Cochrane Center in Milan [63] and the Swedish overview [64] also arrived at the same conclusion.

Recommendation:

10. The addition of chemotherapy to hormonal therapy does not confer a survival benefit for patients with metastatic breast cancer who are already responding to hormonal therapy. Likewise, the addition of hormonal therapy to chemotherapy does not confer a survival benefit for patients with metastatic breast cancer who are already responding to chemotherapy.(Level I, Category A)

6. Are there other treatments which have shown survival or palliative benefits in metastatic breast cancer? If so, what are these and what are their survival or palliative benefits?

Breast cancer patients with metastases confined to the bones had a median survival of 3-4 years. [65] The relatively indolent course of solitary bone metastases due to breast cancer allows patients to survive for a considerably long period of time. Thus, there is a long period of time wherein palliation can be done for symptoms, primarily pain, due to bone metastases.

Mc Quay et al for the Cochrane Group [66] evaluated the role of radiotherapy in the palliation of painful bone metastases. Their analyses showed that radiotherapy resulted in complete pain relief in 25 per cent (395/1580) of patients, and 50 per cent pain relief in 41 per cent (788/1933) of patients with bone metastases. Numbers needed to treat (NNT) to achieve complete relief at 1 month (compared with an assumed natural history of 1/100 patients whose pain resolved without radiotherapy) was 4.2 (95% C.I.= 3.7-4.7). Onset of relief was within 4 weeks in 52 per cent (394/752) of patients. Median duration of complete relief was 12 weeks or 3 months. For more generalized disease, radioisotopes produced similar analgesic results compared to external radiation.

Recommendation:

11. Radiotherapy may be given to symptomatic patients with bone metastases for relief of symptoms. (Level I, Category A)

Bisphosphonates may also be given to patients with bone metastases because they reduce the incidence of skeletal complications and decrease pain medication requirements; however, no survival benefit has been seen.

Hortobagyi et al[67] evaluated the efficacy of pamidronate in 380 patients with lytic bone metastases and found that patients given 90 mg pamidronate IV for 12 cycles had longer median time to first skeletal complication (13.1 mos vs. 7 mos ;. p=0.005); had fewer women developing skeletal complications(43% vs 56% ; p=0.008), reduced the need for radiotherapy to treat bone pain (19% vs. 33%; p=0.01); and reduced the risk of pathologic fracture by 50 per cent (O.R.=2.3,95% C.I.= 1.5-3.5) compared with the placebo group.

Theriault et al[68] obtained similar results; patients given pamidronate had longer median time to first skeletal complication (10.4 mos vs. 6.9 mos; p=0.049); had fewer

skeletal complications (2.4 vs. 3.8 ; p=0.008); and had decreased need for radiotherapy to treat bone pains (25% vs. 34%; p< 0.042).

Paterson et al[69] reviewed oral clodronate and found that patients given 1600 mg daily had fewer hypercalcemic episodes (23% vs 35%; p< 0.01) and fewer incidence of vertebral fractures (84 vs. 124; p < 0.025).

However, none of the trials showed an impact on overall survival.

Recommendation:

12. *For patients with bone metastases, bisphosphonates may be given because they reduce the incidence of skeletal complications and decrease pain medication requirements; however, no survival benefit has been seen. (Level I, Category A)*

Summary of Recommendations

A. Locally Advanced Breast Cancer

1. *Breast cancer cases which are included in the definition of the Early Breast Cancer Trialists Collaborative Group (EBCTCG), namely cases wherein cancer is restricted to the breast and, in the case of node positive patients, the local lymph nodes can be removed surgically, should be managed according to the PCS evidence based clinical practice guidelines on early breast cancer (Philipp J Surg Spec 2001; 56(1):7-36).*
   (Level I, Category A)

2. *The term "locally advanced breast cancer" shall from now on be used for cases that are not considered early breast cancer and have no evidence of distant metastasis. These will comprise T4 tumors or stage IIIB cases. (Level II, Category A)*

3. *Diagnostic tests for detection of distant metastases in patients with locally advanced breast cancer should be individualized and symptom-directed; and not done routinely. Physicians should do exhaustive search for clinical evidence of distant metastases by doing thorough history and physical examination.(Level II, Category B)*

4. *There seems to be some evidence that for locally advanced breast cancer, the use of systemic therapy and radiotherapy may increase survival, but the size and duration of the benefit is unclear.(Level II, Category A)*

5. *In some cases, neoadjuvant systemic therapy may reduce primary tumor size to such an extent that may permit mastectomy or even breast conserving surgery.*
   (Level II, Category A)

B. Locally Recurrent Breast Cancer

1. *Physical examination alone adequately detects locoregional recurrence due to breast cancer in most cases. (Level II, Category A)*

2. *Periodic follow-up aimed at early detection of local recurrences of breast cancer may be recommended, although the prognostic impact of such a policy is probably limited. (Level II, Category A)*

3. *Cytologic or histologic documentation of recurrent disease should be obtained whenever possible, prior to active treatment. (Level III, Category A)*

4. *Core needle biopsy (CNB) is the initial diagnostic procedure in breast cancer patients with a palpable locoregional recurrence. (Level III, Category A)*

5. *Open biopsy, whenever possible, may be done for histologic documentation of recurrent disease when the initial CNB yields unsatisfactory results.(Level III, Category A)*

6. *The determination of estrogen receptor (ER) status of the local recurrence is encouraged. However, women with locally recurrent breast cancer with unknown estrogen receptor status are managed as estrogen receptor positive tumors. (Level III, Category A)*

7. *Metastatic work up to evaluate extent of disease is recommended prior to treatment for recurrent breast cancer. (Level III, Category A)*

8. *Salvage mastectomy is the standard treatment for locoregional control of recurrence after breast conservation treatment. (Level II, Category A)*

9. *Radiotherapy is given for locoregional control of locally recurrent breast cancer appearing after initial treatment with mastectomy. (Level II, Category A)*

10. *Surgical resection of local soft tissue recurrence after initial treatment with mastectomy may be done prior to radiotherapy, for local recurrences measuring 3 centimeters or less, which could be excised completely and safely, recurring 2 years or more after primary treatment.(Level II, Category A)*

11. *Aggressive chest wall resection is not recommended because it carries a high morbidity rate and there is no proven survival benefit. (Level II, Category A)*

12. *For patients with locally recurrent breast cancers which are estrogen receptor positive, hormonal therapy is the initial systemic treatment given. (Level I, Category A)*

13. *Tamoxifen is the preferred first-line hormonal therapy for patients with locally recurrent breast cancers which are estrogen receptor positive.(Level I, Category A) Tamoxifen is given at a dose of 20 mg daily and is given continuously even if there is complete response, until disease progression. (Level III, Category A)*

14. *For elderly postmenopausal women with long disease free interval ($\geq$2 years between primary treatment and local recurrence) whose recurrence is confined to skin and soft tissue, locoregional treatment may not be done and tamoxifen alone may be given. (Level III, Category A)*

15. *For patients with locally recurrent breast cancer which are estrogen receptor negative, chemotherapy may increase survival but the size and duration of the benefit is unclear. (Level II, Category A)*

C. Metastatic Breast Cancer

1. *The primary goal of therapy for patients with metastatic breast cancer is palliation. Palliative care is the active total care of patients whose disease is no longer responsive to curative treatment. The goal of palliative care is achievement of the best possible quality of life for patients and their families. Control of pain and of other symptoms, and alleviation of psychological, social, and spiritual problems are paramount. (Level III , Category A)*

2. *The WHO method of cancer pain relief should be immediately started for all patients with metastatic breast cancer who complain of pain. (Level III , Category A)*

3. *In general, for patients with metastatic breast cancer, systemic chemotherapy may be offered because it has been shown to confer a modest survival benefit of 6-9 months. (Level II, Category A)*

4. *The determination of estrogen receptor (ER) status of the metastatic lesion is encouraged. However, patients with metastatic breast cancer with unknown estrogen receptor status are managed as estrogen receptor positive tumors. (Level III, Category A)*

5. *For patients with metastatic breast cancer which are estrogen receptor positive, hormonal therapy is the initial systemic treatment given. (Level III, Category A)*

6. *Tamoxifen is the preferred first-line hormonal therapy for patients with metastatic breast cancer which are estrogen receptor positive.(Level I, Category A) Tamoxifen is given at a dose of 20 mg daily and is given continuously, even if there is complete response, until disease progression. (Level I, Category A)*

7. *Patients with metastatic breast cancer who responded to tamoxifen initially are offered second line hormonal therapies at the time of disease progression. (Level I, Category A)*

8. *For patients with metastatic breast cancer which are estrogen receptor negative, chemotherapy may increase survival but the size and duration of the benefit is unclear. (Level II, Category A)*

9. *There is no survival benefit among the different polychemotherapy regimens. Continued therapy until disease progression is better compared to limited therapy. However, drug toxicity and complications of chemotherapy should be given serious consideration bearing in mind that palliation of symptoms and not tumor response is the main goal of therapy. (Level I, Category A)*

10. *The addition of chemotherapy to hormonal therapy does not confer a survival benefit for patients with metastatic breast cancer who are already responding to hormonal therapy. Likewise, the addition of hormonal therapy to chemotherapy does not confer a survival benefit*

for patients with metastatic breast cancer who are already responding to chemotherapy. (Level I, Category A)

11. *Radiotherapy may be given to symptomatic patients with bone metastases for relief of symptoms. (Level I, Category A)*

12. *For patients with bone metastases, bisphosphonates may be given because they reduce the incidence of skeletal complications and decrease pain medication requirements; however, no survival benefit has been observed. (Level I, Category A)*

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Tables

Table 1. Relative 5-year survival rates for 50,383 patients with breast carcinoma classified by the AJCC staging. Data taken from the American National Cancer Data Base (Commission on Cancer of the American College of Surgeons and the American Cancer Society) for the year 1989.

Stage	N	5-year survival (%)
0	5,686	100
I	21,604	98
IIA	10,412	88
IIB	5,673	76
IIIA	1,864	56
IIIB	2,035	49
IV	3,109	16

Table 2 Detection rate of asymptomatic distant metastases from stage III breast cancer by stage and test.(Ciatto, 1985).

Stage	Chest X-ray	Bone X-ray	Bone scan	Liver echocardiography
IIIA	0.75%	-----	0.96%	____
IIIB	1.20%	2.09%	1.33%	0.85%

Table 3. Number of examinations to detect one case of asymptomatic distant metastases from stage III breast cancer according to stage and test. (Ciatto, 1985)

Stage	Chest X-ray	Bone X-ray	Bone scan
IIIA	133	-----	104
IIIB	83	48	75

Table 4. Summary of data from three randomized controlled trials on "locally advanced breast cancer" cases according to treatment and survival rates, 2002.

Trial	TNM Stage	n	Intervention	Over-all survival				Median
				5 yr	8 yr	9 yr	10 yr	survival
Olson[9]	IIA	9	MRM + CT/HT	-	-	-	-	-
(ECOG)	IIB	21	MRM + RT	-	-	46%	-	8.3 yrs
	IIIA	226	MRM + OBS	-	-	47%	-	8.1 yrs
	IIIB	170		-	-	-	-	-
Koning[10]	LABC		(1) RT	38%	-	-	13%	-
(Netherlands)		118	(2) RT/CT+HT	35%	-	-	21%	-
			(3) CT/RT/CT+HT	41%	-	-	28%	-
Bartelink[11]	IIIA	111	(1) RT	28%	12%	-	-	-
(EORTC)	IIIB	161	(2) RT+CT	30%	20%	-	-	3.8 yrs

others	103	(3) RT+HT	36%	26%	-	-	4.3 yrs
		(4) RT+HT+CT	49%	35%	-	-	5 yrs

MRM – mastectomy+axillary dissection; CT – chemotherapy; HT – hormonotherapy; RT – radiotherapy; OBS – observation

Table 5. Disease free-survival by treatment arms of "locally advanced" breast cancer patients. (Koning & Hart, 1998)

Treatment	Disease-free survival (%)*	
	5-year	10-year
Radiotherapy (RT) alone	11	4
Radiotherapy/CMF/Tamoxifen	21	15
AV, then RT;AVCMF/Tamoxifen	23	15

*p log rank = 0.26

Table 6. 5-year survival rates by breast cancer stage. (Pierce, et al, 1992)

Stage	Disease-free survival (%)	Over-all survival (%)
IIIA	55	61
IIIB IBC	33	36
IIIB non-IBC	31	31

IBC- inflammatory breast cancer

Table 7. Survival rates with or without polychemotherapy in node positive early breast cancer patients.(EBCTCG report on 47 trials),1998.

Age-group	Intervention	5-year survival (%)	10-year survival (%)
< 50	with chemotherapy	68.6	53.8
	without chemotherapy	61.8	41.4
50 & above	with chemotherapy	70.8	48.6
	without chemotherapy	68.7	46.3

Table 8. Results of two retrospective studies on the prognostic impact of early detection of breast cancer local recurrences.(Ciatto, 1995)

	Asymptomatic Recurrences	Symptomatic Recurrences
Ciatto 1984		
Disease free interval	19 months	22 months
5 yr actuarial survival	54 %	40 %
Median survival	75 months	60 months
Ciatto 1985		
Disease free interval	27 months	30 months
5 yr actuarial survival	60 %	49 %

10 yr actuarial survival	31 %	28 %
Median survival	45 months	46 months

Table 9. Performance of fine needle aspiration cytology in the diagnosis of suspected breast cancer local recurrences. (Ciatto 1995)

Recurrence site	Inadequacy rate (%)	Sensitivity rate (%)	Specificity rate (%)
Axilla	1.9	100	100
Internal mammary	25.0	100	100
Chest wall	31.1	94.1	90.5
Supraclavicular	12.7	98.8	100

Table 10. Complications in 93 chest wall resections for recurrent cancer,U.T.M.D. Anderson Cancer Center, 1989.

	WOUND	PULMONARY	OTHER	TOTAL	NO.OF OPERATIONS W/ COMPLICATIONS
MINOR	9	6	6	21	17
MAJOR	4	4	6	14	12 (12.9%)
TOTAL	13	10	12	35	29 (30.1%)

Table 11. Clinical trials evaluating initial chemotherapy versus initial hormonal therapy in patients with metastatic breast cancer. NHMRC Clinical Trials Centre and the Cochrane Collaboration Review Group in Breast Cancer in Australia, 1998.

	Trial		**Median survival (months)**					**Tumour response (CR + PR)**	
	Exp	**Con**	**N**	**Exp**	**Con**	**Exp/ Con**	**p value**	**% Exp**	**Con**
Priestman T (1978)	CT	ET (various)	92	16	7	2.29	-	49	21
Anon (1986)	AC - > tam	tam - > AC	226	19	22	0.86	-	45	22
		Combined results	318	18	18	1.14	0.73		
	(95% confidence interval)					(0.02-60.3)			

CT = chemotherapy
ET = endocrine therapy
Exp = experimental arm
Con = control arm
CR = complete response
PR = partial response
AC = adriamycin – cyclophosphamide
tam = Tamoxifen

Table 12. Clinical factors that predict response to hormonal treatment in metastatic breast cancer . (Clinical Evidence, British Medical Publishing Journal Group, 2000)

Factors predictive of good response to hormonal treatment
• Postmenopausal status • Disease limited to soft tissue (skin, nodes) • ER positive tumor • Long disease free interval since primary treatment for early breast cancer (> 12- 18 months)
Factors making initial hormonal treatment less appropriate
• Symptomatic visceral metastases • ER negative tumor • Short disease free interval (12-18 months) • Relapse on adjuvant tamoxifen (unless ER positive tumor and other features predictive of good response)

Table 13. Clinical trials evaluating tamoxifen versus other hormonal agents in patients with metastatic breast cancer. NHMRC Clinical Trials Centre and the Cochrane Collaboration Review Group in Breast Cancer in Australia, 1998.

				Median Survival (months)				Tumour response CR+PR %	
	Exp	Con	N	Exp	Con	Exp/ Con	p value	Exp	Con
Muss H (1988)	tam	MA 160	136	36	26	1.38	0.12	31	28
van Veelen H (1986)	tam 40	MPA 900	129	26	20	1.30	-	35	44
Gill P (1993)	tam	MA	118	19	16	1.19	0.30	26	37
Viladiu P (1985)	CMF + tam	CMF + MPA	65	25	22	1.14	-	70	68
Ingle J (1986)	tam	Ooph	53	25	24	1.04	0.40	31	35
Perez Carrion RP (1994)	tam	formestane	409	34	33	1.03	0.70	37	33
Smith I (1982)	tam	AG	117	20	20	1.00	-	30	30
Castiglione-Gertsch M (1993)	tam - > AG	MPA - > AG	64	20	22	0.91	0.40	30	50
Gale K (1994)	tam	AG	216	22	26	0.85	-	35	46
Ingle J (1982)	tam	MA	55	13	17	0.76	0.16	26	14
Muss H (1994)	tam	MPA	182	24	33	0.73	0.09	17	34
Castiglione-Gertsch M (1993)	tam - > MPA	MPA - > tam	60	22	36	0.61	0.40	30	50
Buchanan R (1986)	tam	Ooph	117	15	25	0.60	0.18	24	21
		Combined Results (95% confidence interval)	1721	26	26	0.95 (0.82-1.10)	0.83		

tam = Tamoxifen 20 mg
tam40 = Tamoxifen 40 mg
CMF = cyclophosphamide –methotrexate-5 Fu
AG = aminogluthetimide
MA = megesterol acetate; MA 160 = megestrol acetate 160 mg
MPA = medoxyprogesterone acetate; MPA 900=medoprogesterone acetate 900 mg
Ooph = oophorectomy

Table 14. Clinical trials evaluating anthracyline based versus non-anthracycline based chemotherapy regimens in women with metastatic breast cancer. (Italian Cochrane Center,1998)

Study Name	Regimens: Poly (Anthra)	Regimens: Poly (no Anthra)
Poli(Anthra) vs Poli(no Anthra)		
* 1976 Brambilla C. (27)	AV	CMF
1978 Bull J.M. (28)	FAC	CMF
* 1979 Bezwoda W.R. (30)	CMFA	CMF + VBL
1982 Muss H.B. (33)	VAC	CMF
* 1982 Tormey D.C. (34)	AV	CMF
1984 Creagan E.T. (36)	CA + CDDP – > CF + P	CF + P ± V
* 1984 Tormey D.C. (37)	FACV + P	CMFV + P (CMFVP – I)
* 1984 Tormey D.C. (37)	FACV + P	CMFV + P (CMFVP – C)
* 1987 Alsner J. (40)	FACV + P	CMF
* 1987 Alsner J. (40)	FAC	CMF
* 1987 Leonard R.C.F. (41)	AV + P	MZA + V + P
1988 Bennet J.M. (42)	FAC	F + MZA + C
1990 Cocconi G. (44)	CAMV/CAFV/MAFV	CMF
* 1990 Porzsolt F. (46)	FEC	MF + CLB
1991 Ahmann D.L. (47)	AC + P	CF + P
* 1991 Falkson G. (study B122) (48)	FAC	CMF
* 1991 Powles T.J. (50)	VAC or VEC	MMC + MZA + M
* 1995 Alonso M.C. (52)	FAC	F + MZA + C
1995 Pavesi L. (54)	FEC	F + MZA + C
1996 Green J.A. (55)	VAC	V + MZA + C
[redacted] Subtotal (Deaths/Patients)	1130/1423	1117/1367
Poli(Anthra)vs Poli(no Anthra) + P		
* 1981 Carmo – Pereira J. (32)	VAC	CMF + P
* 1982 Tormey D.C. (34)	AV	CMF + P
* 1983 Smalle[illegible]	FAC	CMFV + P
* 1985 Cumm[illegible] **Mortality rate**	**79.9 %**	**80.5 %** P
* 1989 Rosne[illegible]		P
* 1989 Rosner D. (43)	AV	VF + P
[redacted] Subtotal (Deaths/Patients)	427/527	337/439
[redacted] TOTAL (Deaths/Patients)	1557/1950	1454/1806

Table 15. Clinical trials evaluating less versus more cycles of chemotherapy in patients with metastatic breast cancer. (NHMRC Clinical Trials Centre and the Cochrane Collaboration Review Group in Breast Cancer in Australia, 1998)

				Median Survival (months)				Tumour response (CR + PR) %	
	Exp	Con	N	Exp	Con	Exp/ Con	p value	Exp	Con
Ejlertson B (1993)	FEC x 24 + tam	FEC x 8 + tam	318	23	18	1.28	0.03	52	52
Coates A (1987)	continuous AC or CMF	intermittent AC or CMF	305	11	9	1.22	0.14	49	32
Harris A (1990)	continuous CT	intermittent CT	43	11	12	0.92	-	-	-
		Combined Results	666	17	13	1.23	0.01		
		(95% confidence interval)				(1.01-1.49)			

FEC = 5 Fu-Epirubicin-cyclophosphamide
tam = Tamoxifen
AC = adriamycin – cyclophosphamide
CMF = cyclophosphamide- methotrexate – 5 Fu
CT = chemotherapy

Table 16. Clinical trials evaluating additional chemotherapy versus no additional chemotherapy in patients with metastatic breast cancers who were given hormonal therapy initially. (NHMRC Clinical Trials Centre and the Cochrane Collaboration Review Group in Breast Cancer in Australia, 1998)

				Median Survival (months)				Tumour response (CR + PR) %	
	Exp	Con	N	Exp	Con	Exp/ Con	p value	Exp	Con
Kiang D (1985)	stilboestrol + CF (ER+)	stilboestrol	40	72	29	2.48	0.05	86	53
Ahmann D (1982)	ooph + CT	Ooph	76	31	20	1.55	0.90	-	-
Rossof A (1982)	ooph + CMF	ooph	40	41	29	1.41	-	55	44
Kiang D (1985)	stilboestrol + CF (ER?)	stilboestrol	41	36	33	1.09	0.60	63	23
Bezwoda W (1982)	Tam + CMF	tam -> CMF	50	18	17	1.06	-	65	63
Anon (1986)	Tam + AC	tam -> AC	226	21	22	0.95	-	51	22
Abe O (1995)	MPA + CAF	MPA	48	23	25	0.92	-	43	24

Falkson G (1979)	ooph + CT	ooph	91	26	30	0.87	0.80	75	18
Falkson G (1979)	ooph + cyclo	ooph	92	26	32	0.81	0.80	62	18
		Combined Results	704	28	25	1.06	0.85		
		(95% confidence interval)				(0.85-1.32)			

CF = cyclophosphamide –5 Fu
(ER+) = Estrogen Receptor positive
ooph = oophorectomy
CT = chemotherapy
CMF = cyclophosphamide-methotrexate-5Fu
(ER?) = Estrogen Receptor unknown
MPA = medoxyprogesterone acetate
tam = Tamoxifen
AC = adriamycin – cyclophosphamide
CAF = cyclophosphamide – adriamycin – 5Fu
cyclo = cyclophosphamide

Table 17. Clinical trials evaluating additional hormonal therapy versus no additional hormonal therapy in patients with metastatic breast cancer given chemotherapy initially. (NHMRC Clinical Trials Centre and the Cochrane Collaboration Review Group in Breast Cancer in Australia, 1998)

				Median Survival (months)				Tumour response (CR + PR)	
Author (Year)	**Exp**	**Con**	**N**	**Exp**	**Con**	**Exp/ Con**	**p value**	**% Exp**	**Con**
Boccardo F (1995)	CMFV/AC + tam	CMFV/AC	68	34	20	1.70	0.05	75	42
Falkson G (1995)	CAF + ooph	CAF	80	42	30	1.40	0.60	84	76
Abe O (1995)	CAF + MPA	CAF	48	23	18	1.28	-	43	36
Mouridsen H (1985)	CMF + tam	CMF	220	24	19	1.26	0.07	86	51
Tominaga T (1994)	CAF + MPA	CAF	199	22	19	1.16	0.20	54	37
Anon (1986)	AC + tam	AC-> tam	226	21	19	1.11	-	51	45
Viladiu P (1985)	CMF + tam	CMF	67	25	23	1.09	-	70	46
Perry M (1987)	CAF + tam	CAF	379	21	20	1.05	0.76	64	55
Kiang D (1985)	CF + stilboestrol (ER-)	CF	31	16	16	1.00	0.50	53	29
Viladiu P (1985)	CMF + MPA	CMF	64	22	23	0.96	-	68	46

Gundersen S (1992)	CT + MPA 1000	CT	138	9	13	0.69	0.05	73	46
		Combined Results	1520	22	20	1.10	0.14		
		(95% confidence interval)				(0.97-1.25)			

CMFV = cyclophosphamide –methotrexate – 5Fu – vincristine
AC = adriamycin – cyclophosphamide
tam = Tamoxifen
CAF = cyclophosphamide-adriamycin – 5Fu
ooph = oophorectomy
MPA = medoxyprogesterone acetate
CF = cyclophosphamide – 5Fu
CT = chemotherapy
(ER -) = Estrogen receptor negative

Figures

Figure 1. Ratio of median survival between initial chemotherapy versus initial hormonal therapy in patients with metastatic breast cancer. NHMRC Clinical Trials Centre and the Cochrane Collaboration Review Group in Breast Cancer in Australia, 1998.

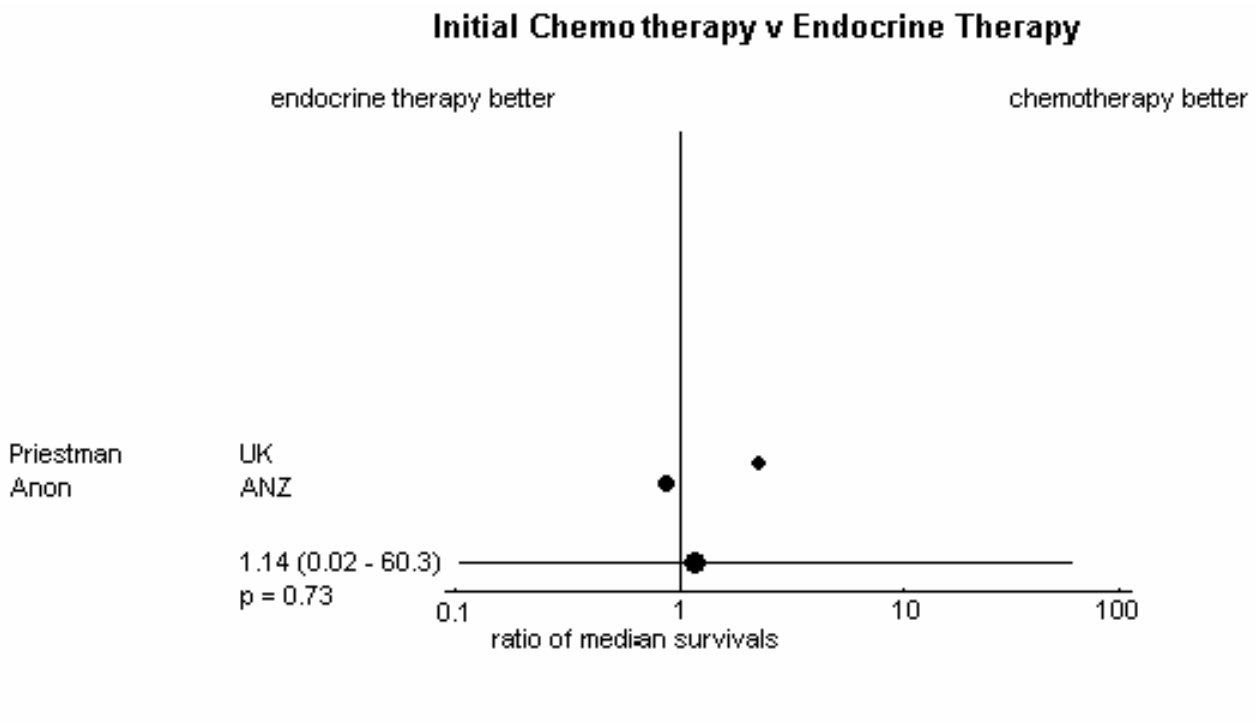
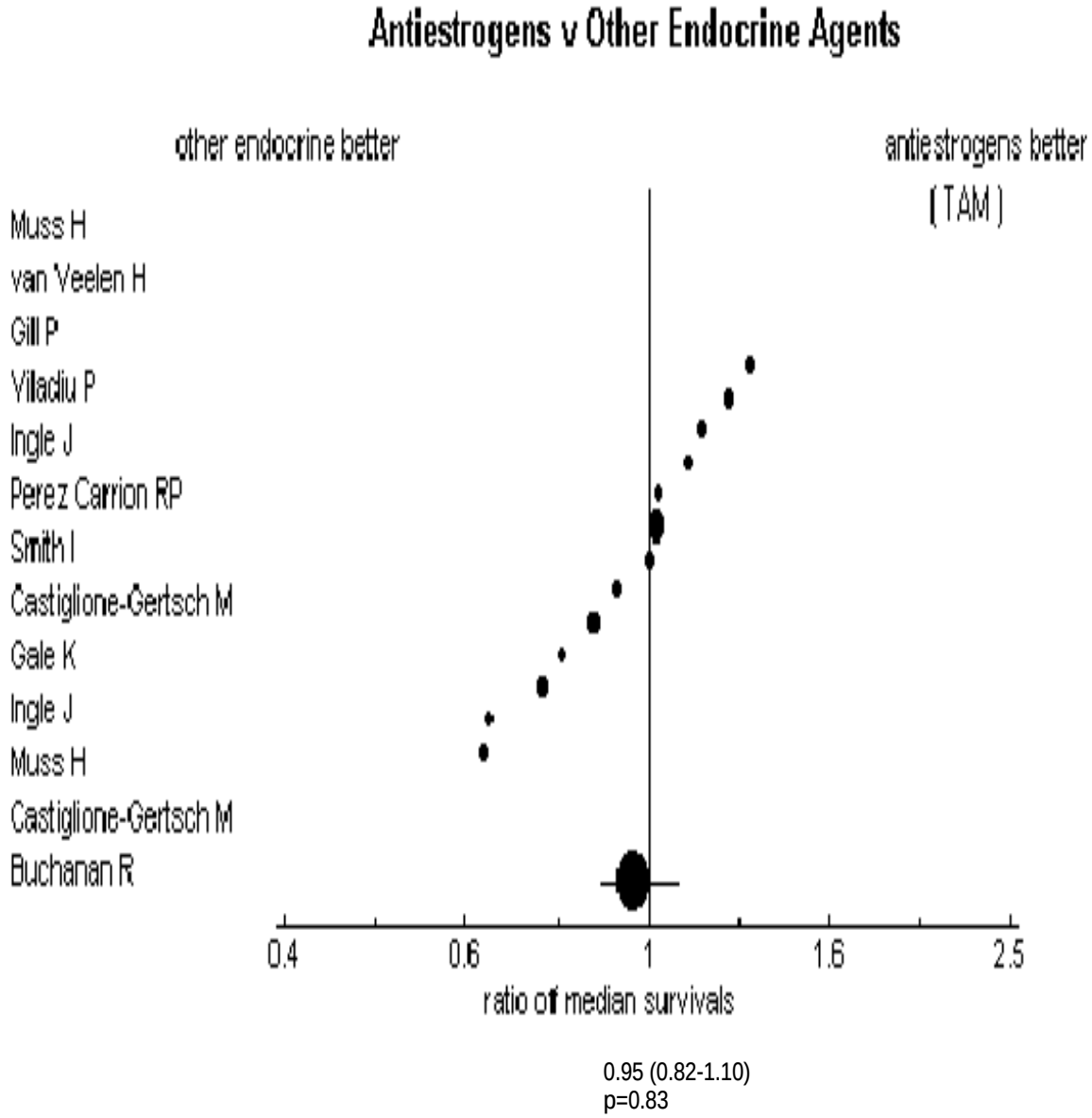
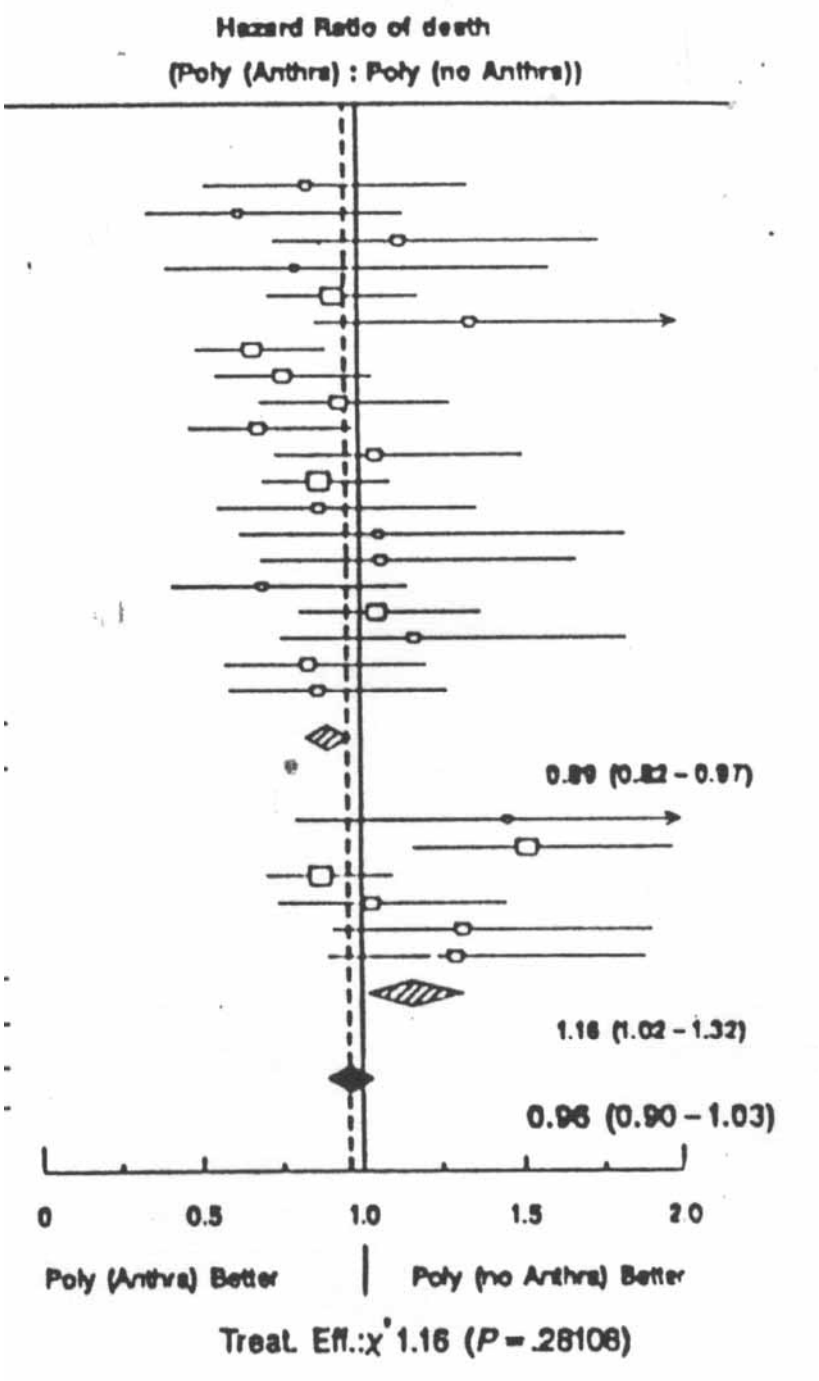


Figure 2. Ratio of median survivals in patients with metastatic breast cancer given tamoxifen versus other hormonal agents.(NHMRC Clinical Trials Centre and the Cochrane Collaboration Review Group in Breast Cancer in Australia, 1998)



TAM=Tamoxifen

Figure 3. Treeplot on the hazard ratios of death of women with metastatic breast cancer given anthracycline-based chemotherapy versus non-anthracycline based hemotherapy. Italian Cochrane Center,1998.



Poly = Polychemotherapy
Anthra= anthracycline - based

Figure 4. Ratio of median survivals in patients with metastatic breast cancer given fewer versus more cycles of chemotherapy. NHMRC Clinical Trials Centre and the Cochrane Collaboration Review Group in Breast Cancer in Australia, 1998.

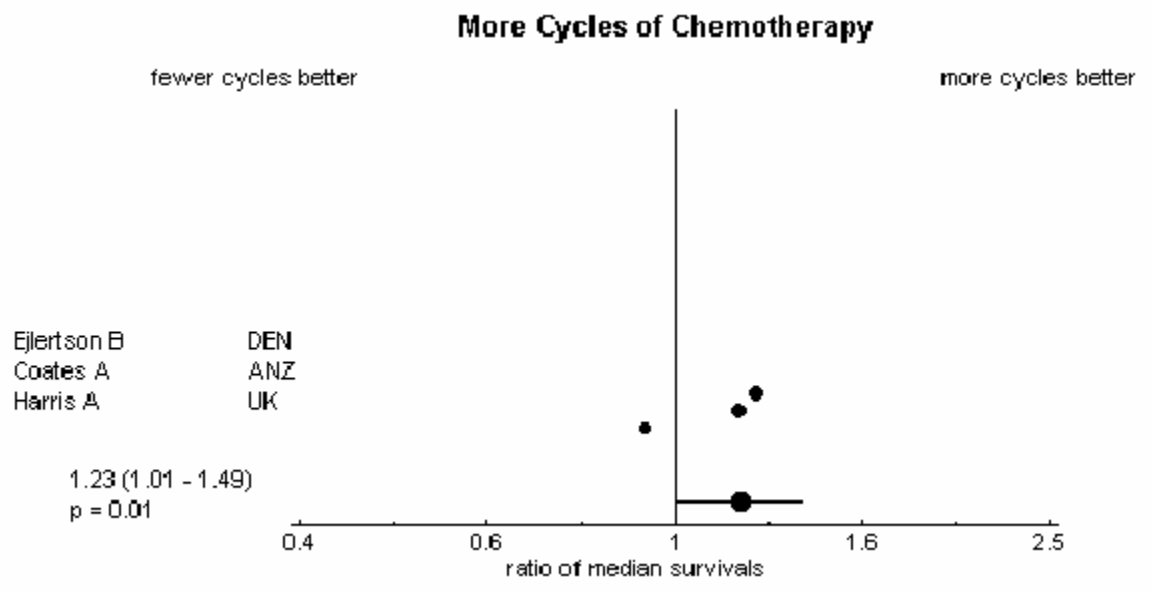


Figure 5. Ratio of median survival between additional chemotherapy versus no additional chemotherapy in patients with metastatic breast cancer who were given hormonal therapy initially.NHMRC Clinical Trials Centre and the Cochrane Collaboration Review Group in Breast Cancer in Australia, 1998.

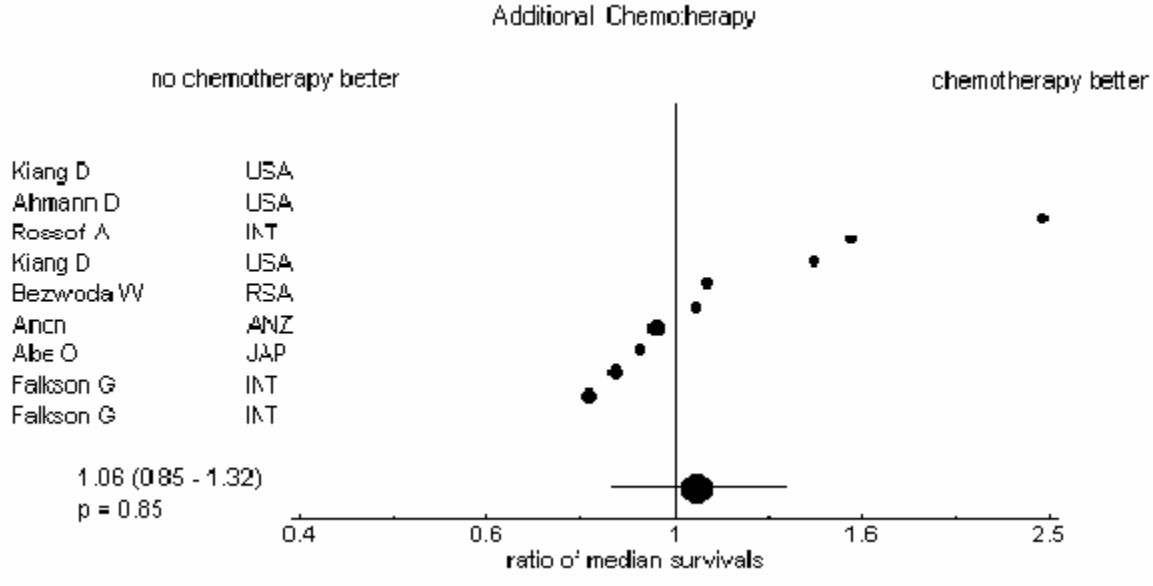


Figure 6. Ratio of median survival between additional hormonal therapy versus no additional hormonal therapy in patients with metastatic breast cancer given chemotherapy initially.NHMRC Clinical Trials Centre and the Cochrane Collaboration Review Group in Breast Cancer in Australia, 1998.