

MANUSCRIPT 1

EVIDENCE – BASED CLINICAL PRACTICE GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF BREAST CANCER PART I. EARLY BREAST CANCER

Maria Lourdes De Leon Matsuda, M.D., F.P.C.S.¹; Adriano V. Laudico, M.D., F.P.C.S.¹;
Victor Ernesto D. Yosunico, M.D., F.P.C.P.², M. Francisco T. Roxas, M.D., F.P.C.S.¹;
Nelson D. Cabaluna, M.D., F.P.C.S.¹, Frances J. Blanco, M.D.¹

¹ Department of Surgery, College of Medicine and Philippine General Hospital, University of the
Philippines, Manila

² Section of Medical Oncology, College of Medicine and Philippine General Hospital, University of the
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¹ Department of Surgery, College of Medicine and Philippine General Hospital, University of the
Philippines, Manila

² Section of Medical Oncology, College of Medicine and Philippine General Hospital, University of the
Philippines, Manila.

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 evidenced- based, and have a large potential of improving major outcomes and even decreasing costs, and the EBCPGs can be implemented 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 of the care of critically ill surgical patients.²

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

Breast cancer had been consistently 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 will occur 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 and lead to wrong perceptions that seriously affect the management of breast cancer.

METHODS

The PCS appointed a Technical Working Group (TWG) composed of 5 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 and 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 two parts: Part I. Early Breast Cancer, and Part II. Locally Advanced and Metastatic Breast Cancer.

The definition of early breast cancer is that used by the Early Breast Cancer Trialists’ Collaborative Group (EBCTG), since the regular systematic reviews (meta – analysis) of the group on the primary and adjuvant therapies of early breast

cancer currently comprise the strongest evidence. “In women with “early breast cancer”, all detectable cancer is, by definition, restricted to the breast and, in the case of node positive patients, the local lymph nodes can be removed surgically.”

The TWG began work on 3 July 2000 and the clinical questions were listed, then revised as the search of the literature progressed. The literature search, limited to English publications, used both electronic and manual methods. Three electronic databases were used:

- 1) The Cochrane Library, Issue 2, 2000;
- 2) National Library of Medicine – Medline (Pubmed, no time limit); and
- 3) Herdin (Health Research and Development Information Network) Version 1, 1997 of DOST – PCHRD.

Manual searching of the reference lists of review articles, meta – analyses, and important randomized controlled trials (RCTs) were also done.

Search (MeSH) terms were:

1) Diagnosis :

diagnosis of breast cancer; fine needle aspiration cytology; core needle biopsy; frozen section; mammography; ultrasonography; in palpable breast tumors.

2) Staging and Follow Up:

staging for breast cancer; chest x-ray; liver ultrasound; liver scan; bone scan; CT scan; liver function tests; alkaline phosphatase; follow up surveillance after treatment for breast cancer

3) Primary Treatment :

breast cancer treatment AND surgery AND survival AND RCT; meta – analysis

4) Adjuvant Therapy :

meta– analysis of adjuvant therapy in early breast cancer;
meta – analysis of survival in early breast cancer; adjuvant therapy AND breast cancer, RCT.

In topics where there were few or no RCTs, cohort studies, case – control studies, case series reports, and review articles were included, and their references manually searched. The primary outcome of interest was survival (overall and disease free) for primary and adjuvant treatment, and for preoperative (staging) and postoperative (follow up) surveillance. Locoregional recurrence was also noted as a secondary outcome of interest in primary and adjuvant treatment. Since there were no studies with the outcome of survival in preoperative surveillance, secondary outcomes evaluated were diagnostic yield or detection rates, and predictive values of the various laboratory tests for metastatic work up. For diagnosis, there were also no studies relating the various diagnostic modalities to survival; therefore, the secondary outcome evaluated was test characteristics of the different exams.

Titles of the articles were printed and members of the TWG went over the list and checked the titles of articles whose abstract they felt should be read. The abstracts of all checked articles were printed. The printed abstracts were read by at least 2 members of the TWG, who then decided which articles were to be included for full text retrieval. The full texts were obtained from the University of the Philippines Manila Library, the Medical Resource Center of the Philippine General Hospital, and the Library of the World Health Organization in Manila. The full texts were appraised using standard forms which included a data extraction sheet. (Appendix 1 - 3)

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.
- 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 were the clinical questions :

1. What are the test characteristics of the following diagnostic procedures in the diagnosis of breast cancer in women with a palpable breast mass with the histologic diagnosis of the resected specimen as the reference standard ?
 - 1.1 Fine needle aspiration cytology (FNAC)
 - 1.2 Core needle biopsy (CNB)
 - 1.3 Frozen section biopsy
 - 1.4 Mammography
 - 1.5 Ultrasonography
 - 1.6 Other breast imaging examinations
2. What is the survival benefit of utilizing specific diagnostic tests to search for possible distant metastases preoperatively in women with early (potentially curable) breast cancer ?
 - 2.1 Chest X – ray
 - 2.2 Liver function tests : SGPT, alkaline phosphatase
 - 2.3 Ultrasound of the liver
 - 2.4 Liver scan
 - 2.5 Bone scan
3. What is the survival benefit of an intensive follow – up regimen which utilizes specific diagnostic tests to search for possible distant metastases for women who underwent surgery for early breast cancer as compared to a symptom – directed follow - up?

- 3.1 Chest X – Ray
 - 3.2 Liver function tests – SGPT, alkaline phosphatase
 - 3.3 Ultrasound of the liver
 - 3.4 Liver scan
 - 3.5 Bone scan
 - 3.6 Chest CT scan
 - 3.7 Brain CT scan
4. What are the survival and locoregional control benefits of the following primary therapies for women with early (potentially curable, ie. Stage I to III A) breast cancer ?
- 4.1 Classical radical mastectomy
 - 4.2 Modified radical mastectomy
 - 4.3 Breast conservation surgery with radiotherapy
 - 4.4 Breast conservation surgery without radiotherapy
5. What are the survival and locoregional control benefits of the following adjuvant therapies following surgery for women with early (potentially curable) breast cancer ?
- 5.1 Radiotherapy
 - 5.2 Hormonal therapy
 - 5.3 Chemotherapy
 - 5.4 Combination

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 November 11, 2000 at the PCS building. A second draft was prepared by the TWG and this was discussed in a Public Forum on December 10, 2000 during the 56th Clinical Congress of the PCS held at the Edsa Shangri-la Hotel. The guidelines were approved by the PCS Board of Regents on December 13, 2000.

RESULTS

A. DIAGNOSIS OF BREAST CANCER

1. What are the test characteristics of the following diagnostic procedures in the diagnosis of breast cancer in women with a palpable breast mass with the histologic diagnosis of the resected specimen as the reference standard ?

1.1 Fine Needle Aspiration Cytology (FNAC)

There were 1,075 titles found, 310 abstracts were reviewed, and 129 full text articles were selected. A total of 7 articles in the use of fine needle aspiration cytology (FNAC) in the diagnosis of breast cancer were used for the formulation of the guidelines.

One meta – analysis (Giard 1992)⁵ included 58 trials of which 29 articles (31,340 aspirations) met the strict inclusion criteria:

- 1) results had to be classified into 4 cytologic outcome categories: definitely malignant, suspect for malignancy, benign, and unsatisfactory specimen for diagnosis ; and
- 2) the final diagnostic category was settled histologically or by combined histologic and clinical follow – up.

There was considerable variation in both prevalence of breast cancer and test characteristics. (Table 1) The only exception was the consistently low false positive (0.00 – 0.02), or “definitely malignant” cytological diagnosis in benign breast disease. The authors partly attributed the variations to the test’s being highly operator dependent. This operator dependency stresses the importance of determining the effectiveness of FNAC in a particular (local) diagnostic setting to provide data for optimal practice policy.

A second meta – analysis came from the University of Naples and focused on all the Italian reports (1,153 aspirations) which were all included in Giard’s meta–analysis.⁶ A year later (1993), 2 reports from prospective studies done at the University of Texas M.D. Anderson Cancer Center⁷ (1,995 aspirations) and the University of South Florida⁸(1,875 aspirations) were published. The three reports showed a high global accuracy of test characteristics done by a team of dedicated surgeons and cytopathologists, and probably represents the best results to be obtained in FNAC. The average values for the

test characteristics were 95 per cent sensitivity, 97 per cent specificity, positive predictive value of 0.98, and negative predictive value of 0.91.

In a recent survey by Laudico et. al. on some practices regarding breast cancer management by surgeons in the Philippines, FNAC was widely available (93.9 %); and was the most preferred diagnostic method (42.6 %), followed by open biopsy (34.4%)⁹

During the en banc modulation by the panel of experts, it was pointed out that since FNAC is a highly operator dependent procedure, the PCS should set up standards regarding FNAC. In localities wherein the standards are not met like in remote places where there are no trained cytopathologists or in centers where the accuracy of FNAC is low, open biopsy should be the standard diagnostic procedure.

Recommendations

- 1. In patients with a palpable breast mass in which cancer is suspected, BIOPSY is mandatory. (Level I, Category A)*
- 2. Fine needle aspiration cytology (FNAC) is the initial diagnostic procedure in patients with a palpable breast mass in which cancer is suspected. (Level I, Category A)*
- 3. If the FNAC result is malignant, the patient is offered the different treatment options. (Level I, Category B)*
- 4. If the FNAC result is benign but clinical findings are really highly suspicious for breast cancer, either a core needle or an open biopsy is done. (Level II, Category A)*
- 5. The PCS should set up standards regarding FNAC. (Level III, Category A)*

1.2 Core Needle Biopsy (CNB)

There were 284 titles found; 161 abstracts were reviewed, 62 full text articles were selected, and 7 articles used for formulation of guidelines.

Core needle biopsy of breast masses had been reported to have acceptable test characteristics. Sensitivity values are in the range of 88 – 96.7 per cent¹⁰⁻¹⁵, with a mean sensitivity of approximately 90 per cent ; and specificity of 100 per cent. In 1996, one retrospective study on 109 patients from the City Hospital in Nottingham, England showed that CNB was better than FNAC because it had the diagnosis confirmed in 88 per cent of cases compared to only 80 per cent on FNAC. However, three prospective cohort

studies on a total of 474 women from the University of Patras in Greece (1996),¹¹ University of Texas M.D. Anderson Cancer Center (1996),¹³ and University of Hong Kong (1987),¹⁵ showed that FNAC had comparable or even higher sensitivity values compared to CNB. Table 2 shows this comparison.

The special aspirating needles used in CNB are not widely available and are expensive. Moreover, CNB is a more painful procedure which requires local anesthesia in most instances. Complications of bruising or hematoma formation have also been commonly reported.¹⁴ Minkowitz et al also showed that the sensitivity of CNB decreases as the size of the tumor decreases; mainly because of nonrepresentative sampling. The sensitivity of CNB was 94 per cent for tumors ≥ 2.5 cm; but sensitivity dropped to 89 per cent when the tumor was < 2 cm.¹⁴

Based on the foregoing data, FNAC seems to be better than CNB as the initial diagnostic exam in women with a palpable breast mass suspicious for cancer. However, in cases wherein the initial FNAC test result was unsatisfactory, Carty et al showed that CNB had a higher sensitivity (89 %) compared to a repeat FNAC (10 % sensitivity).¹⁶

Recommendations

6. If the FNAC is unsatisfactory or interpreted as suspicious, core needle biopsy or open biopsy is advised. (Level I, Category A)

In 1993, Gordon et al¹⁷ published the results of their prospective cohort study on 805 nonpalpable and small palpable solid breast lesions. Of the 805 solid breast lesions, there were 580 benign tumors and 225 cancers, of which 94 per cent were palpable (at least 1 cm in size). Given the small size of the breast masses which were also usually deep seated, the authors hoped to improve the accuracy of diagnosis by providing more accurate sampling using ultrasound guided fine needle aspiration biopsy. There was no direct comparison of palpation guided FNAC versus sonographically guided FNAC. However, if one uses the palpation guided FNAC test characteristics from the meta – analysis of Giard for comparison, it will be seen that sonographically guided FNAC had better results showing sensitivity and specificity values on the high end of the range. There was also evidence of more accurate sampling using sonographically guided biopsy because false negative and inadequate smears were on the low end of the range. Table 3 shows this comparison.

Recommendations

7. *For tumors ≤ 1 cm in size, sonographically guided FNAC or core needle biopsy is recommended. In places where sonography facilities are unavailable, open biopsy is done. (Level II, Category A)*

1.3 Frozen Section

There were 285 titles found, 92 abstracts were reviewed, 30 full text articles were selected, and 16 articles were used in the formulation of the guidelines.

Review of the literature¹⁸⁻³² showed that frozen section histology is a highly reliable procedure for the diagnosis of invasive ductal carcinoma of the breast. These retrospective studies showed that frozen section had a mean sensitivity of 94 per cent, and was practically devoid of false positive results. However, it “ does not allow adequate discussion with the woman about her surgical management.”³³ In addition, it prolongs operating and anesthesia time, and increases costs.

In the previously cited survey , frozen section services were available in 80.08 % of medical centers in the country; and was the third preferred initial diagnostic method (11.1 %), second to FNAC (42.6 %) and open biopsy (34.4%).⁹

This report supports the practice that physicians should not resort to frozen section as the initial diagnostic procedure unless it is the patient herself, who after being enlightened on the advantages and disadvantages of all diagnostic procedures, still prefers it to be her initial diagnostic procedure.

Recommendations

8. *Frozen section histology is done only when the patient requests it. (Level III, Category A)*

1.4 – 1.6 Mammography, Ultrasonography and other breast imaging examinations.

There were 2,820 titles found, 87 abstracts were reviewed, 30 full text articles were selected, and 18 articles were used for the formulation of the guidelines.

Mammography, ultrasonography, and other breast imaging examinations have been used by some physicians to improve the accuracy in arriving at a pre-operative

diagnosis in women with a palpable breast mass suspicious for cancer. However, all the articles, which were either prospective or retrospective studies showed that these breast imaging studies did not provide additional sensitivity in any of the cases.³⁴⁻³⁹ Homer (1985) emphasized the salient point in his review: “Because of the overlapping appearance of benign and malignant lesions, mammography should not be used to decide that a breast mass is benign ... the decision to biopsy the palpable mass must be based on clinical grounds”.³⁸ Other authors of prospective and retrospective studies^{40 - 43} have arrived at basically the same conclusion regarding breast ultrasonography: “Sonography, while capable of imaging or visualizing and categorizing most palpable breast masses; cannot reliably differentiate benign from malignant solid lesions.”

There have been countless women whose breast cancers have been “missed” and allowed to progress to more “advanced “ stages simply because their lesions were not detected or were classified as “benign” by either mammography and sonomammography. With the evidence presented, it is hoped that physicians do not use these imaging studies to diagnose or to change their clinical diagnosis in a woman with a breast mass suspicious for cancer. It should be emphasized that, contrary to the prevailing practice of some physicians, mammography and sonomammography should not be requested to arrive at a clinical diagnosis in women already presenting with a breast mass; instead, these women should immediately undergo a biopsy procedure.

Recently, scintimammography has been introduced and marketed as an “alternative” breast imaging examination with the advantage of being relatively “painless” due to the absence of breast compression associated with mammography. The general public, most especially rich women who have fears and anxieties on the compression pains due to mammography, have been drawn to this examination.

However, review of the published literature^{44 - 49} showed that although breast scintigraphy was a sensitive test with a mean sensitivity of 93 per cent ; it was not specific enough to replace conventional mammography and sonography in the diagnosis of breast cancer ; nor is it to be used alone. False positives (mean = 12 %) were not infrequent and were due to increased blood flow, particularly in phyllodes tumors and fibroadenomas in young patients. In addition, breast scintimammography is roughly 4 times more expensive than conventional mammography. Hence, contrary to the practice

of some physicians, we cannot recommend scintimammography as the initial breast imaging modality at this time.

Regarding magnetic resonance imaging (MRI) of the breast, Drew et al⁵⁰ in their prospective cohort study of 186 palpable breast masses, showed that the addition of MRI to standard triple assessment of physical examination, mammography and FNAC did not significantly improve sensitivity (99.2 % vs. 99.2 %). In addition, it was 10 times more expensive than a conventional mammogram. Once again, because of this, we cannot recommend the indiscriminate use of MRI of the breast for diagnostic purposes.

Recommendations

9. Mammography, sonography, and other breast imaging studies do not improve accuracy in arriving at a preoperative diagnosis and should not be used routinely to alter the clinical diagnosis in patients with a palpable breast mass suspicious for cancer. (Level II, Category A)

In women already diagnosed with breast cancer, the established role of mammography is for the detection of multifocal nonpalpable lesions in the involved breast; particularly for patients who are considering breast conservation treatment; and/or synchronous nonpalpable lesions in the contralateral breast. In a retrospective study of 200 patients, Van Dam (1988) concluded that mammography remains the standard for the detection of isolated microcalcifications and minute tumors.⁵¹ In a prospective “screening” study of 1000 patients, Sickles (1983) also showed that mammography had a 98 per cent detection rate for small and nonpalpable cancers, compared to only a 58 per cent detection rate for sonography.⁴¹ There was also indirect evidence from the overview of the Swedish randomized trials on screening mammography which was based on 282,777 women⁵², and the Edinburgh Randomized Trial of Breast Cancer Screening which was based on 44,288 women⁵³; and the meta-analysis reported in the 1997 NIH Consensus Development Conference and published in the Journal of the National Cancer Institute⁵⁴ which had clearly demonstrated the efficacy of “screening” mammography in decreasing mortality in women aged 40 years or older.

Recommendations

10. *In women with early breast cancer, preoperative mammography is recommended to detect subclinical disease in the contralateral breast ; and also in the ipsilateral breast for those patients who will undergo breast conservation treatment.*
(Level II, Category A)

B. STAGING AND FOLLOW UP OF EARLY BREAST CANCER

There is a controversy in the use of diagnostic tests in the management of early breast cancer regarding their usefulness in preoperative surveillance. Some physicians request for a battery of tests as “ metastatic work-up” in women with early breast cancer prior to treatment. The proponents maintain that preoperative “metastatic work-up” could affect health outcomes by documenting early the presence and extent of disease thereby changing or modifying intervention to a more effective treatment.

2. What is the survival benefit of requesting specific diagnostic tests to search for possible distant metastases preoperatively in women with early (potentially curable) breast cancer?

- 2.1 chest x – ray**
- 2.2 liver function tests – SGPT, alkaline phosphatase**
- 2.3 ultrasound of the liver**
- 2.4 liver scan**
- 2.5 bone scan**

There were 138 titles found, 72 abstracts were reviewed, 43 full text articles were selected, and 15 articles were used for the formulation of the guidelines.

There were no studies which showed a survival benefit by earlier detection of occult distant metastases thru a battery of laboratory tests in women with early breast cancer. Since there was no data in the literature with survival as the outcome of interest, the laboratory tests were evaluated in terms of the outcomes which were reported, which were diagnostic yield or “detection rates”, and predictive values.

In 1988, the Italian National Task Force for Breast Cancer published their retrospective study on 3,627 cases. Eighty five per cent of their cases had early or operable breast cancer. The percentage of cases by clinical stage was 24 % Stage I, 33.8

% Stage II A, 19.8 % Stage II B, 7.3 % Stage III A, and 11.5 % for Stage III B. This multicenter study assumed a maximum “lead time” of 6 months. Symptomatic patients within 6 months of a negative “staging” were assumed to be false negatives. Conversely, patients who had no symptoms within 6 months of a positive staging were assumed to be false positives. Table 4 shows their results on the detection rates of the listed laboratory exams done preoperatively or perioperatively in asymptomatic women with breast cancer.

The Italian data showed that in the absence of clinical indications; chest x – rays, bone scans, bone x-rays, liver ultrasound, and liver scans had a very low diagnostic yield with detection rates of < 1 % for all tests.⁵⁵ Using cost – benefit analysis, to detect 1 case of preclinical distant metastases, hundreds of patients are needed to undergo the tests. Table 5 illustrates this point.

Apart from the Italian Study which thus far included the most number of patients (3,627), other studies with smaller patient numbers were also reviewed. There were no RCTs found , only prospective cohort and retrospective studies.

Because the bone is the most frequent site of distant metastases in breast cancer with a reported frequency of approximately 50 per cent⁵⁶, most of the studies on preoperative work up were on the use of bone scans to detect bone metastases. For women with early breast cancer, it was estimated that 20 per cent of patients will eventually develop bone metastases.⁵⁷

The earlier literature ⁵⁸⁻⁶⁹ which reported a 15–40 per cent detection of bone metastases by bone scan preoperatively were based on small patient numbers and included a lot of patients with locally advanced cancers. Furthermore, these studies used a very “ liberal” criteria in determining a positive bone scan result such that arthritis, osteoporosis, and other benign or physiologic conditions of the bones were incorrectly labeled as bone metastases. Moreover, most of these studies did not exclude patients already symptomatic for bone metastasis.

A review of the more recent literature (1978 and later)⁷⁰⁻⁷⁷ from various centers on about 1400 women, which showed a bone scan positivity rate of 0.8 to 1 per cent, is a more accurate estimate of the incidence of occult bony metastases in women with early breast cancer. The value of 0.9 per cent obtained in the earlier cited series done by the Italian National Task Force for Breast Cancer also falls within this range. In these studies,

patients had early breast cancer by definition, and were asymptomatic for bone metastases on presentation.

It is infrequent that the liver is the first site of metastases; hence, fewer studies on the use of preoperative staging liver scan have been published. Four retrospective studies from the Medical College of Georgia⁷⁶, University of British Columbia⁷⁷, Mt. Sinai Hospital in Cleveland⁷⁸; and the previously cited Italian multicentric study⁵⁵, on a total of 982 women and one prospective cohort study from the Baylor University Medical Center⁷⁹ on 220 women showed a very low mean diagnostic yield for preoperative liver scan of 0.4 per cent.

Thus far, the literature showed a very low diagnostic yield or detection rate of the commonly used laboratory tests for preoperative metastatic work up. In addition, the studies showed that they also had very low predictive values. Table 6 shows the overall sensitivity, specificity, and positive predictive values of the listed laboratory tests.

Other studies with smaller patient numbers showed similar results. A prospective cohort study from the Albert Einstein Medical Center in Philadelphia on 64 women with an 8- year follow up showed that only half of the women (9 / 15) with initial positive bone scans actually developed clinical bone metastases.⁸⁰ This means that only 14 per cent (9 / 64) of patients were correctly predicted of having bone metastases. The authors concluded that bone scan was not a good predictor of bone metastases.

Conversely, Lee (1981) reviewed the literature and wrote that most investigators found that several clinicopathologic factors like axilla node involvement, tumor size, and stage of disease had a higher risk of predicting bone metastases than bone scan.⁸¹ A retrospective review of 250 patients in the University of British Columbia⁷⁷ showed that 84 per cent of the 3 per cent (3 / 250) of the patients with bone scan findings indicative of bone metastases had clinical signs and symptoms. This study further supports the view that clinical information on the stage of disease at the time of initial presentation could detect and foretell subsequent relapses better than routine (and serial) bone scans.

Similar findings were observed regarding preoperative liver scan in the preoperative detection of liver metastases. A prospective cohort study from the Baylor University Medical Center in Texas⁷⁹ on 220 women showed a zero incidence of liver metastases based on liver scan for women with stage I – III breast cancer. After a 2- year follow up, 0.9 per cent of women with Stage I disease , 3.4 % (Stage II), and 12.4 %

(Stage III) developed clinical evidence of liver metastases. Seventy per cent of the metastases were detected by history and physical examination alone.

Regarding the usefulness of obtaining preoperative liver enzymes for metastatic work up, the prospective cohort study from the Queens University and Belfast City Hospital in the U.K. on 309 women showed that routine available liver enzymes, (including alkaline phosphatase for bone metastases), demonstrated a low accuracy and did not accurately predict those who were more likely to have positive liver or bone scans.⁷⁵ The retrospective study done at the Medical College of Georgia on 133 patients likewise showed that alkaline phosphatase was a poor predictor of subsequent abnormal bone scans and bone metastases with a positive predictive value (PPV) of 0.27.⁷⁶ The authors also observed that alkaline phosphatase had to be markedly elevated, at least 2 times greater, for its PPV in detecting bone metastasis to increase.

The earlier cited local survey on breast cancer management by surgeons showed that majority (92.9%) routinely used preoperative diagnostic tests for women with early breast cancer; and the most frequently used were chest x-rays (97.1 %) and liver ultrasound (74.2 %). Less used were bone scans (12.7 %), chest CT scans (6.7 %), and liver CT scan (5.2 %).⁹ However, our search showed that there is no evidence to support this clinical practice of majority of our surgeons and physicians . There is no survival benefit in requesting for a battery of “routine” laboratory exams for pre-operative metastatic work-up in asymptomatic women with early breast cancer and only serves to increase costs and heighten patient anxieties.

Recommendations

11. In asymptomatic women with early breast cancer, there is no evidence that the use of an intensive preoperative metastatic work up increases survival. Furthermore, these exams (chest x ray, bone scan, bone x rays, liver ultrasound, liver scan, and liver enzymes) have low diagnostic yield and are no better than clinicopathologic factors like tumor size, histologic differentiation (grade), axillary nodal status, and hormone receptor status, in predicting distant metastases. Therefore, they should not be routinely done. (Level II, Category B)

The use of a battery of tests for “metastatic work-up” is even more widely practiced in post-treatment follow up. Once again, the proponents strongly believe that earlier detection and treatment of asymptomatic metastases will increase survival.

3. What is the survival benefit of an intensive follow –up regimen with routine use of specific diagnostic tests to search for possible distant metastases for women who underwent surgery for early breast cancer as compared to a symptom – directed follow – up?

3.1 chest x – ray

3.2 liver function tests – SGPT, Alkaline phosphatase

3.3 ultrasound of the liver

3.4 liver scan

3.5 bone scan

3.6 chest CT scan

3.7 brain CT scan

There were 85 titles found, 35 abstracts were reviewed, 28 full text articles were selected, and 3 articles were used for the formulation of the guidelines.

Two Italian multicenter randomized trials which addressed this matter were published in 1994. The GIVIO Investigators (Interdisciplinary Group for Cancer Care Evaluation) randomly allocated 1,320 women in 20 hospitals to two follow up regimens following treatment for Stages I, II, and III breast cancer. One group received a yearly mammogram, seen at regular intervals, and only clinically indicated tests were performed; the other group (intensive surveillance) had in addition, bone scan, liver scan, chest x – ray and laboratory tests at predetermined intervals. Adjuvant therapy and management of recurrences were standardized. At a median follow up of 71 months, there were no differences in mortality between the intensive group (20 %) and the control group (18 %).⁸² Measurement of health – related quality of life at 6, 12, 24, and 60 months of follow up did not also show differences by type of care received, whether conservative or intensive follow up.

Because the bone and the lungs are the more common sites of metastases, the second Italian report by Del Turco, et al. , limited the tests used in the intensive follow up group to chest x – ray and bone scan every 6 months. Other aspects of management

were also standardized. At 5 years, 1,243 women in 11 breast centers had similar overall mortality (18.6 % vs. 19.5 %)⁸³ The authors concluded that “periodic chest x-rays and bone scans allows earlier detection of intrathoracic and bone metastases; but anticipated diagnosis appears to be the only effect of intensive follow – up as there is no difference in overall survival after 5 years.”

Crivellari and colleagues found that among 241, 744 blood tests, 6 per cent of the 52 per cent of women with recurrent disease had an elevated alkaline phosphatase level at some point before the disease was detected; however no data on how it affected overall survival was given.⁸⁴

The three articles cited above were also the evidence used by the Canadian Task Force on Preventive Health Care in their 1999 update on recommendations for follow up after breast cancer. They concluded that “ routine screening (blood tests and diagnostic imaging) for distant disease does not alter survival or quality of life over routine physical examination.”⁸⁵

The previously cited local survey on breast cancer management by surgeons showed that majority (78.6 %) also routinely used diagnostic tests for post-operative surveillance in asymptomatic women with early breast cancer; and the most popular were chest x-ray (88.3 %), liver ultrasound (75.6 %) and bone scans (35.4 %).⁹ However, as in the pre-operative setting, we have found no evidence to support this clinical practice. In this scenario, these laboratory tests do not confer any survival benefit and only increase costs and heighten fears.

Recommendations

12. *The use of an intensive metastatic work up following treatment for women with early breast cancer does not increase survival compared to symptom directed follow up, and should not be routinely used. (Level I, Category A)*

C. SURGICAL TREATMENT OF EARLY BREAST CANCER

Surgical removal of the primary tumor remains to be the mainstay in the treatment of early breast cancer. The extent of the surgical procedure had shifted from extensive radical operations to breast conserving techniques. The most common operation currently used in the Philippines is modified radical mastectomy. In early breast cancer,

breast conservation surgery has been proposed as an equivalent option. The earlier cited local survey on breast cancer management by surgeons showed that although majority (88.8 %) are aware that breast conservation treatment is comparable to mastectomy in early breast cancer, it is not commonly resorted to. The respondents cited unavailability of radiotherapy (52.4 %), cost (42.8 %), and patient reluctance (49.3 %) as barriers to breast conservation treatment.

Some early breast cancer patients have expressed disappointment and even anger, at not being informed of the possibility of not having to lose their entire breast. Physicians should give the patient correct information about comparable options so that she is able to make an informed choice.

The most important outcome of interest when comparing treatment options concerns survival.

4. What are the survival and locoregional control benefits of the following primary therapies for women with early (potentially curable; ie. Stage I to III A) breast cancer ?

4.1 Classical Radical Mastectomy

4.2 Modified Radical Mastectomy

4.3 Breast Conservation Surgery with Radiotherapy

4.4 Breast Conservation Surgery without Radiotherapy

There were 20,072 titles found, 68 abstracts were reviewed, 39 full text articles selected, and 3 articles used in the formulation of the guidelines. The highest level of evidence were contained in several systematic reviews (meta – analysis) of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) on the surgical treatment and various adjuvant therapies of early breast cancer.

The EBCTCG, with a secretariat at Oxford, UK is composed of 119 groups worldwide that had conducted randomized trials on the treatment of operable breast cancer. Since 1985, the group had conducted rigorous systematic reviews and vigorous follow – up of cases. Every 5 years, publication of the updated results appear, and the third cycle of the 5 – yearly updates were published between 1995 to 2000, with an approximately 15 – year follow up.

Ten trials, involving 4,386 women compared more extensive surgery with less extensive surgery (essentially modified radical mastectomy). At 10 years, overall mortality of the more extensive surgery group was 48 per cent, and 50 per cent in the less extensive surgery group. The odds ratio for local recurrence was 0.89 (+ / - 0.12). Nine trials, involving 4,891 women, compared breast conserving surgery plus radiotherapy (BCSRT) with procedures involving total mastectomy. At 10 years, overall mortality was 22.9 per cent for either groups, while local recurrence was 6.2 per cent in the mastectomy group and 5.9 percent in the BCSRT group.⁸⁶ Another meta-analysis published in 1997, done at the Massachusetts General Hospital in Boston, involving 3006 women included in five trials also showed no significant difference in risk of death over 10 years between mastectomy and breast conserving surgery plus radiotherapy. The odds ratio for 10-year survival was 0.91 (+ / - 0.12).⁸⁷

Regarding the extent of local excision in breast conservation surgery, it is mandatory that the tumor is completely excised. The link between completeness of excision and local recurrence after breast conservation was evaluated in 289 women from 16 centers in 1995 by the Stanford University Medical Center group. Their results showed that incomplete excision was associated with an increased relative risk of local recurrence of 3.4 (+ / - 1.2) compared with complete excision.⁸⁸

Recommendations

13. *The primary treatment of early breast cancer is either modified radical mastectomy or breast conserving surgery plus radiotherapy. Breast conserving surgery should include complete excision of the primary tumor in the breast, and an axillary dissection to determine nodal status. (Level I , Category A)*
It is the patient who will make the informed choice.
14. *More extensive surgery is done in order to remove all gross tumor.*
(Level I, Category A)

D. ADJUVANT TREATMENT

5.1 What are the survival and locoregional control benefits of postoperative adjuvant radiotherapy in early breast cancer?

There were 225 titles found, 95 abstracts reviewed and 24 full text articles selected. A total of 6 articles in the use of postoperative adjuvant radiotherapy were used in the formulation of the guidelines.

5.1a. After Breast Conservation Surgery (BCS)

The EBCTCG published their review in 1995, which included 4 trials involving 3,068 women, comparing BCS alone versus BCS plus radiotherapy (RT). Their results showed that women with isolated local recurrence were less likely to have received radiotherapy, with an odds ratio of 0.25 (+ / 0.09) ; however there was no significant difference in overall survival at 10 years (19.9 per cent deaths for radiotherapy group versus 21.1 per cent deaths for no radiotherapy group).⁸⁶ The following year , the Scottish Cancer Trials Breast Group published their RCT on 585 women, also comparing BCS alone versus BCS + RT. Their results showed that after 6 years, the proportion of women free of locoregional disease was significantly higher in women who underwent RT after BCS versus those without RT (93.8 per cent vs. 81.3 per cent), However, there was no significant difference in 6-year survival (80.1 per cent vs. 78.9 per cent).⁸⁹

In 1991, the Uppsala Orebro Breast Cancer Study Group published their RCT comparing sector resection with or without postoperative RT for Stage I breast cancer. This trial involved 381 women with “good prognosis” disease i.e. tumor < 2 cm; node negative. Their results showed a significantly lower local relapse rate with radiotherapy at 5 and 10 years. Five year local relapse rate was 2.3 per cent versus 18.4 per cent in favor of RT; while 10-year local relapse rate was 8.5 per cent versus 24 per cent,also in favor of RT. However, there was also no significant difference in overall survival at 10 years (78 per cent vs. 77.5 per cent).⁹⁰

In summary, the evidence showed that after breast conserving surgery, radiotherapy reduced the risk of isolated local recurrence but did not increase 10- year survival compared with breast conserving surgery alone.

5.1b. After Mastectomy

The 1995 EBCTCG review included 32 trials involving 14; 526 women comparing postmastectomy adjuvant radiotherapy to no radiotherapy. Overall mortality at 10 years was 40 per cent among those who received adjuvant radiotherapy, and 41.1 per

cent among women who did not. Local recurrence was 6.7 per cent in the adjuvant radiotherapy group, and 19.6 per cent in the control group. In short, the EBCTCG review showed that postmastectomy RT reduced the risk of local recurrence by 2/3 ; but there was no significant difference in overall survival at 10 years, with an odds ratio of 0.98 (+/- 0.05).⁸⁶ The outcomes were not affected by type of axillary dissection, nodal status and age.

In 1997, two RCTs were published in the New England Journal of Medicine, which showed a survival benefit with postmastectomy adjuvant RT, combined with systemic treatment (polychemotherapy which was essentially CMF) in “high risk” patients. “High risk” was defined as premenopausal, node-positive, with tumors > 5 cm in size. Both studies specifically included polychemotherapy in their treatment protocol to be able to address systemic control and possibly change survival rates because previous studies were only able to show reduction in locoregional recurrence but no change in survival.

The study from British Columbia in Canada involving 318 women showed that after 15 years of follow up, the women assigned to chemotherapy plus radiotherapy had 33 per cent reduction in the rate of locoregional recurrence (relative risk 0.67, +/- 0.20); and 29 per cent reduction in mortality (relative risk 0.71; + / - 0.20), as compared with the women treated with chemotherapy alone.⁹¹ Meanwhile, the study by the Danish Breast Cancer Cooperative Group (DBCG 82-b trial) which involved 1,708 women showed that after 10 years of follow up, the women assigned to chemotherapy plus radiotherapy had a 23 per cent reduction in the rate of locoregional recurrence (9 per cent versus 33 per cent). In addition, overall survival was 54 per cent among those given radiotherapy compared to 45 per cent among those who received chemotherapy alone.⁹²

In 1999, the Danish Breast Cancer Group published their DBCG 82-c trial which this time involved postmenopausal “high-risk” patients. They defined “high-risk” as node-positive with tumor > 5 cm in size. They enrolled a total of 1,375 women in the trial and randomized them to a control group who just received tamoxifen after mastectomy , and to an experimental group who received adjuvant radiotherapy in addition to tamoxifen after mastectomy. Results showed that adjuvant radiotherapy reduced locoregional recurrence from 35 per cent to 8 per cent; and overall survival at 10 years was also higher with radiotherapy, 45 per cent versus 36 per cent.⁹³

In summary, we can then inform both physicians and the patients alike that post-operative radiotherapy should not be indiscriminately given to all early breast cancer patients. There is however a certain subset of “high risk “ patients who should be advised adjuvant radiotherapy as it results to longer survival and lower rates of locoregional recurrence in this subset of patients.

Recommendations

15. *Adjuvant radiotherapy does not improve survival in early breast cancer and should not be routinely given. (Level I, Category A)*
16. *Adjuvant radiotherapy combined with systemic treatment in certain “high-risk” patients (premenopausal and/or node – positive, T3 lesions) may increase survival and may be considered. (Level I, Category A)*
17. *For women in whom the surgeon is still not certain about the adequacy of the locoregional resection, adjuvant radiotherapy may decrease the probability of locoregional recurrence and may be considered. (Level I, Category A)*

5.2 What are the survival and locoregional control benefits of adjuvant systemic treatment (hormonal or chemotherapy) following surgery for women with early (potentially curable) breast cancer?

There were 19,847 titles found, 516 abstract were reviewed, and 38 full text articles were selected. A total of 8 articles in adjuvant systemic treatment were used in the formulation of the guidelines.

5.2a Adjuvant Systemic Therapy for Women with Node-Negative Breast Cancer

Are there prognostic factors that could be used to identify node- negative breast cancer patients with higher risk for recurrence and mortality?

From the overview data of the EBCTCG, it was known that metastases would develop in about 30 per cent of women with node-negative breast cancer treated surgically without receiving adjuvant therapy.⁹⁴ A number of features of the primary breast tumor had been used to identify patients at increased risk of recurrence. The NSABP trials and the International Breast Cancer Group had shown that tumor size, histologic differentiation (grade) and hormone receptor status are good predictors for tumor recurrence.⁹⁵⁻⁹⁶ The St. Gallen International Consensus Panel in 1995 concluded that the evaluation of risk of recurrence in patients with node-negative breast cancer be

categorized on the basis of patient's age, and on the size, grade and hormone receptor status of the tumor.⁹⁸

Adverse prognostic factors that could be used to identify the 30 per cent among node-negative breast cancer patients with higher risk for recurrence and mortality wherein adjuvant systemic therapy may be of benefit are the following: tumor size > 1 cm (International Breast Cancer Group and NIH Consensus Statement on Adjuvant Systemic Therapy, 2000⁹⁷); tumor size > 2 cm (NSABP trials); poorly differentiated tumors (nuclear and histologic grade); hormone receptor negative tumors; age of patient less than or equal to 35 years; and lymphovascular invasion.

More recently, other factors had been studied as possible predictors, including ploidy, S-phase fraction, cathepsin D, Her-2 neu oncogene overexpression, etc. However, none of these factors had yet consistently been shown to add prognostic information to that associated with the more traditional factors of tumor size, histologic grade and hormone receptor status. The American Society of Clinical Oncology recommended that these newer factors not be used to predict recurrence in routine clinical practice.⁹⁹

Does adjuvant ovarian ablation confer a survival benefit in early breast cancer patients?

The overview of the EBCTCG showed that ovarian ablation, whether induced by surgery or radiotherapy, was associated with significant improvement in recurrence-free and overall survival in women who were under the age of 50 years at the time of treatment.¹⁰⁰ Among women aged under 50 in the overview data, by year 15 there were 6.0 (SD 2-3) fewer recurrences or deaths per 100 women allocated ovarian ablation (45.0 vs 39.0% alive and with no history of local or distant recurrence 15 years after randomization, log rank 2p=0.0007). The overview however, could not reliably estimate the separate effects of ovarian ablation in node-positive and node-negative women. But whether or not the nodes were involved, ovarian ablation in the absence of chemotherapy was associated with significant improvements in recurrence-free survival and in overall survival.

Does adjuvant systemic chemotherapy confer a survival benefit for patients with node-negative breast cancer?

The overview of the EBCTCG showed that chemotherapy will result in a small but definite increase in disease-free and overall survival in patients with node-negative breast cancer. There were 4900 women with node-negative breast cancer in the overview analysis. In these women, the relative reduction in the risk of recurrence was 26 per cent (SD 7%) and the relative reduction in mortality was 18 per cent (SD 8%). The absolute disease free survival at 5 years was 75 per cent for those who received chemotherapy and 67 per cent for the control group ($p < 0.00001$). At 10 years, disease free survival was 61.5 per cent vs 54.5 per cent ($p = 0.0001$). The overall survival at 10 years was 67.2 per cent for those who received chemotherapy vs 63.2 per cent for the control group ($p = 0.03$).¹⁰¹ Data from the overview analysis revealed that proportional risk reductions in risk were similar for women with node-negative and node-positive disease. Applying the proportional mortality reduction observed in all women aged under 50 at randomization would typically change a 10-year survival of 71 per cent for those with node-negative disease to 78 per cent (an absolute benefit of 7%). The smaller proportional mortality reduction observed in all women aged 50-59 at randomization would translate into smaller absolute benefits, changing a 10-year survival of 67 per cent for those with node-negative disease to 69 per cent (an absolute benefit of 2%).¹⁰¹

Does adjuvant tamoxifen confer a survival benefit for patients with node-negative breast cancer?

The overview of the EBCTCG showed that tamoxifen will result in a small but definite increase in disease-free survival and overall survival in patients with node-negative breast cancer. In over 12,000 women with node-negative disease in the overview analysis, the relative reduction in risk of recurrence associated with tamoxifen was 25 per cent (SD 4%), and the relative reduction in mortality was 17 per cent (SD 5%). The disease free survival rates at 5 years were 83.5 per cent for the tamoxifen group and 77.3 per cent for the control group ($p < 0.00001$). The corresponding rates at 10 years were 68.1 per cent vs 63.1 per cent ($p < 0.00001$). Overall survival rates at 10 years were 74.5 per cent for the tamoxifen group and 71 per cent for the control group ($p = 0.0002$).¹⁰²

Subgroup analysis by age in women with node-negative disease showed that tamoxifen was associated with reduction in the risk of recurrence in women both under and over 50 years of age but survival benefit was detected only in the over 50 age group.

No benefit regarding recurrence or survival was detected in women with ER-negative tumors.

The overview data on adjuvant tamoxifen therapy also showed that the proportional mortality reductions were similar for women with node-positive or node-negative disease, but the absolute mortality reductions were greater in node-positive disease. In the trials of about 5 years of adjuvant tamoxifen the absolute improvement in 10 year survival was 5.6 per cent (SD 1.3) for node-negative (78.9% vs 73.3% survival, $2p < 0.00001$).¹⁰²

Are there factors which could predict response to systemic adjuvant therapy among node-negative breast cancer patients?

Most evidence concerning the influence of ER and menopausal status on response to therapy is based on studies on women with metastatic disease or node-positive disease. Evidence based on studies of women with node-negative disease is more sparse. In the overview analysis, chemotherapy was associated with risk reduction for recurrence and mortality in all age groups, but the greatest effect was in the women who were under 50 years of age. Conversely, the greatest effect of tamoxifen was found in women over 50 years of age. Data from the overview analysis also showed that patients with node-negative and node-positive disease who were receiving tamoxifen had an 11 per cent (SD 5%) reduction in the odds of death in those with ER-poor tumors, compared with a 21 per cent (SD 3%) reduction in those with ER-positive tumors.¹⁰²

The evidence on which to base therapeutic choices is still incomplete. In making decisions based on the available evidence, the physician should give the patient the information so that she can evaluate the potential gains and side effects of each option.

Recommendations

18. *In general, for node-negative breast cancer patients, adjuvant systemic treatment should not be routinely given.*
19. *For "high risk" node-negative breast cancer patients, the following systemic adjuvant therapies may be offered: (there is no agreement on the definition of "high-risk")*

- a). *Chemotherapy, regardless of age and ER status. (Level I, Category B)*
- b). *Tamoxifen, regardless of age, in ER positive or ER unknown tumors. (Level I, Category B)*
- c). *Ovarian ablation, either by irradiation or surgical oophorectomy, in women less than 50, in ER positive or ER unknown tumors. (Level I, Category A)*

5.2b Adjuvant Systemic Therapy for Women with Node-Positive Breast Cancer

Adjuvant systemic chemotherapy, adjuvant hormonal therapy and ovarian ablation have been shown to prolong disease-free survival and overall survival in patients with early breast cancer, both in clinical trials and population based studies. The overview analyses by the Early Breast Cancer Trialists Collaborative Group cited previously have shown the evidence to make the following recommendations.

Does adjuvant ovarian ablation confer a survival benefit in early breast cancer patients?

The meta-analysis of the EBCTCG showed ovarian ablation, whether induced by surgery or radiotherapy, was associated with significant improvement in recurrence-free and overall survival in women who were under the age of 50 years at the time of treatment. Among women aged under 50 in the overview data, by year 15 there were 6.0 (SD 2-3) fewer recurrences or deaths per 100 women allocated ovarian ablation (45.0 vs 39.0% alive and with no history of local or distant recurrence 15 years after randomization, log rank $p=0.0007$).¹⁰⁰ The overview however, could not reliably estimate the separate effects of ovarian ablation in node-positive and node-negative women. But whether or not the nodes were involved, ovarian ablation in the absence of chemotherapy was associated with significant improvements in recurrence-free survival and in overall survival.

Does adjuvant systemic chemotherapy confer a survival benefit for patients with node-positive breast cancer?

The meta-analysis of the EBCTCG showed that chemotherapy will result in a small but definite increase in disease-free and overall survival in patients with node-positive breast cancer. The overview included 133 randomized trials involving 75,000 women who were randomised in trials involving adjuvant chemotherapy. From this analysis, it can be estimated that in patients of all ages, polychemotherapy that is taken

for at least one month (usually up to 1 year) can be expected to result in absolute improvement in 10-year survival of 6.8 per cent (SD 1.6%) in patients with node-positive cancer. For premenopausal women under the age of 50 years, the crude death rate was reduced from 37 per cent to 31 per cent.¹⁰¹

The overview analysis also revealed that proportional risk reductions in risk were similar for women with node-negative and node-positive disease. Applying the proportional mortality reduction observed in all women aged under 50 at randomization would typically change a 10-year survival of 42 per cent for those with node-positive disease to 53 per cent (an absolute benefit of 11%). The smaller proportional mortality reduction observed in all women aged 50-59 at randomization would translate into smaller absolute benefits, changing a 10 year survival of 46 per cent for those with node-positive disease to 49 per cent (an absolute benefit of 3%).¹⁰¹

Does adjuvant tamoxifen confer a survival benefit for patients with node-positive breast cancer?

The overview of the EBCTCG showed that tamoxifen will result in a small but definite increase in disease-free survival and overall survival in patients with node-positive breast cancer. No benefit regarding recurrence or survival was detected in women with ER-negative tumors. The overview showed that the proportional mortality reductions were similar for women with node-positive or node-negative disease, but the absolute mortality reductions were greater in node-positive disease. In the trials of about 5 years of adjuvant tamoxifen the absolute improvement in 10-year survival was 10.9 per cent for node positive women (61.4 % versus 50.5 %, $p < 0.00001$). These benefits appeared to be largely irrespective of age, menopausal status, daily tamoxifen dose and of whether chemotherapy has been given.¹⁰²

The daily tamoxifen dose was 20 mg. There were neither increased survival nor decreased recurrence among those whose daily tamoxifen dose was higher than 20 mg. The duration of tamoxifen treatment recommended was 5 years although there were also reductions in recurrence and mortality with shorter durations of treatment. For trials of 1 year, 2 years and 5 years of adjuvant tamoxifen, the proportional recurrence reductions produced among these 30,000 women during about 10 years of follow up were 21 per cent, 29 per cent, and 47 per cent respectively. The corresponding proportional mortality reductions were 12 per cent, 17 per cent, and 26 per cent respectively. Among those who

had tamoxifen for 5 years, there was 47 per cent proportional reduction in contralateral breast cancer and a quadrupling of endometrial cancer. Adjuvant tamoxifen had no apparent effect on the incidence of colorectal cancer and on the other main categories of cause of death.¹⁰²

The evidence on which to base therapeutic choices is still incomplete. In making decisions based on the available evidence, women must personally evaluate the potential gains and side effects of each option.

Recommendations

20. *For node positive patients, the following systemic adjuvant therapies should be offered:*

- a). Chemotherapy, regardless of age and ER status.(Level I, Category A)*
- b). Tamoxifen, regardless of age, in ER positive or ER unknown tumors.
(Level I, Category A)*
- c). Ovarian ablation, either by irradiation or surgical oophorectomy, in women less than 50 years of age with ER positive or ER unknown tumors.
(Level I, Category A)*

To conclude, since there is very strong evidence that specific forms of systemic adjuvant treatments produce survival benefits that are both statistically and clinically significant in some women with early breast cancer, patients and the public should be provided the current best information to assist them in making intelligent choices. The following data in tabular form (Tables 7-9) may help in improving information dissemination.

Recommendations

1. *In patients with a palpable breast mass in which cancer is suspected, BIOPSY is mandatory. (Level I, Category A)*
2. *Fine needle aspiration cytology (FNAC) is the initial diagnostic procedure in patients with a palpable breast mass in which cancer is suspected.(Level I, Category A)*
3. *If the FNAC result is malignant, the patient is offered the different treatment options. (Level I, Category B)*
4. *If the FNAC result is benign but clinical findings are really highly suspicious for breast cancer, either a core needle or an open biopsy is done. (Level II, Category A)*
5. *The PCS should set up standards regarding FNAC. (Level III, Category A)*
6. *If the FNAC is unsatisfactory or interpreted as suspicious, core needle biopsy or open biopsy is advised. (Level I, Category A)*
7. *For tumors ≤ 1 cm in size, sonographically guided FNAC or core needle biopsy is recommended. In places where sonography facilities are unavailable, open biopsy is done. (Level II, Category A)*
8. *Frozen section histology is done only when the patient requests it. (Level III, Category A)*
9. *Mammography, sonography, and other breast imaging studies do not improve accuracy in arriving at a preoperative diagnosis and should not be used routinely to alter the clinical diagnosis in patients with a palpable breast mass suspicious for cancer. (Level II, Category A)*
10. *In women with early breast cancer, preoperative mammography is recommended to detect subclinical disease in the contralateral breast ; and also in the ipsilateral breast for those patients who will undergo breast conservation treatment. (Level II, Category A)*

11. *In asymptomatic women with early breast cancer, there is no evidence that the use of an intensive preoperative metastatic work up increases survival. Furthermore, these exams (chest x ray, bone scan, bone x rays, liver ultrasound, liver scan, and liver enzymes) have low diagnostic yield and are no better than clinicopathologic factors like tumor size, histologic differentiation (grade), axillary nodal status, and hormone receptor status, in predicting distant metastases. Therefore, they should not be routinely done.*
(Level II, Category B)
12. *The use of an intensive metastatic work up following treatment for women with early breast cancer does not increase survival compared to symptom directed follow up, and should not be routinely used. (Level I, Category A)*
13. *The primary treatment of early breast cancer is either modified radical mastectomy or breast conserving surgery plus radiotherapy. Breast conserving surgery should include complete excision of the primary tumor in the breast, and an axillary dissection to determine nodal status. (Level I, Category A)*
It is the patient who will make the informed choice.
14. *More extensive surgery is done in order to remove all gross tumor.*
(Level I, Category A)
15. *Adjuvant radiotherapy does not improve survival in early breast cancer and should not be routinely given. (Level I, Category A)*
16. *Adjuvant radiotherapy combined with systemic treatment in certain “high-risk” patients (premenopausal and/or node – positive, T₃ lesions) may increase survival and may be considered. (Level I, Category A)*

17. *For women in whom the surgeon is still not certain about the adequacy of the locoregional resection, adjuvant radiotherapy may decrease the probability of locoregional recurrence and may be considered. (Level I, Category A)*
18. *In general, for node-negative breast cancer patients, adjuvant systemic treatment should not be routinely given.*
19. *For "high risk" node-negative breast cancer patients, the following systemic adjuvant therapies may be offered: (there is no agreement on the definition of "high-risk")*
- a). Chemotherapy, regardless of age and ER status. (Level I, Category B)*
 - b). Tamoxifen, regardless of age, in ER positive or ER unknown tumors.
(Level I, Category B)*
 - c). Ovarian ablation, either by irradiation or surgical oophorectomy, in women less than 50 , in ER positive or ER unknown tumors. (Level I, Category A)*
20. *For node positive patients, the following systemic adjuvant therapies should be offered:*
- a). Chemotherapy, regardless of age and ER status.(Level I, Category A)*
 - b). Tamoxifen, regardless of age, in ER positive or ER unknown tumors.
(Level I, Category A)*
 - c). Ovarian ablation, either by irradiation or surgical oophorectomy, in women less than 50 years of age with ER positive or ER unknown tumors.
(Level I, Category A)*

Tables

Table 1. Ranges of conditional probabilities, given the final diagnosis, for different fine – needle aspiration cytologic test results.(Giard 1992)

FNAC Test Result				
	Malignant	Suspect	Benign	Unsatisfactory
Final Diagnosis				
Malignant	0.35 – 0.92	0.00 – 0.48	0.00 – 0.21	0.00 – 0.23
Benign	0.00 – 0.002	0.00 – 0.62	0.30 – 0.93	0.01 – 0.53

Table 2. Comparison of Sensitivities of FNAC and CNB from 3 reports.

STUDY SITE	SENSITIVITY(%)	
	FNAC	CNB
1. University of Hongkong 1987	96.7	96.7
2. University of Patras, Greece 1996	90	89
3. University of Texas, M.D. Anderson Cancer Center 1996	97.5	90

Table 3. Comparison between palpation guided FNAC (Giard 1992),and sonographically guided FNAC (Gordon 1993).

	Palpation Guided FNAC (Giard 1992) %	Sonographically Guided FNAC (Gordon 1993) %
1. Sensitivity	65 – 98	95
2. Specificity	34 – 100	92
3. Inadequate Smears	0 – 50	3.6
4. False Negatives	0 - 30	5.3

Table 4. Detection rate (%) of asymptomatic preclinical distant metastases by staging tests (Italian National Task Force for Breast Cancer 1988)

Clinical Stage	CXR	Bone XR	Bone Scan	Liver UTZ	Liver Scan
I	0.11	0.23	0.18	-	-
II A	0.24	0.65	0.78	0.42	0.72
II B	-	0.65	1.46	-	-
III A	0.75	-	0.96	-	-
III B	1.20	2.09	1.33	0.85	-
TOTAL	0.30 (11 / 3,627)	0.64 (11 / 1,708)	0.90 (22 / 2,450)	0.24 (2 / 836)	0.23 (1 / 435)

Table 5. Number of patients required to detect 1 case of asymptomatic preclinical distant metastases for the specific laboratory test per stage of breast cancer. (Italian National Task Force for Breast Cancer. 1988)

Laboratory Test	Clinical Stage of Breast Cancer			
	Stage I	Stage II	Stage III A	Stage III B
1. Chest X Ray	909	417	133	83
2. Bone X Ray	435	154	154	83
3. Bone Scan	555	196	104	75

Table 6. Overall sensitivity, specificity, and positive predictive values of the staging tests (Italian National Task Force for Breast Cancer. 1988)

Staging Test	Sensitivity	Specificity	PPV
CXR	0.31	0.996	0.44
Bone X Ray	0.35	0.986	0.32
Bone Scan	0.48	0.948	0.15
Liver UTZ	0.29	0.995	0.33
Liver Scan	0.20	0.972	0.08

Table 7. Survival benefits of adjuvant tamoxifen, 20 mg daily for five years, primary tumors either ER positive or ER unknown, irrespective of age and menopausal status

10-year survival in per cent		
Nodal status	With Tamoxifen	without Tamoxifen
Node positive	61.4	50.5
Node negative	78.9	73.3

Table 8. Survival benefits of adjuvant CMF chemotherapy, 3-6 months, irrespective of menopausal status, ER status and tamoxifen treatment

Age Group	10 year-survival in per cent			
	Node Positive		Node Negative	
	With	Without	With	Without
< 50 years	53.8	41.4	77.6	71.3
50-69 years	48.6	46.3	69.0	67.0

Table 9. Survival benefits of adjuvant ovarian ablation, by surgery or radiotherapy, in women aged less than 50 years, with ER positive or ER unknown tumors

15-year survival in per cent		
Nodal status	With Ablation	Without Ablation
Node positive	61.4	50.5
Node negative	78.9	73.3

REFERENCES

1. Roxas MFT, Dans AL, Laudico AV, Valera BDS, Gutierrez RR, Cruz MC. Evidence-based clinical practice guidelines on seeking referral for pre-operative cardiac evaluation for elective noncardiac surgery. *Philipp J Surg Spec* 1999 ; 54(4): 171-223.
2. Laudico AV, Roxas MFT, Bautista ER, Aquino MLD, Dela Pena ASD, Crisostomo AC, Navarro Jr. NS, Roa CC, Balgos AA, Maranon DR. evidence-based clinical practice guidelines on some important aspects of the care of critically ill surgical patients. *Philipp J Surg Spec*...
3. Laudico AV, Esteban DB, Reyes LM, Liquido JC (1998). *Philippine Cancer Facts and Estimates* Philippine Cancer Society, Inc; Manila, Philippines.
4. Laudico AV, Esteban DB, Reyes LM, Liquido JC. 1998 *Philippine Cancer Facts and Estimates*. Philippine Cancer Society Inc; Manila, 1998; 24-25.
5. Giard RW, Hermans J. The value of aspiration cytologic examination of the breast. A statistical review of the medical literature. *Cancer* 1992 15;69(8):2104-2110.
6. Vetrani A, Fulciniti F, Di Benedetto G, Zeppa P, Troncone G, Boscaino A, de Rosa G, Palombini L. Fine-needle aspiration biopsies of breast masses. An additional experience with 1153 cases (1985 to 1988) and a meta-analysis. *Cancer* 1992;69(3):736-740.
7. Sneige N. Fine-needle aspiration of the breast: a review of 1,995 cases with emphasis on diagnostic pitfalls. *Diagn Cytopathol* 1993;9(1):106-112.
8. Nicosia SV, Williams JA, Horowitz SA, Ku NN, Shabaik AS, Mela N, Reintgen DS, Cox CE. Fine needle aspiration biopsy of palpable breast lesions. Review and statistical analysis of 1875 cases. *Surg Oncol* 1993;2(3):145-160.
9. Laudico AV, De Leon-Matsuda ML, Roxas MFT. Results of a survey on some practice regarding breast cancer management by surgeons in the Philippines. May 2000; (unpublished).
10. Cusick JD, Dotan J, Jaecks RD, Boyle WT Jr. The role of Tru-Cut needle biopsy in the diagnosis of carcinoma of the breast. *Surg Gynecol Obstet* 1990;170(5):487-490.
11. Scopa CD, Koukouras D, Spiliotis J, Harkoftakis J, Koureleas S, Kyriakopoulou D, Tzoracoleftherakis E. Comparison of fine needle aspiration and Tru-Cut biopsy of palpable mammary lesions. *Cancer Detect Prev* 1996; 20(6):620-624.

12. Vega A, Goriyo F, Ortega E. Core needle aspiration biopsy of palpable breast masses. *Acta Oncologica* 1995;34(1):31-34.
13. Ballo MS, Sneige N. Can core needle biopsy replace fine-needle aspiration cytology in the diagnosis of palpable breast carcinoma. A comparative study of 124 women. *Cancer* 1996;78(4):773-777.
14. Minkowitz S, Moskowitz R, Khafif RA, Alderete MN. TRU-CUT needle biopsy of the breast. An analysis of its specificity and sensitivity. *Cancer* 1986 ;57(2):320-323.
15. Cheung PS, Yan KW, Alagaratnam TT. The complementary role of fine needle aspiration cytology and Tru-cut needle biopsy in the management of breast masses. *Aust N Z J Surg* 1987;57(9):615-620.
16. Carty NJ, Ravichandran D, Carter C, Mudan S, Royle GT, Taylor I. Randomized comparison of fine-needle aspiration cytology and Biopty-Cut needle biopsy after unsatisfactory initial cytology of discrete breast lesions. *Br J Surg* 1994;81(9):1313-1314.
17. Gordon PB, Goldenberg SL, Chan NH. Solid breast lesions: diagnosis with US-guided fine-needle aspiration biopsy. *Radiology* 1993;189(2):573-580.
18. Nakazawa H, Rosen P, Lane N, Lattes R. Frozen section experience in 3000 cases. Accuracy, limitations, and value in residency training. *Am J Clin Pathol* 1968 ;49(1):41-51. No Abstract available.
19. Sakai Y, Lauslahti K. Comparison and analysis of the results of cytodiagnosis and frozen sections during operation. *Acta Cytol* 1969; 13: 359-368.
20. Holaday WJ, Assor D. Ten thousand consecutive frozen sections: A retrospective study focusing on accuracy and quality control. *Am J Clin Pathol*. 1974; 61: 769-777.
21. Lessells AM, Simpson JG. A retrospective analysis of the accuracy of immediate frozen section diagnosis in surgical pathology. *Br J Surg* 1976; 63: 327-329.
22. Rosen PP. Frozen section diagnosis of breast lesions. Recent experience with 556 consecutive biopsies. *Ann Surg* 1978;187(1):17-19.
23. Abrahams C. The "Scrimp" technique - a method for the rapid diagnosis of surgical pathology specimens. *Histopathology* 1978;2: 255-266.
24. Rosai J, Ackerman LV. The pathology of tumors. Part II: Diagnostic techniques. *Cancer* 1979; 29: 22-39.
25. Kagali VA. The role and limitations of frozen section diagnosis of a palpable mass in the breast. *Surg Gynecol Obstet* 1983;156(2):168-170.

26. Agnantis NJ, Apostolikas N, Christodoulou I, Petrakis C, Garas J. The reliability of frozen-section diagnosis in various breast lesions: a study based on 3451 biopsies. *Recent Results Cancer Res* 1984;90:205-210.
27. Dankwa EK, Davies JD. Frozen section diagnosis: an audit. *J Clin Pathol* 1985 ;38(11):1235-1240.
28. Kaufman Z, Lew S, Griffel B, Dinbar A. Frozen-section diagnosis in surgical pathology. A prospective analysis of 526 frozen sections. *Cancer* 1986 ;57(2):377-379.
29. Esteban JM, Zaloudek C, Silverberg SG. Intraoperative diagnosis of breast lesions. Comparison of cytologic with frozen section technics. *Am J Clin Pathol* 1987;88(6):681-688.
30. Eskelinen M, Collan Y, Puitinen J, Valkamo E. Frozen section diagnosis of breast cancer. *Acta Oncol* 1989;28(2):183-186.
31. Torp SH, Skjorten FJ. The reliability of frozen section diagnosis. *Acta Chir Scand.* 1990 Feb;156(2):127-130.
32. Fessia L, Ghiringhello B, Arisio R, Botta G, Aimone V. Accuracy of frozen section diagnosis in breast cancer detection. A review of 4436 biopsies and comparison with cytodiagnosis. *Pathol Res Pract* 1984;179(1):61-66.
33. [No Author]. *Clinical Practice Guidelines for the Management of Early Breast Cancer.* National Health and Medical Research Council. Commonwealth of Australia 1995.
34. Lister D, Evans AJ, Burrell HC. The accuracy of breast ultrasound in the evaluation of clinically benign discrete, symptomatic breast lumps. *Clin Radiol* 1998;53:490.
35. Hindle WH, Davis L, Wright D. Clinical value of mammography for symptomatic women 35 years of age and younger. *Am J Obstet Gynecol* 1999;180(6 Pt 1):1484-1490.
36. Max MH, Klamer TW. Breast cancer in 120 women under 35 years old: a 10-year community-wide survey. *Am Surg* 1984; 50:23-25.
37. Lesnick GL. Detection of breast cancer in young women. *JAMA* 1997;327:967-969.
38. Homer MJ. Breast imaging: Pitfalls, controversies and some practical thoughts. *Radiol Clin North America* 1985;23(3):459-472.
39. Charnvises S. The accuracy of mammography: a comparison with fine needle aspiration cytology. *J Med Assoc Thai* 1996;79(1):27-30.
40. Maturo VG, Zusmer NR, Gilson AJ, Bear B. Ultrasonic appearance of mammary carcinoma with a dedicated whole breast scanner. *Radiology* 1982; 142: 713 - 718.

41. Sickles EA, Filly RA, Callen PW. Breast cancer detection with sonography and mammography: comparison using state-of-the-art equipment. *Am J Roentgenol* 1983; 140:843-845.
42. Hilton SV, Leopold GR, Olson LK, Willson SA. Real-time breast sonography: application in 300 consecutive patients. *Am J Roentgenol* 1986 Sep; 147(3):479-486.
43. Reinikainen HT, Rissanen TJ, Piippo UK, Paivansalo MJ. Contribution of ultrasonography and fine-needle aspiration cytology to the differential diagnosis of palpable solid breast lesions. *Acta Radiol* 1999; 40(4) :383-389.
44. Burak Z, Argon M, Memis A, Erdem S, Balkan Z, Duman Y, Ustun EE, Erhan Y, Ozkilic H. Evaluation of palpable breast masses with ⁹⁹Tcm-MIBI: a comparative study with mammography and ultrasonography. *Nucl Med Commun* 1994 Aug;15(8):604-612.
45. Palmedo H, Schomberg A, Gruenwald F, Mallmen P, Krebs D, Biersack HJ. Scintimammography with TC ^{99m} MIBI in suspicious breast lesions. *J Nucl Med* 1996;37:626-630.
46. Lam WWM, Yang WT, Chan YL, Stewart ET, King W, Metreweli C. Role of MIBI breast scintigraphy in evaluation of palpable breast lesions. *Br J Radiol* 1996;69:1152-1158.
47. Khalkhali, I, Mena I and Diggles L. Review of imaging techniques for the diagnosis of breast cancer: a new role of prone scintimammography using technetium - ^{99m} sestamibi. *Eur J Nucl Med* 1994;21:357-362.
48. Kao CH, Yong MD, Wang SD. The Tc ^{99m} MIBI in the evaluation of mass abnormalities of the breast. *Eur J Nucl Med* 1993;20:979.
49. Adalet I, Demirkol MO, Muslumanoglu M, Bozfakioglu Y, Cantez S. ⁹⁹ Tcm-tetrofosmin scintigraphy in the evaluation of palpable breast masses. *Nucl Med Commun* 1997;18(2):118-121.
50. Drew PJ, Turnbull LW, Chatterjee S, Read J, Carleton PJ, Fox JN, Monson JR, Kerin MJ. Prospective comparison of standard triple assessment and dynamic magnetic resonance imaging of the breast for the evaluation of symptomatic breast lesions. *Ann Surg* 1999;230(5):680-685.
51. Van Dam PA, Van Goethem ML, Kersschot E, Vervliet J, Van den Veyver IB, De Schepper A, Buytaert P. Palpable solid breast masses: retrospective single- and multimodality evaluation of 201 lesions. *Radiology* 1988;166(2):435-439.
52. Nystrom L, Rutquist LE, Wall S et al. Breast cancer screening with mammography: overview of Swedish randomized trials. *Lancet*.1993; 341: 973-978.
53. Alexander FE, Anderson TJ, Brown HK, et al. The Edinburgh Randomized Trial of Breast Cancer Screening: Results after 10 years of follow-up. *Br J Cancer* : 542-548.

54. Shapiro S, Venet W, Strax P et al. Ten-to fourteen - year effect of screening on breast cancer mortality. J Natl Cancer Inst.1982;69:349-355.
55. Ciatto S, Pacini P, Azzini V, et al. Preoperative staging of primary breast cancer. A multicentric study. Cancer. 1988 ;61(5):1038-1040.
56. Patanaphan V, Salazar OM, Risco R. Breast cancer: metastatic patterns and their prognosis. South Med J 1988;81: 1109-1112.
57. Baker RR, Holmes ER, Alderson PO, et al. An evaluation of bone scan as screening procedures for occult metastases in primary breast cancer. Am Surg 1977; 186: 367-368.
58. Sklaroff DM, Charles ND. Bone metastases from breast cancer at the time of radical mastectomy. Surg Gynecol Obstet 1968; 127:763-768.
59. Hoffman HC, Marty R. Bone scanning: it's value in preoprative evaluation of patients with suspicious breast masses. Am J Surg 1972; 124: 194.
60. Campbell DJ, Banks AJ, Oates GD. The value of preliminary bone scanning in staging and assesing the prognosis of breast cancer. Br J Surg 1976;63: 11-816.
61. Roberts JG, Bligh AS, Gravelle IH, et al. Evaluation of radiography and isotopic scintigraphy for detecting skeletal metastases in breast cancer. Lancet 1976;1:237-239.
62. Citrin DL, Furnival CM, Bessent RG, et al. Radioactive technetium phosphate bone scanning in preoperative assessment and follow up study of patients with primary cancer of the breast. Surg Gynecol Obstet 1976; 143: 360-364.
63. Bessler WT. Bone scanning in breast cancer staging. Breast Cancer; New York: Alan R. Liss, Inc., 1977:303-338.
64. Galasko CSB. The significance of occult skeletal metastasis detected by skeletal scintigraphy in patients with otherwise apparently "early" mammary carcinoma. Br J Surg 1975; 62: 694-696.
65. O'Connell MJ, Wahner HW, Ahmann DI, et al. Value of preoperative radionuclide bone scan in suspected primary breast carcinoma. Mayo Clin Proc 1978; 53:221-226.
66. El Domieri AA, Shroff S. Role of preoperative bone scan in carcinoma of the breast.Surg Gynecol Obstet 1976; 142:722-724.
67. Butzelaar RMJM, Van Donger JA, Van Jeer Schoot JB et al. Evaluation of routine preoperative bone scintigraphy in patients with breast cancer. Eur J Cancer 1977;13:19-21.
68. Gerber FH, Goodreau JJ, Kirchner PT, et al. Efficacy of preoperative and postoperative bone scanning in the management of breast cancer. N Engl J Med 1977; 297: 300-302.

69. Davies CJ, Griffiths PA, Preston BJ, et al. Staging breast cancer: role of bone scanning. *Br Med J* 1977;2: 603-605.
70. Wilson GS, Rich MA, Brennan MJ. Evaluation of bone scan in preoperative clinical staging of breast cancer. *Arch Surg* 1980 Apr;115(4):415-419.
71. Khandekar JD, Burkett F, Scanlon EF. Sensitivity, specificity and predictive value of bone scans in breast cancer. *Proc AACR-ASCO* 1978; 19:379.
72. Mc Neil BJ. Rationale for the use of bone scans in selected metastatic and primary bone tumors. *Semin Nucl Med* 1978; 8:336-345.
73. Nomura Y, Kondo H, Yamagata J, et al. Evaluation of liver and bone scanning in patients with early breast cancer, based on results obtained from more advanced cancer patients. *Eur J Cancer* 1978; 14: 1129-1136.
74. Burkett FE, Scanlon EF, Garces RM, Khandekar JD. The value of bone scans in the management of patients with carcinoma of the breast. *Surg Gynecol Obstet* 1979;149(4):523-525.
75. Cox MR, Gilliland R, Odling-Smee GW, Spence RA. An evaluation of radionuclide bone scanning and liver ultrasonography for staging breast cancer. *Aust N Z J Surg* 1992;62(7):550-555.
76. Brar HS, Sisley JF, Johnson RH Jr. Value of preoperative bone and liver scans and alkaline phosphatase in the evaluation of breast cancer patients. *Am J Surg* 1993;165(2):221-223; discussion 224.
77. Samant R, Ganguly P. Staging investigations in patients with breast cancer: the role of bone scans and liver imaging. *Arch Surg* 1999;134(5):551-553; discussion 554.
78. Weiner SN, Sachs SH. An assessment of positive liver scanning in patients with breast cancer. *Arch Surg* 1978; 113: 126-127.
79. Clark CP 3d, Foreman ML, Peters GN, Cheek JH, Sparkman RS. Efficacy of preoperative liver function tests and ultrasound in detecting hepatic metastasis in carcinoma of the breast. *Surg Gynecol Obstet* 1988 ;167(6):510-514.
80. Sklaroff RB, Sklaroff DM. Bone Metastases from breast cancer at the time of radical mastectomy as detected by bone scan; eight-year follow-up. *Cancer* 1976; 38: 107-111.
81. Lee YT. Bone scanning in patients with early breast carcinoma: should it be a routine staging procedure? *Cancer* 1981;47(3):486-495.
82. [No authors listed] Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO investigators. *JAMA* 1994 25;271(20):1587-1592.

83. Del Turco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. JAMA 1994 ;271(20):1593-1595.
84. Crivellari D, Price KN, Hagen M, et al. Routine test during follow-up of patients after primary treatment for operable breast cancer. Ann Oncol 1995; 769-776.
85. Temple LK, Wang EE, McLeod RS. Preventive health care, 1999 update: 3. Follow-up after breast cancer. Canadian Task Force on Preventive Health Care. Can Med Assoc J 1999;161(8):1001-1008.
86. [No authors listed] Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. N Engl J Med 1995 Nov 30;333(22):1444-1455.
87. Morris AD, Morris RD, Wilson JF, White J, Steinberg S, Okunieff P, Arriagada R, Le MG, Blichert-Toft M, van Dongen JA. Breast-conserving therapy vs mastectomy in early-stage breast cancer: a meta-analysis of 10-year survival. Cancer J Sci Am 1997;3(1):6-12.
88. Smith NC, Nowels KW, Zdeblick MJ et al. The Importance of the lumpectomy surgical margin status in long term results of breast conservation. Cancer. 1995;76:259-267.
89. Forrest AP, Stewart HJ, Everington D, et al. On behalf of the Scottish Cancer Trials Breast Group. Randomized controlled trial of conservation therapy in breast cancer: 6 year analysis of the Scottish trial. Lancet 1996;348:708-713.
90. Liljegren G, Holmberg J, Bergh J et al. and the Uppsala - Orebro Breast Cancer Study Group. 10-year results after sector resection with or without postoperative radiotherapy for Stage I breast cancer: A randomized trial. J Clin Oncol 1999;17:2326-2633.
91. Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, Wilson KS, Knowling MA, Coppin CM, Paradis M, Coldman AJ, Olivotto IA. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med. 1997 Oct 2;337(14):956-962.
92. Overgaard M, Hansen PS, Overgaard J et al. for the Danish Breast Cancer Cooperative Group -82b trial. Postoperative radiotherapy in high risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 1997; 337 (14):949-955.
93. Overgaard M, Jensen MB, Overgaard J et al. for the Danish Breast Cancer Cooperative Group. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: DBCG 82c. Randomized trial. Lancet 1999; 353:1641-1648.

94. [No authors listed] Systemic treatment of early breast by hormonal, cytotoxic or immune therapy. 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. Lancet 1992;339:1-15,71-85.
95. Fisher B, Redmond C. Systemic therapy in node-negative patients: updated findings from NSABP clinical trials. National Surgical Adjuvant Breast and Bowel Project. J Natl Cancer Inst Monogr. 1992;(11):105-116.
96. Neville AM for the International Breast Cancer Group. Factors predicting treatment responsiveness and prognosis in node-negative breast cancer. J Clin Onco 1992;10:696-705.
97. National Institute of Health Consensus Statement on Adjuvant Systemic Therapies. 2000.
98. Goldhirsch A, Wood WC, Senn HJ, Glick JH, Gelber RD. International Consensus Conference on Primary Treatment of Breast Cancer. Recent Results Cancer Res 1996;140:325-335.
99. Clinical Practice Guidelines For The Use of Tumor Markers in Breast and Colorectal Cancer. Adopted on May 17, 1996 by the American Society of Clinical Oncology. J Clin Oncol 1996;14:2843-2877.
100. [No authors listed] Ovarian ablation in early breast cancer: overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1996;348(9036):1189-1196. With update in the Cochrane Library 2000 Issue 2.
101. [No authors listed] Polychemotherapy for early breast cancer: an overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;352(9132):930-942.
102. [No authors listed] Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;351(9114):1451-1467.

