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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. These guidelines are statements of the PCS regarding the scientific evidence and its view of currently accepted approaches to treatment.

These guidelines are not intended to replace but to assist the expertise and clinical judgment of physicians in the management of individual patients. Each patient's situation must be evaluated individually. It is important to discuss the guidelines and all pertinent information regarding treatment options with the patient because it is the preference of a well-informed patient which ought to be the major consideration in the decision-making process.

Acknowledgment

This project of the Philippine College of Surgeons was partly supported by the International Breast Cancer Research Foundation (IBCRF) and the Surgical Research Unit (SRU) of the Department of Surgery, Philippine General Hospital and College of Medicine, University of the Philippines Manila. The SRU staff who provided assistance was Ms. Madonna R. Balbacal.

Executive Summary

The Philippine College of Surgeons (PCS) published its first Evidence-based Clinical Practice Guidelines (EBCPG) on the diagnosis and management of breast cancer in 2001. Since then, numerous high quality clinical trials have been published, particularly on the beneficial role of hormonal therapy in both the adjuvant and metastatic setting and the beneficial role of cytotoxic chemotherapy. These publications have resulted in modifications in other clinical practice guidelines including that of the U.S. National Comprehensive Cancer Network (NCCN) in the 2005 and the St. Gallen International Expert Consensus in 2003.

The incidence of breast cancer among women in the Philippines is expected to continue to rise. The global observation that fertility decreases as a country's economic development progresses and the increasing "westernization" of Philippine lifestyles are the major factors that are expected to contribute to the anticipated rise in incidence.

The 2001 PCS EBCPG was reviewed in its entirety, and when no new evidence was discovered, the 2001 guidelines were retained. Only those publications that were not included in the 2001 guidelines are cited in the update.

The literature search method, levels of evidence, categories of recommendations, and clinical questions were essentially similar to those used in the 2001 guidelines. The Technical Working Group (TWG) had been regularly monitoring the major sources of publications since the formulation of the first set of
Operational Definitions

Early Breast Cancer

The definition of early breast has been retained, namely that used by the EBCTCG: "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."

Unresectable Locally Advanced Breast Cancer

Using the EBCTCG definition of early breast cancer and the 2002 AJCC Cancer Staging, unresectable locally advanced breast will include: 1) unresectable clinically staged III B lesions (unresectable T4 lesions); and, 2) clinically staged IIIC lesions (N3 lesions)- N3a, metastasis in ipsilateral infraclavicular lymph node(s); N3b, metastasis in ipsilateral internal mammary node(s) and axillary lymph node(s); N3c, metastasis in ipsilateral supraclavicular lymph node(s).

Recurrent breast cancer is the reappearance of the disease anywhere in the body following primary treatment (usually mastectomy or breast conserving surgery, with or without adjuvant therapy).

Hormone-responsive metastasis refers to metastatic lesions which decrease in size or disappear after endocrine therapy.

Hormone-refractory metastasis refers to metastatic lesions which fail to respond to at least 3 types of endocrine treatment.

Levels of Evidence

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

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

3. 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 (at least 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 TWG prepared the first draft of the manuscript which consisted of a summary of the strongest evidence associated with the clinical questions and the suggested recommendations. The first draft was discussed and modified by a Panel of Experts convened by the PCS on November 12, 2005 at the PCS building. A second draft was prepared by the TWG and this was discussed in a Public Forum on December 6, 2005 during the 61st Annual Clinical Congress of the PCS held at the EDSA Shangrila Hotel. The updated guidelines were then approved by the PCS Board of Regents on March 25, 2006.

Panel of Experts:

1. Ray B. Malilay, M.D. (Chairman; Philippine Society of General Surgeons)
2. Samuel D. Ang, M.D. (Philippine Society of General Surgeons)
3. Eric Arcilla, M.D. (Philippine Association of Plastic, Reconstructive and Aesthetic Surgeons)
4. Kathleen Baldivia, M.D. (Philippine Radiation Oncology Society)
Summary of Recommendations

1. Early Breast Cancer

A. Diagnosis

1. In patients with a palpable breast mass in which cancer is suspected, BIOPSY is mandatory. (Level, Category A)
12. In asymptomatic women with early breast cancer, there is no evidence that the use of an intensive preoperative metastatic workup 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 A).

B. Staging and Follow Up of Early Breast Cancer

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

14. Follow-up consists of careful history and physical examination and annual mammography of the contralateral and preserved breast. (Level I, Category A)

C. Surgical Treatment of Early Breast Cancer

15. 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.

16. More extensive surgery is done in order to remove all gross tumor. (Level I, Category A)

D. Adjuvant Treatment

Adjuvant Radiotherapy

17. Adjuvant radiotherapy following modified radical mastectomy does not improve survival in all cases of early breast cancer and should not be routinely given. (Level I, Category A)

18. Adjuvant radiotherapy following modified radical mastectomy may decrease the probability of local recurrence in certain patients with a high risk of local recurrence (tumor greater than 5 cm; less than 1 mm pathologic margin; 4 or more positive axillary nodes), or when the surgeon is not certain about the adequacy of the locoregional resection. (Level I, Category A)

19. Radiotherapy to the preserved breast tissue is an integral part of breast conserving surgery for early breast cancer (Level I, Category A)

Adjuvant Systemic Therapy

20. Hormone receptor status (estrogen/progesterone) should be the main consideration used in selecting the type of adjuvant treatment. (Level I, Category A)

21. There should be a determined effort to make immunohistochemistry hormone receptor assays available in strategic locations in the country, as well as efforts at standardizing the method standard. (Category A)

22. Interpretation of immunohistochemistry hormone receptor assays should be done using the Allred scoring system. (Level II, Category A)

23. Estrogen receptor assay may be determined first, and if the result is negative, progesterone receptor assay is done. (Category A)

Hormone (estrogen/progesterone) Receptor-Positive Cases

24. Patients with invasive early breast cancers that are estrogen or progesterone receptor-positive should be considered for adjuvant endocrine therapy regardless of patient age, menopausal status, lymph node status, HER2/neu status and whether or not adjuvant chemotherapy is to be given. (Level I, Category A)
25. In premenopausal women who are considered for adjuvant endocrine therapy, the combination of ovarian suppression (surgical or radiation ovarian ablation, or by LHRH analogs) plus tamoxifen results in a greater survival benefit compared to either treatment alone. (Level I, Category A)

26. In premenopausal women with hormone receptor-positive tumors who are considered for adjuvant oophorectomy, luteal phase oophorectomy offers greater survival benefit compared to follicular phase oophorectomy. (Level II, Category A)

27. There should be a determined and continuing effort to establish a standardized national breast cancer pathology reporting system that routinely and reliably includes prognostic features, such as the presence or absence of angiolymphatic invasion, and nuclear and histologic grades standard. (Category A)

28. Women with hormone receptor-positive tumors, negative axillary nodes and favorable prognostic features do not derive a clinically favorable risk/benefit outcome with the addition of adjuvant cytotoxic chemotherapy to adjuvant endocrine therapy. (Level II, Category A)

29. Women with hormone receptor-positive tumors, positive axillary nodes and unfavorable prognostic features may derive a clinically favorable risk/benefit outcome with the addition of adjuvant cytotoxic chemotherapy to adjuvant endocrine therapy. (Level II, Category A)

30. In women with hormone receptor-positive tumors who will receive both tamoxifen and cytotoxic chemotherapy, tamoxifen should be started after the completion of chemotherapy. (Level I, Category A)

31. In postmenopausal women with hormone receptor-positive tumors, tamoxifen or aromatase inhibitors may be used as adjuvant therapy. (Level I, Category A)

32. In women with hormone receptor-negative tumors, adjuvant endocrine therapy is generally not indicated and adjuvant chemotherapy may be beneficial. (Level I, Category A)

33. The use of a combination of cytotoxic chemotherapeutic drugs for adjuvant therapy results in a greater survival benefit compared to the use of a single drug. The use of anthracycline containing combinations may result in a greater survival benefit compared to the CMF regimen. (Level I, Category A)

34. The use of four cycles of AC (adriamycin + cyclophosphamide) combination for adjuvant chemotherapy may result in a survival benefit that is similar to that obtained with six cycles of CMF. (Level I, Category A)

35. The use of newer combinations of adjuvant chemotherapy, which are in general more toxic and more expensive should not be routinely used, and should be reserved for women with unfavorable prognostic factors for whom a particular chemotherapeutic combination may offer a clinically favorable risk/benefit outcome. (Level I, Category A)

36. Premenopausal women with hormone receptor-negative tumors who will not be able to receive adjuvant chemotherapy, should be offered adjuvant luteal phase oophorectomy may provide some survival benefit. (Level II, Category A)

2. Unresectable Locally Advanced Breast Cancer

37. Hormone receptor status (estrogen/progesterone) should be the main consideration used in selecting the type of neoadjuvant therapy. (Level, Category A)

Hormone (estrogen/progesterone) Receptor-Positive Cases

38. Women with locally advanced breast cancers that are hormone receptor-positive should be considered for neoadjuvant endocrine therapy regardless of patient age, menopausal status, HER2/neu status, or whether or not neoadjuvant chemotherapy is to be given. (Level II, Category A)
39. In premenopausal women with hormone receptor-positive tumors who are considered for adjuvant oophorectomy, luteal phase oophorectomy may offer greater survival benefits compared to follicular phase oophorectomy. (Level II, Category A)

40. Women with hormone receptor-positive tumors who have bad local primary tumor characteristics and other unfavorable prognostic features may have a better clinical risk/benefit outcome with the addition of neoadjuvant cytotoxic chemotherapy compared to neoadjuvant endocrine therapy. (Level II, Category A)

41. Women with hormone receptor-positive tumors who are going to receive both tamoxifen and cytotoxic chemotherapy should be started on tamoxifen only after the completion of chemotherapy. (Level II, Category A)

42. Premenopausal women with hormone receptor-positive tumors but may not be able to receive neoadjuvant chemotherapy. (Level II, Category A)

47. When neoadjuvant treatment results in a resectable primary tumor, modified radical mastectomy followed by radiotherapy to the chest wall may delay local recurrence. (Level II, Category A)

3. Recurrent or Metastatic Breast Cancer (Stage IV)

48. The primary goal of therapy for patients with Stage IV 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 the achievement of the best quality of life for patients and their families. Control of pain and other symptoms, and alleviation of psychological, social and spiritual problems are paramount. (Level I, Category A)

49. The WHO Method of cancer pain relief should be immediately started for all patients with Stage IV breast cancer who complain of pain. (Level I, Category A)

50. Active anticancer treatment does not replace palliative care, and palliative care should be maintained in patients who are receiving active anticancer treatment. (Level I, Category A)

Hormone Responsive Metastasis

51. Patients with hormone responsive metastatic lesions and whose general condition indicates that they could benefit from systemic anticancer treatment, benefit from sequential endocrine therapy. (Level I, Category A)

52. Sequential endocrine treatment should be continued until the patient is considered to be hormone refractory. A minimum of three types of endocrine treatment should have been given before being considered as hormone refractory. (Level I, Category A)

53. Premenopausal women with hormone responsive metastatic lesions and whose general condition indicates that they could benefit from endocrine therapy, may derive more benefit from ovarian suppression plus tamoxifen compared to ovarian suppression alone. (Level I, Category A)
Hormone Refractory Metastasis

54. Women with Stage IV breast cancer whose disease is hormone refractory, or with symptomatic visceral metastasis, or with tumors that are hormone receptor-negative, and whose general condition indicates that they could benefit from systemic anticancer treatment, may benefit from cytotoxic chemotherapy. (Level I, Category A)

55. When cytotoxic chemotherapy is being considered for women with Stage IV breast cancer and their general condition indicates that they may benefit from it. The potential benefits and toxicities should be carefully explained to the patient. (Level I, Category A)

Radiotherapy For Painful Bone Metastasis

56. Radiotherapy may be beneficial in relieving painful bone metastasis. (Level I, Category A)

Radiotherapy/surgery For Skin or Soft Tissue Metastasis

57. Radiotherapy or limited surgery may be beneficial in some cases of skin or soft tissue metastasis. (Level II, Category A)

Bisphosphonates For Bone Metastasis

58. Breast cancer patients with evidence of bone destruction on plain radiographs, or Computed Tomography (CT), or Magnetic Resonance Imaging (MRI) may benefit from bisphosphonates. (Level I, Category A)

59. The use of bisphosphonates in the absence of radiographic evidence of destructive bone metastases is not recommended. (Level I, Category A)

60. The use of bisphosphonates in women with Stage IV breast cancer without evidence of bone metastases is not recommended. (Level I, Category A)

61. The use of bisphosphonates as adjuvant therapy is not recommended. (Level II, Category A)

Bone Health In Women With Breast Cancer

62. Health care professionals who take care of women with breast cancer should take an active role in the monitoring of bone health, particularly in the regular assessment of osteoporosis risk. (Category A)

Introduction

The Philippine College of Surgeons (PCS) had published its Evidence-based Clinical Practice Guidelines (EBCPG) on the diagnosis and management of breast cancer in 2001. Since then, numerous high quality clinical trials have been published, particularly on the beneficial role of hormonal therapy in both the adjuvant and metastatic setting, and the consequent effects on the beneficial role of cytotoxic chemotherapy. These publications have resulted in modifications in other clinical practice guidelines including that of the National Comprehensive Cancer Network (NCCN) in the United States and the International Expert Consensus (St. Gallen).

The incidence of breast cancer among women in the Philippines is expected to continue to rise. The global observation that fertility decreases as a country’s economic development progresses, and the increasing “westernization” of Philippine lifestyles are the major factors that are expected to contribute to the anticipated rise in incidence.

The 2001 PCS EBCPG was reviewed in its entirety, and when no new evidence was discovered, the 2001 guidelines were retained. Only those publications that were not included in the 2001 guidelines are cited in the update.

Methods

The literature search method, levels of evidence, categories of recommendations, and clinical questions were essentially similar to those used in the 2001 guidelines.
Results

A. Diagnosis

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. In areas where there is no cytopathologist, core needle biopsy is an acceptable initial diagnostic option. (Level I, Category A)

3. If the FNAC result is malignant, the patient is offered the different treatment options. (Level I, Category A)

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. (Category A)

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

7. For deep seated 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 II, Category A)

9. In premenopausal women who are suspected to have early breast cancer and who prefer to undergo adjuvant oophorectomy, a core needle biopsy (CNB) will provide sufficient tumor tissue to determine hormone receptor status preoperatively. (Level I, Category A)

The recommendations on the role of preoperative breast imaging examinations in women with a suspicious palpable breast mass are retained.

10. 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)

11. 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)

12. 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 A)

B. Staging and Follow Up of Early Breast Cancer

The recommendations on postoperative surveillance are similar. The 2005 NCCN Guidelines and the 1999 Guidelines of the American Society of Clinical Oncologists (ASCO) both recommend careful history, physical examination and mammography of the contralateral and preserved breast. "Data are not
sufficient to recommend routine bone scans, chest radiographs, hematologic blood counts, tumor markers, liver ultrasonograms, or computed tomography scans.

13. The routine use of an intensive metastatic workup 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)

14. Follow up consists of a careful history and physical examination and annual mammography of the contralateral and preserved breast. (Level I, Category A)

C. Surgical Treatment of Early Breast Cancer

The 2001 recommendations are retained. The 20-year and 25-year follow up of two trials comparing radical mastectomy, total mastectomy and breast-conserving surgery followed by irradiation had reported survival benefits that were similar to earlier results.

15. 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.

16. More extensive surgery is done in order to remove all gross tumor. (Level I, Category A)

D. Adjuvant Treatment

It is in the adjuvant treatment of early breast cancer that major changes are recommended because of the subsequent publication of high level evidence, and, in some instances the consensus of some expertpanel guidelines that may be applicable to the Philippine practice setting.

Adjuvant Radiotherapy

The role of adjuvant radiotherapy following total mastectomy is essentially unchanged except for some general agreement on what constitutes a patient who is at “high risk” of local recurrence and for whom adjuvant radiotherapy may decrease the risk of local recurrence.

While there had been quality reports on survival benefits following adjuvant radiotherapy, the precise characteristics of the subsets of patients that could derive a clinically significant survival benefit, the long term side effects and the cost-effectiveness are still to be determined. The St. Gallen International Expert Consensus report states that “Tailoring postmastectomy radiation therapy recommendations for individual patients remains a priority for additional research.” The 2005 NCCN Guidelines also stated that there was substantial controversy among panel members when they were deliberating on postmastectomy radiation to the chest wall, supraclavicular lymph nodes, and internal mammary nodes.

It should also be noted that axillary radiation following a total axillary dissection substantially increases the risk of permanent and severe lymphedema. Furthermore, it had been reported that an increased risk of lung fibrosis may occur following the combined use of radiation and tamoxifen.

17. Adjuvant radiotherapy following modified radical mastectomy does not improve survival in all cases of early breast cancer and should not be routinely given. (Level I, Category A)

18. Adjuvant radiotherapy following modified radical mastectomy may decrease the probability of local recurrence in certain patients with a high risk of local recurrence (tumor greater than 5 cm; less than 1 mm pathologic margin; 4 or more positive axillary nodes), or when the surgeon is not certain about the adequacy of the locoregional resection. (Level I, Category A)

19. Radiotherapy to the preserved breast tissue is an integral part of breast conserving surgery for early breast cancer (Level I, Category A)
Adjuvant Systemic Therapy

It is in the adjuvant systemic therapy for early breast cancer that the major changes in the recommendations occur. Practically all updated treatment guidelines now stress the paramount importance of hormone receptor status in the choice of adjuvant systemic therapy. "The NCCN Guidelines call for the determination of estrogen and progesterone receptor content in all primary invasive cancers." The St. Gallen International Expert Consensus report states that "Recommendations for patient care are so critically dependent on assessment of endocrine responsiveness that the importance of high-quality steroid hormone receptor determination and standardized quantitative reporting cannot be overemphasized."

The determination and quantification of estrogen and progesterone receptors by means of immunohistochemistry (IHC) methods have facilitated hormone receptor determination and has now replaced the very expensive and relatively less reliable ligand-banding assay. Although IHC may be an even better predictor of response to adjuvant endocrine therapy, problems in standardization and interpretation still occur and account for the large number of false-negative results in many countries. An unpublished observation in India credits the use of buffered formalin as fixative for specimens and the use of the Allred scoring system for a substantial decrease in false-negative readings and a hormone receptor positive proportion that approximates those in developed countries.

The Allred scoring system is perhaps the only method that has been prospectively validated with disease free survival probability in a large number of patients (1,982 women with early breast cancer). It involves the proportion of positive-staining tumor cells (0 = none; 1 ≤ 1/100; 2 = 1/100 to 1/10; 3 = 1/10 to 1/3; 4 = 1/3 to 2/3; and 5 > 2/3), and an intensity score which represents the average intensity of positive tumor cells (0 = none; 1 = weak, 2 = intermediate; and 3 = strong). The best cut point is a score of greater than 2. Thus, only those slides which either had no tumor cell staining at all (score = 0) or weak staining was observed in less than 1/100 cells (score = 2) were read as negative. Currently, however, many pathologists still use the arbitrarily determined cut point of less than 1/10 staining cells and read such slides as a negative assay.

20. Hormone receptor status (estrogen/progesterone) should be the main consideration used in selecting type of adjuvant treatment. (Level I, Category A)

21. There should be a determined effort to make immunohistochemistry hormone receptor assay available in strategic locations in the country, as well as efforts at standardizing the method. (Category A)

22. Interpretation of immunohistochemistry hormone receptor assays should be done using the Allred scoring system. (Level II, Category A).

Most of the primary tumors that are considered to be hormone receptor-positive are estrogen receptor (ER)-positive. In the report by Harvey, et al., 71 percent of all tumors were determined to be ER-positive. A Vietnamese report included sending some paraffin blocks from Vietnam (105 of 1,622) to a reference laboratory in Australia for staining and interpretation. Table I shows the comparison in two age-groups between slides stained in Vietnam and Australia. (Van To T, et al; Unpublished data)

The proportion of tumors that are ER-negative but are PR-positive is much smaller, and it may not be cost-effective to routinely order assays of both hormones simultaneously. Sequential assays may be more practical.

23. Estrogen receptor assay may be determined first, and if the result is negative, progesterone receptor assay is done. (Category A)

Hormone (estrogen/progesterone) Receptor-Positive Cases

In 1993, the Scottish trial (not included in the EBCTCG meta-analyses) reported comparable survival rates between adjuvant ovarian ablation (surgical or radiation) versus CMF chemotherapy among premenopausal women with positive axillary nodes. When analyzed by estrogen receptor status, "it seems that ovarian ablation is the more effective treatment for
Table 1. Comparison between estrogen receptor immunohistochemistry in two age-groups between Vietnamese paraffin blocks stained in Vietnam and those stained in a reference laboratory in Australia.

<table>
<thead>
<tr>
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<th>Hospital-K blocks stained in Australia (n = 1622)</th>
<th>Australian Cases (n = 32)</th>
<th>Hospital-K blocks stained in Vietnam (n = 105)</th>
<th>p-value</th>
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<tr>
<td></td>
<td>N</td>
<td>ER+ (%)</td>
<td>N</td>
<td>ER+ (%)</td>
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<tr>
<td>&lt; 50 years</td>
<td>58</td>
<td>68.9</td>
<td>13</td>
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<td>≥ 50 years</td>
<td>47</td>
<td>85.1</td>
<td>19</td>
<td>84.2</td>
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patients with ER-positive tumors, whereas CMF may be more effective for patients with low ER content or none.19

In 2002, Jonat, et al. reported that adjuvant medical oophorectomy using goserelin, a luteinizing hormone-releasing hormone (LHRH) analog, resulted in a disease-free survival (DFS) similar to adjuvant CMF chemotherapy among ER-positive patients with positive axillary nodes.20 In the same journal issue, Jackesz, et al. reported that goserelin plus tamoxifen resulted in significantly better relapse-free survival (RFS) and local recurrence-free survival compared to CMF chemotherapy.21

Also in 2002, Love, et al. published an RCT that compared adjuvant oophorectomy plus tamoxifen versus observation followed by the same hormonal therapy upon recurrence in 709 premenopausal Vietnamese and Chinese women. For all study patients (ER-positive, ER-negative, ER-unknown) The 5-year disease-free survival increased from 58 percent to 72 percent and overall survival (OS) from 68 percent to 77 percent with adjuvant treatment. Among 288 cases with ER-positive tumors, the 5-year disease-free survival increased from 58 percent to 80 percent and over-all survival from 78 percent to 83 percent.22

The Asian population involved in the Love report demonstrated that the frequency and intensity of hot flushes, vaginal discharge, and genital pruritus were the only symptoms to occur more frequently in the oophorectomy plus tamoxifen-treated patients. In the first 12 months, 77 percent reported hot flushes of grade 1 or more and 44 percent reported grade 2 or more (3-5 hot flushes per day or more). Over 3 years, these episodes had dropped to 23 percent with majority being grade 1.23

Beith, et al. reported that among women who received doxorubicin plus cyclophosphamide as adjuvant chemotherapy, the occurrence of grade 4 neutropenia was observed to be higher at 54 percent as among Asians compared to 19 percent in Caucasians.24 The higher likelihood of not receiving the planned dose is important for clinical decision making. Bonadonna, et al., had reported that with CMF chemotherapy, the 20-year probability of survival significantly decreased in those who received less than 85 percent of the planned dose. Those who received less than 65 percent of the planned dose had the same survival rate as those who did not receive adjuvant chemotherapy.25

It has also long been suspected that a major mechanism of action of adjuvant cytotoxic chemotherapy is endocrine related. Survival benefits (DFS and OS) are proportionally higher among premenopausal women who developed permanent amenorrhea compared to those whose menses persisted.26-27 In the Scottish trial, among patients who had regular menses, 30 percent of patients under 40 years and 85 percent of those 40 years or older became amenorrheic after CMF adjuvant chemotherapy.19 In the CMF arm of the ZEBRA study, 26 percent of patients younger than 40 years and 90 percent of those older than 40 years were amenorrheic after 3 years.20

The observation that the probability of inducing amenorrhea, and the possible greater survival benefit that comes with it, is much lower among younger women following adjuvant chemotherapy can also have important clinical implications. In the Vietnamese population, multivariate analysis showed that age less
than 40 years was an independent significant predictor of shorter survival. This observation has been repeated in many other reports.

The 15-year follow up of patients included in the meta-analysis by the EBCTCG on the effects of chemotherapy and hormonal therapy shows that the benefits observed after 10 years have been retained.

Although HER-2 overexpression was a negative prognostic factor for overall survival, Love et al. found that premenopausal women with HER-2 positive tumors are more likely to respond to adjuvant treatment with ovarian ablation and tamoxifen than those whose tumors are non-overexpressing. 

24. Patients with invasive early breast cancers that are estrogen or progesterone receptor-positive should be considered for adjuvant endocrine therapy regardless of patient age, menopausal status, lymph node status, HER2/neu status, or whether or not adjuvant chemotherapy is to be given. (Level I, Category A)

25. In premenopausal women who are considered for adjuvant endocrine therapy, the combination of ovarian suppression (surgical or radiation ovarian ablation, or by LHRH analogs) plus tamoxifen results in a longer survival benefit compared to either treatment alone. (Level I, Category A)

Endocrine adjuvant treatment has traditionally been mostly the use of tamoxifen at 20 mg daily for 5 years in both premenopausal and postmenopausal women. Among premenopausal women, the use of combined endocrine therapy consisting of tamoxifen plus ovarian suppression (surgical or radiation ovarian ablation, or by the use of an LHRH analog) has been found to confer larger survival benefits compared to using each type of endocrine therapy alone.

26. In premenopausal women with hormone receptor-positive tumors who are considered for adjuvant oophorectomy, luteal phase oophorectomy may offer greater survival benefit compared to follicular phase oophorectomy. (Level II, Category A)

From the Vietnamese study, Love, et al. in a subset (post-hoc) analysis discovered that the highest probability of DFS was observed among women who underwent luteal phase oophorectomy (DFS 83%) as compared to those who had follicular phase oophorectomy (DFS 54%). The subset consisting of women 44 years of age or younger and with a menstrual cycle duration of at most 35 days were interpreted to be a population more likely to have ovulatory menstrual cycles and were therefore more likely to be producing progesterone during the luteal phase of their menstrual cycle. Another intriguing subset analysis showed that even women with ER-negative tumors could have benefitted from luteal phase oophorectomy plus tamoxifen. These observations add evidence to lingering theories that an abrupt lowering of elevated estrogen and progesterone can influence micrometastatic growth.

There are two important clinical questions regarding adjuvant endocrine therapy for hormone receptor-positive cases: 1) Is adjuvant endocrine therapy clinically beneficial for axillary node-negative cases?, and, 2) When is the addition of combination chemotherapy to endocrine therapy clinically beneficial?

While there are no robust findings from randomized trials to answer the specific and numerous clinical situations that could be involved to answer these two questions, there is now wide agreement based on retrospective and post-hoc analysis of numerous trials as to what constitutes “favorable prognostic features” and conversely, what “unfavorable prognostic features” are.

The absence of spread to the axillary nodes and a hormone receptor positive tumor are the most established and strongest good prognostic factors. On top of these, 1) absence of angiolymphatic invasion; 2) low nuclear grade (Grade 1); 3) low histologic grade (Grade 1); 4) small primary tumor (<2 cm); 5) not of young age (> 40 years); and, 6) no HER-2 overexpression, may be considered as favorable prognostic features. Thus, a 52 year old woman with a 0.7 cm tumor which shows no angiolymphatic invasion, and low nuclear and histologic grade, and no HER-2 overexpression, would have to ponder long and hard in order to decide if the potential
risk of the harmful effects of adjuvant endocrine therapy will be worth the very modest expected survival benefit. On the other hand, the presence of spread to the axillary nodes and a hormone receptor negative tumor are the most established and strongest unfavorable prognostic factors. On top of these, 1) presence of angiolymphatic invasion; 2) high nuclear grade (Grade 3); 3) high histologic grade (Grade 3); 4) big primary tumor (>5 cm); 5) bad clinical primary tumor characteristics (T4 tumors); 6) young age (<35 years); and 7) presence of HER-2 overexpression, may decrease survival and can be considered unfavorable prognostic factors. Thus, a 32 year old woman with a 7.0 cm tumor which shows angiolymphatic invasion and Grade 3 nuclear and histologic grades may benefit substantially from the addition of combination cytotoxic chemotherapy to combined endocrine therapy.

In between these two extremes wherein the risk/benefit expectations appear to be clear cut there are numerous situations comprising a “middle ground” wherein the risk/benefit expectations are less clear and less precisely predictable. The preference of the individual patient should therefore be respected after thoroughly and truthfully informing her of the risks and benefits of the various treatment options that are applicable to her clinical situation.

There have been many reports on the use of HER-2 overexpression as a prognostic and predictive factor in breast cancer. Currently, there is should be a determined effort to standardize the assay method and there remains some controversy as to the cost-effectiveness of its routine use. It has been reported that HER-2/neu overexpression was highly associated with negative hormone receptor status, Grade 3 lesions and young age. The likelihood of HER2/neu positivity in a hormone receptor positive, Grade 1 or 2 tumor was 6.1 percent.

27. There should be a determined and continuing effort to establish a standardized national breast cancer pathology reporting system that routinely and reliably includes prognostic features, such as the presence or absence of angiolymphatic invasion, and nuclear and histologic grades. (Category A)

28. Women with hormone receptor-positive tumors and negative axillary nodes and who have favorable prognostic features may not derive a clinically favorable risk/benefit outcome with the addition of adjuvant cytotoxic chemotherapy to adjuvant endocrine therapy. (Level II, Category A)

29. Women with hormone receptor-positive tumors and positive axillary nodes and who have unfavorable prognostic features may derive a clinically favorable risk/benefit outcome with the addition of adjuvant cytotoxic chemotherapy to adjuvant endocrine therapy. (Level II, Category A)

The simultaneous use of adjuvant tamoxifen and adjuvant combination chemotherapy had been shown to result in poorer survival benefit compared to the sequential use of chemotherapy followed by tamoxifen.44,45

30. In women with hormone receptor-positive tumors who will receive both tamoxifen and cytotoxic chemotherapy, tamoxifen should be started after the completion of chemotherapy. (Level I, Category A)

Several trials have provided preliminary evidence that the use of a new class of endocrine therapy drugs, the aromatase inhibitors result in significant but modest survival benefit compared to tamoxifen in the adjuvant therapy of postmenopausal women with hormone receptor-positive breast cancer. The ATAC trial demonstrated that the use of anastrozole alone as first line adjuvant treatment conferred a significant 2.9 percent absolute survival benefit over tamoxifen alone at year 4.46 After 5 years on tamoxifen, letrozole use resulted in a significant 6.0 percent absolute disease-free survival benefit at year 4 compared to placebo.47 Switching to exemestane after two to three years of tamoxifen therapy resulted in a significant 4.7 percent absolute disease-free survival benefit at year 4 compared to women who continued tamoxifen therapy.48 While there are still no published reports that directly compare the three aromatase inhibitors in the clinical settings involved in these three trials, it may be currently assumed that their efficacy and toxicity profiles are
comparable. Aromatase inhibitors, when compared to tamoxifen, had consistently demonstrated lower risks for endometrial cancer and thromboembolic events and cerebrovascular accidents but higher risks for osteoporosis, arthralgia, myalgia and elevation of serum cholesterol.

Aromatase inhibitors should not be used in premenopausal women. The NCCN definition of menopause is: “Menopause is generally the permanent cessation of menses, and as the term is utilized in breast cancer management includes a profound and permanent decrease in ovarian estrogen synthesis. Reasonable criteria for determining menopause include any of the following:

- Prior bilateral oophorectomy
- Age ≥ 60 years
- Age < 60 years and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and estradiol level in the postmenopausal range
- If taking tamoxifen or toremifene, and age < 60 years, then FSH and plasma estradiol level in postmenopausal ranges

It is not possible to assign menopausal status to women who are receiving an LH-RH agonist or antagonist. In women premenopausal at the time of adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status.33

31. In postmenopausal women with hormone receptor-positive tumors, tamoxifen or aromatase inhibitors may be used as adjuvant therapy. (Level I, Category A)

**Hormone (estrogen/progesterone) Receptor-Negative Cases**

32. In women with hormone receptor-negative tumors, adjuvant endocrine therapy is generally not indicated and adjuvant chemotherapy may be beneficial. (Level I, Category A)

33. The use of a combination of cytotoxic chemotherapeutic drugs for adjuvant therapy results in greater survival benefit compared to the use of a single drug. The use of anthracycline containing combinations may result in a greater survival benefit compared to the CMF regimen. (Level I, Category A)

34. The use of four cycles of AC (adriamycin + cyclophosphamide) combination for adjuvant chemotherapy may result in a survival benefit that is similar to that obtained with six cycles of CMF. (Level I, Category A)

35. The newer chemotherapeutic regimens should not be routinely used because they are more toxic and expensive. They should be reserved for women with unfavorable prognostic factors for whom a particular chemotherapeutic combination may offer a clinically favorable risk/benefit outcome. (Level I, Category A)

36. Premenopausal women with hormone receptor-negative tumors who will not be able to receive adjuvant chemotherapy should be offered adjuvant luteal phase oophorectomy may provide some survival benefit. (Level II, Category A)

Unfortunately, many of the published randomized trials on neoadjuvant therapy for “locally advanced” breast cancer included T3 primary tumors (> 5 cm) and many Western treatment guidelines include Stage IIIA cases in their definition of locally advanced breast cancer. This has resulted in an overlap of clinical categories as many cases labeled as locally advanced would also fall within the EBCTCG definition of early breast cancer. This has also resulted in the paucity of Level I evidence on the management of breast cancer cases that fall under our definition of locally advanced breast cancer. An explanation for this may be the fact that such cases are getting to be quite rare in Western populations so that trials may neither be feasible nor worthwhile.

Despite the global shift in preference for the use of endocrine treatment for hormone receptor-positive breast cancer in both the adjuvant and metastatic setting,
neoadjuvant chemotherapy is still widely considered as the standard form of treatment for "locally advanced" breast cancer. Notwithstanding the fact that no survival benefit over postoperative adjuvant treatment has been demonstrated, there has been an increasing interest in the role of hormonal therapy for locally advanced breast cancer. The main considerations for the new recommendations are therefore indirect evidence and the necessity for consistency in the recommendations on the use of systemic treatment.

37. Hormone receptor status (estrogen/progesterone) should be the main consideration used in selecting the type of neoadjuvant therapy. (Level II, Category A)

Hormone (estrogen/progesterone) Receptor-Positive Cases

38. Women with locally advanced breast cancers that are hormone receptor-positive should be considered for neoadjuvant endocrine therapy regardless of patient age, menopausal status, HER2/neu status, or whether or not neoadjuvant chemotherapy is to be given. (Level II, Category A)

39. In premenopausal women with hormone receptor-positive tumors who are considered for adjuvant oophorectomy, luteal phase oophorectomy may offer greater survival benefit compared to follicular phase oophorectomy. (Level II, Category A)

40. Women with hormone receptor-positive tumors who have bad local primary tumor characteristics and other unfavorable prognostic features may have a better clinical risk/benefit outcome with the addition of neoadjuvant cytotoxic chemotherapy compared to neoadjuvant endocrine therapy. (Level II, Category A)

41. Women with hormone receptor-positive tumors who are going to receive both tamoxifen and cytotoxic chemotherapy should be started on tamoxifen after the completion of chemotherapy. (Level II, Category A)

42. Postmenopausal women with hormone receptor-positive tumors may be given either tamoxifen or an aromatase inhibitor for neoadjuvant therapy. (Level II, Category A)

Hormone (estrogen/progesterone) Receptor-Negative Cases

43. In women with hormone receptor-negative tumors, neoadjuvant endocrine therapy is generally not indicated, and neoadjuvant chemotherapy may be beneficial. (Level II, Category A)

44. The use of anthracycline containing chemotherapy combinations may be more beneficial than those that do not contain anthracycline. (Level II, Category A)

45. The newer chemotherapeutic combinations which are in general more toxic and more expensive should not be routinely used but instead be reserved for women in whom a particular chemotherapeutic combination may offer a clinically favorable risk/benefit outcome. (Level II, Category A)

46. In premenopausal women with hormone receptor-negative tumors but may not be able to receive neoadjuvant chemotherapy, neoadjuvant luteal phase oophorectomy may provide some benefit. (Level II, Category A)

47. When neoadjuvant treatment results in a resectable primary tumor, a modified radical mastectomy followed by radiotherapy to the chest wall may delay local recurrence. (Level II, Category A)

3. Recurrent or Metastatic Breast Cancer (Stage IV)

Metastatic breast cancer can either be recurrent cancer or it can be the initial clinical presentation. Both are Stage IV (M1) breast cancer. The management of both are essentially similar so that the 2005 update groups the two together, unlike the 2001 Guidelines.

Although active anticancer treatment may prolong the life of some patients with Stage IV breast cancer, they are not curative. Furthermore, many patients with
Stage IV breast cancer suffer from distressing symptoms that severely impair the quality of life of the patient and the patient's family. The primary goal of therapy for Stage IV breast cancer is to deliver the best palliative care.54-56

48. The primary goal of therapy for patients with Stage IV 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 the achievement of the best quality of life for patients and their families. Control of pain and other symptoms, and alleviation of psychological, social and spiritual problems are paramount. (Level I, Category A)

49. The WHO Method of cancer pain relief should be immediately started for all patients with Stage IV breast cancer who complain of pain. (Level I, Category A)

50. Active anticancer treatment does not replace palliative care, and palliative care should be maintained in patients who are receiving active anticancer treatment. (Level I, Category A)

The active anticancer treatment of patients with Stage IV breast cancer may prolong life and improve the quality of life of some patients with specific characteristics of metastatic disease, but is not curative. The NCCN Guidelines summarizes the current philosophy on the active anticancer treatment of Stage IV breast cancer: "Therefore, treatments associated with minimal toxicity are preferred. Thus, the use of the minimally toxic endocrine therapies is preferred to the use of cytotoxic therapy whenever reasonable."53

The characteristics of metastatic disease among women with Stage IV breast cancer that have a high probability of not responding to endocrine therapy are: 1) metastatic lesions are not limited to soft tissue and/or bone; and/or, 2) metastatic lesions are not limited to asymptomatic visceral metastasis; and/or, 3) a short disease-free interval (< 2 years following primary treatment). These are considered hormone nonresponsive metastatic lesions.

Hormone Responsive Metastasis

51. Patients with hormone responsive metastatic lesions and whose general condition indicates that they could benefit from systemic anticancer treatment, may benefit from sequential endocrine therapy. (Level I, Category A)

The initial endocrine treatment is continued until the development of new metastatic lesions, and/or, progression of current lesions which indicate refractoriness to the current endocrine treatment. A second type of endocrine treatment is started until a refractory status is reached, and a third endocrine treatment is given, and so on. A minimum of three types of endocrine treatment should have been given until the patient is considered to be hormone refractory.

Tamoxifen (20 mg daily) has been the traditional initial endocrine treatment for hormone responsive metastatic lesions, and megestrol acetate (80-160 mg daily) the second line drug. Aromatase inhibitors (anastrozole 1 mg daily; letrozole 2.5 mg daily; exemestane 25 mg daily) have been reported to have clinically significant advantages over tamoxifen and megestrol acetate when used either as first line or as second line endocrine therapy.57-61 Other endocrine drugs that are beneficial are diethylstilbestrol (DES) and fulvestrant62-63 but both are not currently available in the Philippines. There is still no good evidence to recommend the optimal sequence of endocrine treatments.

52. Sequential endocrine treatment should be continued until the patient is considered to be hormone refractory. A minimum of three types of endocrine treatment should have been given before being considered as hormone refractory. (Level I, Category A)

A meta-analysis of four clinical trials that randomized 506 premenopausal women with advanced breast cancer to LHRH agonist alone versus LHRH agonist plus tamoxifen reported that the combined treatment had a significant survival benefit and
progression-free survival benefit with a median survival of 6.8 years.

53. Premenopausal women with hormone responsive metastatic lesions and whose general condition indicates that they could benefit from endocrine therapy, derive more benefit from ovarian suppression plus tamoxifen compared to ovarian suppression alone. (Level I, Category A)

**Hormone Refractory Metastasis**

54. Women with Stage IV breast cancer whose disease is hormone refractory, or with symptomatic visceral metastasis, or with tumors that are hormone receptor-negative, and whose general condition indicates that they could benefit from systemic anticancer treatment, may benefit from cytotoxic chemotherapy. (Level I, Category A)

The Cochrane Database of Systematic Reviews included the observation that: 1) combination chemotherapy showed modest significant improvement in overall survival and time to progression but significantly worse toxicities, and, 2) taxane-containing combinations appear to improve overall survival, time to progression and overall response.

55. When cytotoxic chemotherapy is being considered for women with Stage IV breast cancer and their general condition indicates that they may benefit from it, the potential benefits and toxicities should be carefully explained to the patient. (Level I, Category A)

Painful bone metastases may benefit from a short course of radiotherapy, often given in addition to endocrine therapy. The fractionation schedule should be tailored to individual patients by taking into consideration the general condition of the patient, accessibility and the life expectancy of the patient.

**Radiotherapy for Painful Bone Metastasis**

56. Radiotherapy may be beneficial in relieving painful bone metastasis. (Level I, Category A)

Radiotherapy, and occasionally limited surgery, may be beneficial in some instances of skin or soft tissue metastasis, also often done in addition to endocrine therapy.

McQuay, et al. reviewed the literature on the utility of radiation therapy for painful bone metastasis as published in the Cochrane Database. Sze, et al. on the other hand reviewed the use of single versus multifraction radiotherapy in the 2002 edition of the Cochrane Database.

**Radiotherapy/Surgery for Skin or Soft Tissue Metastasis**

57. Radiotherapy or limited surgery may be beneficial in some cases of skin or soft tissue metastasis. (Level II, Category A)

In 2003, Hillner, et al. published an update of the recommendations on the role of bisphosphonates and bone health issues in women with breast cancer by the American Society of Clinical Oncology (ASCO). The extensive evidence cited in the publication is the main basis for the following recommendations that may be useful in the Philippines. The bisphosphonates recommended were parenteral since sufficient evidence on oral preparations in American patients were not yet available. They recommended either intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg given over 15 minutes every 3 to 4 weeks. Once initiated, they are to be continued until there was evidence of substantial decline in the patient’s general performance status. The current standards of care for cancer pain management should be continued throughout bisphosphonate therapy. There was insufficient evidence to recommend a role for intravenous bisphosphonate in addition to radiation therapy for painful bony metastases.

**Bisphosphonates for Bone Metastasis**

58. Breast cancer patients with evidence of bone destruction on plain radiographs, Computed Tomography (CT), or Magnetic Resonance Imaging
(MRI) may benefit from bisphosphonates. (Level I, Category A)

59. The use of bisphosphonates in the absence of radiographic evidence of destructive bone metastases is not recommended. (Level I, Category A)

60. The use of bisphosphonates in women with Stage IV breast cancer without evidence of bone metastases is not recommended. (Level I, Category A)

61. The use of bisphosphonates for adjuvant therapy is not recommended. (Level II, Category A)

**Bone Health in Women with Breast Cancer**

62. Health care professionals who take care of women with breast cancer should take an active role in the monitoring of bone health, particularly in the regular assessment of osteoporosis risk standard. (Category A)

**References**


2005 Update. EBCPG on the Diagnosis and Management of Breast Cancer


