Evidence-Based Clinical Practice Guidelines for Early Breast Cancer

Foreword

In June 2012, the Philippine College of Surgeons (PCS) through the Committee on Cancer tasked the Philippine Society of General Surgeons (PSGS) to update the then existing evidence-based clinical practice guidelines for different cancer sites. The PSGS then delegated the responsibility of updating and revising the practice guidelines on breast cancer to the Breast Study Group (BSG). The BSG decided to focus its efforts on early breast cancer initially, with plans to also update the guidelines on advanced breast cancer in the near future. With approval from the PCS Board of Regents, it was recommended that instead of revising the manual following the evidence-based process in making guidelines, the guidelines published by different groups and organizations be adapted [i.e. National Comprehensive Cancer Network (NCCN), National Institute for Health and Care Excellence (NICE), National Breast Cancer Center (NBCC), etc], taking into consideration the applicability of such guidelines in the local setting.

The practice guidelines presented here are the work of the PSGS Breast Study Group headed by Dr. Ray B. Malilay has the following as members: Drs. Aldine Astrid A. Basa, Melanie D. Cruz, Sherry L. Lee, Joseph Jude A. Mercado, Felicidad Claudia R. Ordoñez, Maria Cecilia M. Pagdanganan, Mary Geraldine B. Remucal, Joan S. Tagorda, Michelle S. Uy. In order to provide a comprehensive discussion, the practice guidelines were divided into several parts including guidelines on diagnostic work-up, management of ductal carcinoma-in-situ and early invasive breast cancer, preoperative work-up and post-op surveillance, specimen handling and histopath reporting.

The group would like to acknowledge the support of the following during the conduct of this project: Dr. Maximo H. Simbulan Jr., Dr. Alfred H. Belmonte, Dr. Alberto P. Paulino, Jr., Dr. Nilo C. De Los Santos, and Roche Philippines. Likewise, this project will not have reached its completion without the unwavering dedication of the BSG secretary, Ms. Maria Angela P. Umlas.

Introduction

The incidence of breast cancer in the Philippines is increasing. In 2005, breast cancer ranked 2nd to lung cancer as the most common cancer in the country. In 2010, the Philippine Cancer Society reported that breast cancer is now the leading cause of cancer in the country. It has overtaken lung cancer which for several decades has been the leading cause of cancer in our country. It is also the 3rd leading cause of cancer deaths. The median survival among females is 60 months. Survival at the 5th year is 50.10% and 32.38% at the 10th year. In 2007, the 65 PSGS accredited training programs reported that a total of 2,749 patients underwent surgery for breast cancer. Of these 2,749 breast cancer patients, 2,632 (96%) underwent mastectomy and only 117 (4%) had breast conserving surgery. It is therefore imperative that we not only update our clinical practice guidelines but also institute breast cancer screening programs country wide to help us diagnose breast cancer in its earlier stages.

Practice guidelines are systematically developed statements to assist practitioners and patients in making

decisions about appropriate health care for specific clinical circumstances. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence and documentation. The authors acknowledge that guidelines do not dictate the management as each patient scenario is unique and clinical judgement should prevail. These guidelines should hopefully assist the physician in discussing all the relevant treatment options with the patient before she makes a truly informed decision about her treatment.

Executive Summary

The Philippine College of Surgeons (PCS) published the first Evidence-based Clinical Practice Guidelines (EBCPG) on the diagnosis and management of breast cancer in 2001. These guidelines were subsequently updated in 2005. Since then, numerous clinical trials on breast cancer management have been published, particularly on chemotherapy, hormonal therapy and the surgical management of breast cancer.

The BSG gathered and appraised all the relevant evidence on the management of early breast cancer. The literature search method was essentially similar to those used in the 2001 and 2005 EBCPG, utilizing the Pubmed Central (Medline) of the US Library of Medicine and the Cochrane Library as the major sources of publications. The level of evidence was based on the publication of the American Academy of Orthopedic Surgeons *(http://www2.aaos.org/bulletin/apr05/fline9.asp)*. The category of evidence was adapted from the previously published EBCPG. The 2001 and 2005 EBCPG on the diagnosis and management of breast cancer were also reviewed by the BSG. Guideline statements with no new evidence were retained. The guideline statements on histopath reporting were based on the publication of the Philippine Society of Pathologists in 2008.

An initial draft of the manuscript was prepared by the BSG which consisted of a summary of the guideline statements as well as discussions on the strongest available evidence pertaining to the statements. This initial draft was presented, discussed, modified and voted on by a Panel of Experts which convened last July 5, 2013 at the PCS Building. The Panel of Experts was comprised of representatives from the different specialty societies. Revision of the manuscript was done based on the suggestions and modifications discussed during the Expert Panel presentation. The summary of guideline statements was presented in a public forum during the PSGS 11th Surgical Forum held at the SMX Convention Center last August 3, 2013. The final manuscript was then submitted to the PCS Board of Regents for approval.

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Definition of Terms

Early-stage breast cancer - breast cancer that has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ and stage I, stage IIA, stage IIB, and stage IIIA breast cancers

Total mastectomy – consists of en bloc resection of the breast including the nipple-areola complex with preservation of the pectoralis muscles and axillary lymph nodes; synonymous with *simple mastectomy*

Partial mastectomy – surgical removal of tumor as well as a rim of normal breast tissue surrounding the tumor; anything less than a total mastectomy; synonymous with *lumpectomy, segmentectomy, quadrantectomy* and *wide excision*

Modified radical mastectomy - consists of an en bloc resection of the breast, including the nipple-areola complex, the axillary lymphatics, and the overlying skin near the tumor

Skin-sparing mastectomy – surgery to remove the entire breast and nipple-areola complex with preservation of as much skin as possible including the inframammary fold

Sentinel lymph node – first lymph node/nodes that drains the tumor

Sentinel lymph node biopsy (SLNB) - surgical procedure used to determine if cancer has spread beyond a primary tumor into the lymphatic system; involves injecting a blue dye and/or tracer material (radioactive colloid) that helps the surgeon locate the sentinel nodes during surgery

Axillary lymph node dissection (ALND) - surgical removal of axillary lymph nodes, through an incision in the axilla or as part of modified radical mastectomy for women with invasive breast cancer

Neoadjuvant therapy – treatment given before the definitive surgical management. The main purpose among other things is to downstage the tumor. The usual agents are chemotherapy and hormonal therapy. Synonymous with preoperative or induction therapy.

Adjuvant therapy - additional cancer treatment given after the surgery; may include chemotherapy, radiation therapy, hormonal therapy or targeted therapy

Systemic therapy - treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body

Targeted therapy - a type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells by blocking the action of certain enzymes, proteins and other molecules involved in the growth and spread of cancer cells or by helping the immune system kill cancer cells; most targeted therapies are either small molecule drugs or monoclonal antibodies

Radiotherapy – locoregional treatment of disease by means of ionizing radiation

Hormonal therapy - a form of systemic treatment for hormone-receptor-positive breast cancers that slows or stops the growth of hormone-sensitive tumors by blocking the body's ability to produce hormones (oophorectomy, ovarian suppression, or aromatase inhibitors) or by interfering with hormone action (anti-estrogen). Tumors that are hormone-insensitive do not respond to hormone therapy.

Level of Evidence

Level of Evidence	Therapeutic Studies	Prognostic Studies	Diagnostic Studies	Economic and Decision Analyses
I	High quality randomized clinical trial (RCT) with statistically significant difference or no statistically significant difference but narrow confidence intervals	High quality prospective study (all patients were enrolled at the same point in their disease with ≥ 80% follow-up of enrolled patients)	Testing of previously developed diagnostic criteria on consecutive patients (with universally applied reference "gold" standard)	Sensible costs and alternatives; values obtained from many studies; with multiway sensitivity analyses
	Systematic review of Level I RCTs (and study results were homogenous)	Systematic review of Level I studies	Systematic review of Level I studies	Systematic review of Level I studies
II	Lesser quality RCT (e.g. < 80% follow-up, no blinding, or improper randomization) Prospective comparative study Systematic review of Level II studies or Level 1 studies with inconsistent results	Retrospective study Untreated controls from an RCT Lesser quality prospective study (e.g. patients enrolled at different points in their disease or <80% follow-up.) Systematic review of Level II studies	Development of diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) Systematic review of Level II studies	Sensible costs and alternatives; values obtained from limited studies; with multiway sensitivity analyses Systematic review of Level II studies
III	Case control study Retrospective comparative study Systematic review of Level III studies	Case control study	Study of non-consecutive patients; without consistently applied reference "gold" standard Systematic review of Level III studies	Analyses based on limited alternatives and costs; and poor estimates Systematic review of Level III studies
IV	Case series	Case series	Case-control study Poor reference standard	Analyses with no sensitivity analyses
V	Expert opinion	Expert opinion	Expert opinion	Expert opinion

Categories of Recommendations

Category A   :   Recommendations that were approved by consensus (75 % of the multi-sectoral 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.

Part I: Practice Guidelines on the Diagnostic Work-up for Clinically Suspicious Breast Lesions

A. Diagnostic Work-up for Patients with Palpable Breast Mass

For patients seeking consult for a palpable breast mass, it is recommended that imaging be done prior to any surgical intervention. For patients ≥ 40 years of age, mammography and/or breast ultrasound are recommended. For patients < 40 years of age, breast ultrasound is recommended.

The 2013 National Comprehensive Cancer Network (NCCN) Guidelines for Breast Cancer Screening and Diagnosis recommend that the initial imaging for patients who seek consult for a palpable breast mass should be mammography and breast ultrasound.[1]

Breast imaging has experienced tremendous improvements over the past decades that imaging now aids in the reliable detection and diagnosis of breast disease. Previously, ultrasound was used only to distinguish between a cyst and a solid mass. Presently, features found on ultrasound may aid in the reliable diagnosis of breast lumps. Stavros, et al. found out in a prospective research that the negative predictive value of sonography for solid breast nodules is 99.5%. The study established that sonography is an essential problem solving tool in breast diseases and that sonography can accurately classify some solid lesions as benign. This allows imaging as follow up and obviates unnecessary

biopsies.[2] A similar study conducted by Mainiero, et al. published in 2005 had similar results, with a negative predictive value of 99.3%. They likewise concluded that follow-up can be an acceptable alternative to biopsy for sonographically probably benign solid masses.[3] Soo, et al. concluded that combined mammography and sonography in the setting of a palpable breast lump have a negative predictive value of 99.8%. This helps physicians in their decision making and supports clinical follow up rather than biopsy for palpable lesions that are not clinically suspicious.[4] A study published in 2001 by Dennis, et al. showed the same results with both sonography and mammography having a negative predictive value of 100%.[5]

Various studies have shown that the accuracy of mammography is dependent on breast density among other factors. It is for this reason that the initial imaging modality for older patients be mammography and for younger patients, breast ultrasound. The NCCN guidelines for example recommend that a diagnostic mammography be done for patients ≥ 30 years of age followed by an ultrasound for patients whose mammography results are BIRADS 1 to 3. For patients < 30 years of age, a diagnostic ultrasound is recommended.[1] The American Society of Breast Surgeons in their Position Statement on Screening Mammography recommended that mammography be encouraged for patients ≥ 40 years of age. For patients <40 years, a breast ultrasound is recommended.[6]

Kolb, et al. in 2002 analyzed the factors affecting breast screening and the comparative accuracy of mammography and breast ultrasound. The study showed mammography had a sensitivity of 58% while breast ultrasound had a sensitivity of 78.6% for patients <50 years of age. It was concluded that mammographic sensitivity declines significantly with increasing breast density and is independently higher in older women with dense breasts.[7] Houssami, et al. in 2003 published their paper comparing mammography and sonography in symptomatic young women. The results showed that the sensitivity of ultrasound was significantly higher for younger patients and that sensitivity of mammography increased substantially for patients > 50 years of age. They concluded that breast ultrasound is the more appropriate initial imaging test for women <45 years of

age with breast symptoms.[8] In 2004, Foxcroft, et al. published their study analyzing the diagnosis of breast cancer in women younger than 40. In their study, mammography revealed an abnormality only in 72.6% of young women with breast cancer compared to 92.2% for ultrasound. The results suggested that bilateral breast ultrasound should be considered the diagnostic modality for all women under 40 years with dense or very dense breasts. They concluded that mammography may be less sensitive and specific in younger patients compared to breast ultrasound. Benefits of mammography for younger patients should however, not be overlooked.[9] Osako, et al. in 2007 revealed that among women aged 30-39 years with a palpable breast lump, mammography had a sensitivity of 88.1% compared to breast ultrasound which had a sensitivity of 100%. For non-palpable cancers, ultrasound was not reliable.[10] In 2009, Devolli-Disha, et al. published their study comparing the accuracy of mammography and sonomammography for symptomatic women according to age and breast density. Breast ultrasound was found to be statistically more sensitive than x-ray mammography with sensitivity rates of 72.6% and 52.1%, respectively. The largest difference in sensitivity for both modalities was found in the 30-39 age group.[11] The latest study by Loving which analyzed the sensitivity of breast ultrasound alone for symptomatic women <30 years of age was 100%. It was concluded that breast ultrasound is the appropriate imaging modality in young women.[12]

Some members of the Panel of Experts disagreed with the mandatory use of ultrasound as a diagnostic tool in patients with a clinically suspicious palpable breast mass. It was suggested that breast ultrasound should not be mandatory and should only be used as an adjunct if the mammography is inconclusive. It was also suggested that for patients younger than 40 years old with a clinically suspicious breast mass, biopsy may be done immediately since the lesion is palpable. There were some members of the panel who felt that ultrasound is still necessary because for early breast cancer sometimes it is very difficult to determine if the mass is truly suspicious without imaging unlike with locally advanced breast cancer.

Core needle biopsy is recommended in patients with a palpable breast mass suspicious for cancer. In cases where a core needle is inaccessible, fine needle aspiration cytology may be done provided an experienced cytopathologist is available.

Over the years, core needle biopsy has replaced fine needle aspiration biopsy (FNAB) in the diagnosis of breast masses. This is due to the inherent advantages of core needle biopsy: there is an increase in diagnostic accuracy; it provides histological diagnosis; it can differentiate non-invasive from invasive cancer; and immunohistochemical staining can be done on the core specimens to determine hormone receptor status and other prognostic markers. Also, a trained cytopathologist is not needed for interpretation.[13-15] FNAB has been a well-established method of diagnosis for breast masses despite its limitations. Its main advantage is that the cost is significantly lower than a core needle biopsy.[14,17]

If feasible, ultrasound-guided core needle biopsy is preferred over free-hand biopsy to minimize sampling errors and repeat biopsies, and to improve diagnostic sensitivity. There was some controversy regarding this recommendation during the Expert Panel discussion as some members of the panel believed that core needle biopsy may be done without image-guidance since the lesion is already palpable.

Numerous papers have been conducted supporting the use of image guidance in core needle biopsy. Image guidance improves diagnostic sensitivity, minimizes sampling errors and prevents unnecessary repeat biopsies. Imaging allows direct visualization of the trajectory of the needle assuring that the area concerned is adequately sampled. In a retrospective paper published in 2012 in the Singapore Medical Journal, it was found that the sensitivity of ultrasound-guided gauge 14 core needle biopsy was 96% and the false negative rate was 4%.[18] Ciatto, et al. conducted a retrospective study involving 4035 palpable and non-palpable lesions biopsied consecutively. Results showed a 94.2% overall sensitivity for stereotactic biopsies of non-palpable lesions and an 88.1% specificity for ultrasound-guided biopsies of palpable masses. Positive predictive value was 84.8%, negative predictive value was 95.6% and the false negative rate was 4.4%. It was also found that where the core histology was benign but discordant with imaging, the likelihood of malignancy is 33.1%. This shows how important imaging is in diagnosing breast lesions. Even if

the histology of a lump is benign, discordance dictates further investigation.[19] In a retrospective paper comparing the accuracy of ultrasound-guided, stereotactic and clinical core biopsies, it was found that the false negative rates were 3.4%, 8.9% and 13% respectively.[20] Shah, et al. concluded that false negative core needle biopsies are more common without image guidance. Their research showed that ultrasound-guided core needle biopsy had a false negative rate of 3.6% while core biopsy without image guidance had a false negative rate of 13.3%. These figures are similar to the results of Dillon, et al.[21] Schoonjans, et al. conducted a study in January 1995 to August 1999 which includes 367 patients with 424 ultrasound- guided core needle biopsies for palpable and non-palpable breast lumps. Results showed an overall sensitivity of 96.3%. Sensitivity for palpable lumps was 99.2% and 93.2% for non-palpable lumps.[22] Free hand core needle biopsies and ultrasound-guided biopsies done from November 13, 2007 to August 18, 2009 in the United Kingdom were compared and results showed that 24% of freehand biopsies had to undergo repeat biopsies and that 69% of those undergoing repeat biopsy were upgraded in histopathology. This showed a missed out rate of 16% for the free hand biopsy group. Ward, et al. stated that ideally, all core biopsies should be performed under image guidance to maximize diagnostic accuracy and to obviate the need for repeat biopsies.[23] In a paper published in 2008 by Youk and colleagues, 2420 cases were reviewed and ultrasound-guided core needle biopsy was found to have a sensitivity of 96% and a false negative rate of 2.4%. Results obtained were similar to the previous journals cited. However, they also stated that core needle biopsy had an underestimation rate of 29% for DCIS and 27% for high risk lesions.[24] A retrospective study published in 2001 utilizing results from 500 consecutive breast biopsies concluded that ultrasound-guided large core needle biopsy is an accurate alternative for evaluating breast lesions that require tissue sampling.[25]

If the core needle biopsy result is benign but discordant with imaging or clinical features, ultrasound-guided biopsy (if not yet done) or excision biopsy is recommended. There is evidence to support that there is an increase in diagnostic accuracy of ultrasound-guided biopsies over free hand biopsies even for palpable lesions. Ultrasound guidance allows the surgeon to see that the needle has traversed the lesion, minimizing the risk of missed lesions. Ultrasound-guided biopsy also allows fewer needle passes during biopsy.[23]

If the result of the core needle biopsy is atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), sclerosing adenosis or radial scar, an excision biopsy is recommended. Patients with ADH, ALH or LCIS found on percutaneous biopsy should undergo surgical excision since the same site may harbor DCIS or invasive cancer.[26] Complex sclerosing lesions or radial scars are benign breast lesions but are known to be associated with a 2-fold increase risk for cancer. It is thus recommended to perform excision biopsy in such cases.[27] A study by Houssami, et al. determined that borderline core needle histology is associated with high underestimation of malignancy with highest underestimation for ADH. It was concluded in this study that a reliable diagnosis of ADH may not be made on core needle biopsy.[28]

B. Diagnostic Work-up for Patients with Non-palpable Breast Lesions

There is a significant increase in the number of non-palpable suspicious breast lesions over the years due to the advent of screening mammography. Image-guided percutaneous needle biopsy is the diagnostic procedure of choice for image-detected lesions.[26] Suspicious microcalcifications, densities, parenchymal deformities and architectural distortion can be biopsied by stereotactic needle biopsy (core or vacuum-assisted). Previously, the gold standard for the diagnosis of such lesions was the needle-localized open breast biopsy.[27] The introduction of percutaneous image-guided biopsy techniques have decreased the cost of the diagnostic procedure without sacrificing accuracy.[29] Stereotactic needle biopsy can be done under local anesthesia and on an out-patient basis.

In cases where the mammographic abnormality can also be seen by the ultrasound, ultrasound is the image guidance of choice for the biopsy. It gives minimal discomfort and no radiation exposure to the patient. There is real-time visualization of the needle traversing

Table 1. Diagnostic work-up for patients with palpable breast mass.

Guideline Statements	LoE	Category of Recommendation	Consensus
1. For patients seeking consult for a palpable breast mass, it is recommended that imaging be done prior to any surgical intervention.			
a. For patients ≥ 40 years of age, mammography and breast ultrasound are recommended.	II	B	Yes 56.3% No 31.2% Abstain 12.5%
b. For patients < 40 years of age, breast ultrasound is recommended.	II	B	Yes 56.3% No 37.5% Abstain 6.2%
2. Core needle biopsy is recommended in patients with a palpable breast mass suspicious for cancer.	II		
a. When a core needle is not available, fine needle aspiration cytology may be done provided an experienced cytopathologist is available.	II	A	Yes 87.5% No 6.3% Abstain 6.2%
b. It is ideal that core needle biopsy be done under image guidance.	II	B	Yes 56.3% No 37.5%
3. The Philippine College of Surgeons (PCS) and the Philippine Society of General Surgeons (PSGS) should set up standards regarding core needle biopsy.	V		Yes 100%
4. If the core needle biopsy result is benign but discordant with the imaging or clinical features, ultrasound-guided core needle biopsy (if not yet done) or excision biopsy is recommended.	II	A	Yes 100%
5. If not yet done prior to biopsy, mammography is still recommended to assess the contralateral breast for patients undergoing mastectomy as well as the ipsilateral breast for patients undergoing breast conserving surgery.	V		Yes 93.8% Abstain 6.2%

the target lesion, the procedure time is shorter and the cost is much lower.[27]

Complications of open biopsy such as infection or massive hematomas can be avoided through percutaneous image-guided techniques. This is less invasive, causes minimal or no scarring in subsequent mammograms and avoids unnecessary surgery.[25-26,30]

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Table 2. Diagnostic work-up for patients with non-palpable breast lesions.

Guideline Statements	LoE	Category of Recommendation	Consensus
6. Image-guided needle biopsy is recommended for non-palpable or difficult to palpate suspicious lesions detected by breast imaging.	II		
a. For mammography-detected lesions, mammography-guided biopsy (stereotactic needle biopsy or wire-localized excision) is recommended.	II	A	Yes 93.8% Abstain 6.2%
b. For ultrasound-detected lesions, ultrasound-guided biopsy (core needle or wire-localized excision) is recommended.	II	A	Yes 100%
c. For lesions detected by both mammography and ultrasound, ultrasound is the image-guidance of choice.	II	A	Yes 75.0% Abstain 25.0%

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Part II: Practice Guidelines for the Management Of Ductal Carcinoma-in-Situ

A.   Surgical Treatment

Total mastectomy is the traditional surgical management for ductal carcinoma-in-situ (DCIS) especially for patients with widespread disease. However, for patients with limited disease, as long as negative margins can be achieved, partial mastectomy with whole breast irradiation is an appropriate treatment option. Several prospective randomized studies have shown that the addition of whole breast irradiation to a margin-free excision decreases the rate of in-breast recurrence and the cause-specific survival appears to be equivalent to that of mastectomy.[1-8]

A retrospective study by MacDonald, et al. (2005) concluded that margin width was the single most important predictor of local recurrence.[9] There is controversy, however, regarding the optimal margin for excision and there is conflicting evidence on whether wider margins can replace the need for radiotherapy in patients with DCIS. There is consensus that margins equal to or greater than 10mm are adequate while margins less than 2 mm are inadequate,[9-15] but there is no uniform consensus regarding excision margins between 2 mm and 10 mm. There is consistent data that shows that the addition of radiotherapy to excision margins of at least 2 mm reduces the risk of local recurrence.[16-18] The Panel recommends that a microscopic margin of at least 10 mm should be achieved for patients undergoing partial mastectomy. Intraoperative frozen section analysis of margins may be performed to reduce the incidence of reoperations due to a close or positive margin[19-21]. Total mastectomy is recommended for patients with widespread disease (multifocal or multicentric disease) or if   negative margins are not achievable.

There are no prospective randomized trials to date to assess whether a wider margin (10 mm or more) can obviate the need for whole breast irradiation in patients with DCIS. A retrospective series involving 469 patients showed that radiation does not lower the recurrence rate among patients with wide margins (≥10mm).[22] The study also demonstrated the addition of radiotherapy if the margins were between 1 mm and 10 mm provided a non-statistically significant reduction in local recurrence.[22] A non-randomized prospective trial involving patients with low-risk DCIS (low or intermediate grade with size of 2.5 cm or less) who underwent breast conserving surgery with ≥ 10 mm margin showed that the rate of ipsilateral breast events after 5 years in this subset of patients was acceptably low (6.7%) even without irradiation.[23] The option of partial mastectomy alone should be considered only in cases where the physician views the patient as "low risk".

Axillary dissection is not recommended in patients with apparent pure DCIS since nodal involvement is extremely rare.[21-22] However, as high as 25% of cases of apparent pure DCIS on core needle biopsy will be found to have invasive cancers on excision[23-25] and axillary staging is warranted. In centers where a sentinel node team is available, it is recommended that sentinel node biopsy be offered to patients with DCIS diagnosed by core needle biopsy that will undergo mastectomy, with or without reconstruction, as sentinel node biopsy will no longer be possible after a mastectomy should invasive cancer be found on final histopathology. Sentinel node biopsy is also recommended if the partial mastectomy is performed in an anatomic location which could make the future performance of a sentinel node biopsy essentially impossible (i.e. axillary tail, upper outer quadrant). In all other cases, the finding of an invasive component after definitive surgery to the breast warrants a second surgery to assess the axilla.

Immediate breast reconstruction, whether tissue or implant reconstruction following skin-sparing mastectomy can provide an excellent cosmetic result. A retrospective analysis by Spiegel and Butler demonstrated the oncologic safety of skin-sparing mastectomy followed by immediate breast reconstruction, with none of the 44 patients with pure DCIS developing local recurrence nor distant metastasis[26]. This study however is limited by its small sample size and short term follow-up.

Table 3. Surgical treatment of ductal carcinoma-in-situ.

Guideline Statements	LoE	Category of Recommendation	Consensus
1. In patients with ductal carcinoma-in-situ, options for the primary treatment of the breast are: a) total mastectomy; b) partial mastectomy plus radiotherapy			
a. Total mastectomy is recommended for patients with widespread disease (multifocal or multicentric disease) or if negative margins are not achievable.	I	A	Yes 93.8% Abstain 6.2%
b. For patients undergoing total mastectomy, radiotherapy is not necessary.	I	A	Yes 93.8% Abstain 6.2%
c. For patients undergoing partial mastectomy, the microscopic margin of excision should be at least 10 mm and radiotherapy is necessary.	II	A	Yes 93.8% Abstain 6.2%
2. Axillary staging is not recommended for patients with pure DCIS diagnosed by excision biopsy.	II	A	Yes 100%
3. In patients with DCIS diagnosed by core needle biopsy who will be treated with total mastectomy, sentinel node biopsy should be offered if a sentinel node team is available. It should also be offered to patients who will be treated with partial mastectomy in an anatomic location which could compromise the future performance of a sentinel node biopsy (i.e. upper outer quadrant, axillary tail).	II	A	Yes 93.8% Abstain 6.2%

B. Adjuvant Treatment

Chemotherapy and targeted therapy

Cytotoxic chemotherapy and targeted therapy have no role in the management of patients with non-invasive breast cancer.

Hormonal therapy

The updated long term follow up of NSABP-24 trial done by Fisher et.al, have consistently shown that hormonal therapy using tamoxifen given after partial mastectomy and radiotherapy significantly decreased all breast cancer events[5]. In this study, 1804 patients with DCIS who were treated with partial mastectomy and radiotherapy were randomized either to receive tamoxifen or placebo. Tamoxifen was concurrently given with radiotherapy and started not later than 56 days after lumpectomy at 20 mg daily for 5 years. The primary endpoint of this study was the occurrence of invasive and non-invasive cancer both in the ipsilateral and contralateral breast. There was a significant reduction in all breast cancer related events in the tamoxifen group than in the placebo. The main advantage of tamoxifen was a significant reduction in invasive ipsilateral breast tumor recurrence (I-IBTR) by 32% compared with the placebo group. It has also shown to decrease contralateral non-invasive and invasive breast cancer. There was a non-significant reduction of ipsilateral DCIS breast tumor recurrence.

Factors that increased the rate of tumor recurrence include young age and positive surgical margins. Young age at the time of diagnosis in both the tamoxifen and placebo group was associated with increased recurrence of ipsilateral invasive breast cancer. A 38% reduction in ipsilateral invasive breast cancer recurrence in patients younger than 50 years of age and a 22% reduction in women above 50 years old was observed in the tamoxifen group. There was an increase in the rate of endometrial

cancer in the tamoxifen-treated group (1.53 vs. 0.45 per 1000 patients annually in the placebo group). However, no deaths were reported from endometrial cancer in the tamoxifen group. Overall survival after 5 years was 97% for both groups.

Contrary to the NSABP-24, the United Kingdom, Australia, and New Zealand (UK/ ANZ) DCIS Trial reported in their first analysis of 1694 DCIS patients (some with and some without radiation by choice) that tamoxifen did not reduce the incidence of I-IBTR[7]. In a recent update, tamoxifen continued to have a minimal effect on I-IBTR but did reduce DCIS-IBTR, especially among those with low- and/or intermediate-grade tumors.

The differences in the result of these two trials may be due to patient and tumor characteristics. In the NSABP 24 trial, there were a significantly higher proportion of young patients, ER positive and low-grade DCIS compared with the UK/ANZ DCIS trial. Also, NSABP-24 included patients with positive margins which could in part explain the discrepancies in the results.

The Panel recommends that hormonal therapy using tamoxifen be administered to pre- and post-menopausal women with ER and/or PR-positive DCIS after surgical treatment. It should be started not later than 6 weeks after surgery and may be given concurrently or sequentially with radiotherapy. Tamoxifen is given for 5 years as chemoprevention.

Radiation Therapy

Radiation therapy is recommended after partial mastectomy to decrease local recurrences. In 1985, The National Surgical Adjuvant Breast Project (NSABP) Started Protocol B-17, 814 women with DCIS were randomly assigned to lumpectomy with irradiation vs lumpectomy alone. The main endpoint was local recurrence.[30]

The initial clinical and pathologic results were published in 1993 and 1995.[30-31] Cumulative incidence of invasive and non-invasive ipsilateral breast tumors combined after 12 years follow up was 31.7% in the lumpectomy alone arm and 15.7% in the lumpectomy plus irradiation arm (P= 0.001). However, no difference in overall survival has been observed between the two groups (86% vs 87%, P= 0.80).[32]

The European Organization for Research and Treatment of Cancer (EORTC) trial enrolled 1010 women with a median follow up of 10.5 years. The 10-year local recurrence (LR) free rate was 74% in the group treated with local excision alone compared to 85% in the women treated with local excision plus radiation therapy (RT). The risk of DCIS and invasive LR was reduced by 48% (P = 0.0011) and 42% (P = 0.0065) respectively. Both groups had similar low risk of metastasis and death.[1]

Schouten van der Velden, et al. published the results of a Dutch multicenter retrospective study on 798 women treated between 1989 and 2003 comparing the outcomes after different treatment strategies for ductal carcinoma-in-situ of the breast. This resulted in a 5 year recurrence free survival of 75% for breast conserving surgery alone (237 patients) compared to 91% for breast conserving surgery followed by RT (153 patients) and 99% for mastectomy (408 patients) (P <0.01). Independent risk factors for LR were treatment strategies, symptomatically detected DCIS, and presence of comedonecrosis.[33]

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Table 4. Adjuvant treatment for ductal carcinoma-in-situ

Guideline Statements	LoE	Category of Recommendation	Consensus
4. Cytotoxic chemotherapy and targeted therapy have no role in the management of patients with non-invasive breast cancer. HER-2/neu determination is not recommended for patients with pure DCIS.	V		Yes 100%
5. Hormonal therapy using Tamoxifen is recommended for pre- and post-menopausal women with ER and/or PR-positive DCIS after surgical treatment.	I	A	Yes 87.5% Abstain 12.5%
a. Hormonal Therapy should be started not later than 6 weeks after surgery.	I	A	Yes 87.5% Abstain 12.5%
b. Hormonal Therapy may be given concurrently or sequentially with radiotherapy in patients who have undergone partial mastectomy.	V		Yes 93.8% Abstain 6.2%
6. Tamoxifen should be given for 5 years as chemoprevention.	I	A	Yes 93.8% Abstain 6.2%
7. Radiation therapy is recommended after partial mastectomy to decrease local recurrences.	I	A	Yes 93.8% Abstain 6.2%

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Part III: Practice Guidelines for the Management of Early Invasive Breast Cancer

A.   Surgical Treatment

Surgical treatment of the breast

In patients with early invasive breast cancer, options for the primary treatment of the breast are: a) total mastectomy; b) partial mastectomy with radiation therapy. The NSABP B-04 trial is the landmark trial showing that more radical surgery for early breast cancer is not necessarily better than less extensive surgery in terms of local recurrence and survival rates.[1] Almost 1600 women were randomized to radical mastectomy, or total mastectomy with or without radiation therapy. Decades after the study, Fisher et al published its 25-year analysis in 2002 and the data still shows that there is no significant difference in either group in terms of disease free survival, relapse free survival, distant disease free survival or overall survival.

The NSABP B-06 trial further investigated whether breast conserving surgery with radiation therapy is equivalent to total mastectomy.[2] A total of 1851 women with tumors of 4cm or less, were randomized to lumpectomy and axillary lymph node dissection (ALND) with or without radiation therapy or to total mastectomy with ALND [modified radical mastectomy (MRM)]. In the 20-year analysis published in 2002, there was no significant difference in disease free survival, distant disease free survival and overall survival in either treatment arms. However, in terms of local control, there was significant difference in lumpectomy alone (39%) compared with lumpectomy plus radiation therapy (14%).

Several prospective randomized trials on breast conserving therapy[3-5] showed similar outcomes in terms of local recurrence and overall survival. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis on the role of radiation therapy on local control and its impact on long term survival.[6] In the analysis of breast conserving surgery involving 7300 women from 10 trials, there was an absolute decrease in local recurrence by 19% between lumpectomy alone and lumpectomy with irradiation (26% vs 7%). The meta-analysis also demonstrated a 5.4% decrease in the 15 year risk of death between the two arms. An updated analysis published in 2011[7] involving 10,801 women from 17 trials again showed an absolute reduction in local recurrence by 15.7% at 10 years between lumpectomy alone and lumpectomy with irradiation (35% vs 19.3%). Overall about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10.

In addition to radiation therapy, ensuring an adequate microscopic margin during breast conserving surgery further decreases local recurrence.[2-6] What constitutes an adequate negative margin has been largely

unanswered. More than 25% of patients with less than 2mm margins were found to have residual carcinoma. Thus re-excision of margins is recommended when margins are clear of tumor by 2mm or less.[8] Several studies have demonstrated similar results.[9-11]

In 2010, a large meta-analysis of the impact of surgical margins on local recurrence in women with early stage breast cancer undergoing breast conserving surgery was published.[12] There is some evidence that local recurrence decreased as negative margins increased for the subgroup of patients with at least a 2-mm margin as well as those with at least a 5-mm margin. In one group which assessed margin distance, the odds ratios for 1 mm, 2 mm, and 5mm margins are 1.0, 0.75, and 0.51 respectively. The results were significant for margins at 2 mm and 5 mm. In the group which assessed margin status (positive vs negative, close vs negative), the same significance was evident. However, adjustment of adjuvant radiation and endocrine therapies for these patients obviates the significance of the margin distance. A larger margin of more than 10 mm is unlikely to have additional benefit in long term decrease in local recurrence.[12] The Panel agreed that for patients undergoing partial mastectomy, a microscopic margin of 2-5 mm is considered adequate.

Frozen section analysis of surgical margins may be done. It decreases re-excision rates by less than 20%.[13-15] Following lumpectomy, once the specimen is removed, orientation of the specimen is critical to ensure that the proper margins are inked and identified by the pathologist. The cavity bed is marked with metallic clips for future localization.

To date, there is no randomized controlled trial comparing skin-sparing mastectomy (SSM) versus non-skin sparing mastectomy. This mastectomy technique is performed for patients who will have immediate breast reconstruction. A meta-analysis of observational studies was published by Lanitis S, et al.[16] in 2010 evaluating the differences between the two arms. A total of almost 4000 women from 9 studies were evaluated. There was no difference in local recurrence between the SSM versus the non-SSM group. Skin sparing mastectomy followed by immediate breast reconstruction has proven to be oncologically safe with superior cosmetic outcomes for early stage breast cancer.[16-19]

Breast reconstruction after mastectomy should not compromise oncologic safety. Patients who are candidate for breast reconstruction should be evaluated by a multidisciplinary team involving the surgical, medical and radiation oncologists, and the plastic and reconstructive surgeons, regarding options and timing of reconstruction. Several studies demonstrated that there is no significant difference in the incidence of loco-regional recurrence and distant metastasis for patients having breast reconstruction.[20-22]

Immediate breast reconstruction may be considered in patients with ductal carcinoma in situ and early invasive carcinomas. Careful patient selection for immediate breast reconstruction should be made by the multidisciplinary team to ensure low failure rate. Cowen, et al. published a prospective multicenter, non-randomized trial in 2010 to determine the factors contributing to reconstruction failure and capsular contracture in patients with post-mastectomy radiation therapy (PMRT). The study identified T3 or T4 lesions, smoking, and positive axillary nodal status to be associated with post mastectomy breast reconstruction failure.[23] Obesity may also contribute to increased morbidity in patients with PMRT.[24-25]

In general, delayed breast reconstruction is offered to patients who will not need further radiation therapy because of post-radiation complications and possible poor cosmetic outcomes.[26-27] The timing of breast reconstruction in relation to post-mastectomy radiation therapy remain controversial because there is no large prospective randomized trials addressing the issue for ethical reasons. A meta-analysis published by Barry, et al. in 2011 evaluated the optimum sequencing of breast reconstruction and postmastectomy radiation therapy.[28] In a total of 1,105 patients from 11 trials, patients who had PMRT and breast reconstruction had higher morbidity (ie. capsular contracture, infection, fat necrosis, fibrosis, and necessity to reoperate on the patient), compared with patients without PMRT. Comparing the method of reconstruction after PMRT, reconstruction using autologous flaps resulted in less morbidity compared with implant based reconstruction (OR=0.21; 95% CI).

Even with lower morbidity rates, autologous tissue reconstruction are still subject to radiation-related complications. In patients with early stage breast

carcinoma undergoing mastectomy, the definitive pathologic status needed to determine the need for radiation therapy may take several days. Some investigators recommend the "delayed-immediate" reconstruction technique.[29] In this method, a tissue expander is placed at the time of skin sparing mastectomy while waiting for the final pathologic result. If PMRT is required, a delayed reconstruction is advised; and if PMRT is not necessary, an immediate reconstruction is performed. This technique allows patients who do not require postmastectomy radiation therapy to receive the benefits of skin-sparing mastectomy with aesthetic outcomes similar to those of immediate reconstruction.[30]

The rate of detection of routine mammography for non-palpable breast cancer recurrence in a reconstructed breast is about 1-3%.[31-33] Published data have small sample sizes to detect true cancer detection rates. Thus, at present, there is insufficient evidence for recommending routine surveillance mammography for non-palpable recurrent cancer in the reconstructed breast.

In a study by Langstein, et al. in 2003, it was found that 39 of 1694 patients who had undergone immediate breast reconstruction had local recurrence. More than 70% were found in the skin and subcutaneous tissue, and the remaining were chest wall recurrences. Patients with skin and subcutaneous tissue recurrences had better survival rates and had decreased incidence of metastasis.[34] Chest wall recurrence is associated with distant metastasis and is likely to have systemic symptoms. The survival rate of these patients does not

seem to be affected by early detection. Physical examination alone detects majority of recurrences in reconstructed breasts.

Magnetic resonance imaging (MRI) of the breast has potential in the detection of non-palpable cancer recurrence in the reconstructed breast. It can differentiate benign from malignant changes in the reconstructed breast especially for chest wall lesions or if superficial lesions are clinically misinterpreted as fat necrosis.[35-36]

Surgical treatment of the axilla

In patients with early invasive breast cancer, options for the surgical management of the axilla are: a) Sentinel Lymph Node Biopsy (SLNB); b) Axillary Lymph Node Dissection (ALND). Several large randomized prospective trials have evaluated the experience of sentinel node identification for staging and its morbidity rates compared to axillary dissection. The NSABP B-32 trial established that sentinel lymph node biopsy (SLNB) can achieve the same therapeutic goals as conventional ALND but with less morbidity.[37] Five thousand six hundred eleven women with clinically node negative operable breast cancer were randomized to SLNB followed by ALND or to observation if the SLN was negative for metastasis. The overall survival (OS), disease free survival (DFS) and regional control were statistically equivalent between the 2 groups. When the SLN is histologically negative for metastasis, SLNB alone with no further ALND is an appropriate, safe, and effective

Table 5. Surgical treatment of the breast in early invasive breast cancer.

Guideline Statements	LoE	Category of Recommendation	Consensus
1. In patients with early invasive breast cancer, options for the primary treatment of the breast are: a) total mastectomy; b) partial mastectomy with radiation therapy.	I	A	Yes 100%
2. For patients undergoing partial mastectomy, a microscopic margin of 2 - 5mm is considered adequate.	II	A	Yes 93.8% Abstain 6.2%
3. Breast reconstruction may be done immediately after mastectomy (immediate reconstruction) or after completion of cancer treatment (delayed reconstruction).	II	A	Yes 100%

therapy for patients with clinically node-negative breast cancer.[38] The morbidity rates from SLNB compared to ALND from the NSABP B-32 trial were reported in 2010 and SLNB was showed to have significantly less shoulder abduction deficits, lymphedema and arm numbness over a 3 year follow period compared to ALND.[39]

The Royal Australian College of Surgeons' multicenter trial of the Sentinel Node versus Axillary Clearance (SNAC) was a randomized trial designed to determine if sentinel node biopsy produces less morbidity and equivalent cancer-related outcomes when compared with immediate axillary clearance in women with early-stage breast cancer.[40] Stage 1 tested the performance measures for SLNB and found 5% false-negative rate, 95% sensitivity, and 98% negative predictive value. Stage 2 was a randomized controlled trial of SLNB alone versus axillary clearance in women with clinically node-negative breast cancer less than 3cm. The SNAC trial had insufficient power on its own to detect differences in recurrence and survival. Given the low false negative rate, the differences would likely be small. SLNB resulted in accurate staging with less morbidity.[41]

The Italian Sentinella/Gruppo Interdisciplinare Veneto Oncologia Mammaria (GIVOM) study was a multicenter randomized trial that assessed the efficacy and safety of SLNB compared with ALND.[42] Seven hundred forty-nine patients with less than 3cm breast cancer were randomly assigned to SLNB with ALND or SLNB followed by ALND only if sentinel node was metastatic. A 95% sentinel node identification rate and a 16.7% false-negative rate were reported. Locoregional recurrences were more in the SLNB arm when compared to the ALND arm (16 vs. 3 out of 352 patients). Postoperative side effects were significantly less in the SLNB group. The 5-year disease-free survival was 89.9% in the ALND arm and 87.6% in the SLNB arm. However, the number of patients enrolled in this study was insufficient to draw definite conclusions.

The accuracy of SLNB depends greatly on the proficiency of the surgeon performing the procedure.[43] A learning curve exists, and surgeons master the procedure at different rates. The American Society of Breast Surgeons guidelines recommend 20 cases of SLNB with back-up ALND with an identification rate of

85% and a false-negative rate less than 5% before abandoning ALND when the sentinel node is metastatic.[44] The NCCN 2013 guidelines recommend that an experienced sentinel lymph node (SLN) team is mandatory for the SLN mapping and excision and if patients do not have access to an experienced SLN team then they should be referred to one for the surgical treatment of the axilla.[45-46] The Panel recommends that SLNB should be performed by an experienced or validated sentinel lymph node team (which may include a nuclear medicine specialist, pathologist, surgeon) to ensure accuracy of the procedure. In centers where a sentinel lymph node team is not available or facilities are lacking, a standard ALND should be done.

Morrow, et al.[47] performed a randomized controlled trial comparing the use of blue dye alone with that of combined dye and isotope. The success rate of SLNB was higher with combined blue dye and isotope than with blue dye alone. (100% vs. 86%, P= .002) The American College of Surgeons Oncology Group (ACOSOG) Z0010 trial also evaluated the success rate of SLNB using blue dye, radiocolloid and the combination of blue dye and radiocolloid, however no statistically significant difference in sentinel node identification failure rate was seen (1.7%, 2.3% and 1.2% for the blue dye, radiocolloid and the combination of dye with isotope, respectively).[48] The combined use of radiocolloid and blue dye for SLN identification is ideal; however, with adequate experience, the use of either modality alone has also shown equal success rates.

The College of American Pathologists published guidelines for processing sentinel nodes[49] and they recommend that sentinel lymph nodes be sectioned as close to 2 mm as possible, embedded in paraffin, and stained with hematoxylin-eosin (H&E). Routine cytokeratin staining of histologically negative SLNs should not be considered the standard until clinical trials demonstrate its clinical significance.

The St. Gallen International Expert Consensus on the Primary Therapy of Breast Cancer 2011[50] does not recommend the routine use of immunohistochemistry to look for low-volume metastatic disease in sentinel nodes, since metastases shown only by immunohistochemistry would not alter management. Furthermore, isolated tumor cells, and even metastases up to 2 mm (micrometastases)

in a single sentinel node, were not considered to constitute an indication for axillary dissection regardless of the type of breast surgery carried out.

ALND remains indicated in women with metastatic lymph nodes on sentinel node biopsy. In addition, clinically node negative tumors measuring >5 cm in maximum diameter or those patients with inflammatory cancers should undergo ALND at the outset. There is no clinical trial data on the efficacy of SLNB as a staging procedure for tumors exceeding 5 cm for which false-negative rates are likely to be unacceptably high. Clinical examination of the axilla is notoriously inaccurate with a 30% error rate either way i.e. 30% of clinically node-negative patients will prove to have pathological nodal involvement whilst 30% of clinically node-positive patients will have no evidence of axillary metastases. Pre-operative axillary ultrasound and percutaneous node biopsy is increasingly being used to identify node-positive patients who can then proceed to ALND as either primary surgical treatment or following induction chemotherapy. Percutaneous needle biopsy of lymph nodes will confirm positivity in more than 90% of women with >/= 4 positive nodes and select 40–50% of node-positive cases overall.[51-52] It remains unclear whether patients with a negative axillary ultrasound and core biopsy are candidates for SLNB when tumor size exceeds 5 cm. Traditional level I and II ALND required that at least 10 lymph nodes be provided for pathologic evaluation to accurately stage the axilla.[51-52] ALND should be extended to include level III only if gross disease is apparent in level II nodes.

The ACOSOG Z0011 trial for patients with a clinically node negative axilla who underwent lumpectomy and tangential whole-breast irradiation showed at a median follow-up of 6.3 years that axillary dissection can be omitted without adversely affecting prognosis even in the presence of one or two positive sentinel nodes.[53] The St. Gallen International Expert Consensus on the Primary Therapy of Breast Cancer 2011 accepted the option of omitting axillary dissection for macrometastases in those patients who fulfilled the inclusion criteria for the Z0011 trial (undergoing breast conserving surgery and radiotherapy, with clinically T1 or T2 node negative breast cancer and only 1-2 positive sentinel nodes). The St Gallen Panel however emphasized that this recommendation should not be extended to include patients undergoing mastectomy, those who will not receive whole-breast tangential field radiotherapy, those with more than 2 positive sentinel nodes and patients receiving neoadjuvant chemotherapy.[50]

It was recommended by the Panel that guidelines for sentinel lymph node biopsy and its validation process be set up by the Philippine College of Surgeons (PCS) and the Philippine Society of General Surgeons (PSGS).

Table 6. Surgical treatment of the axilla in early invasive breast cancer.

Guideline Statements	LoE	Category of Recommendation	Consensus
4. In patients with early invasive breast cancer, options for the surgical management of the axilla are: a) Sentinel Lymph Node Biopsy (SLNB); b) Axillary Lymph Node Dissection (ALND).	I	A	Yes 100%
5. Sentinel Lymph Node Biopsy is the recommended surgical staging technique of the axilla for invasive cancers less than or equal to 5 cm in diameter with a clinically negative axilla.	I	A	Yes 93.8% Abstain 6.2%
a. If the SLN is positive for macrometastases or is not identified, ALND is recommended; if the SLN is negative for metastases, ALND can be avoided.	I	A	Yes 87.5% Abstain 12.5%
b. The presence of isolated tumor cells or micrometastases (metastases up to 2mm) in a sentinel node is not an indication for ALND.	I	A	Yes 87.5% Abstain 12.5%

Guideline Statements	LoE	Category of Recommendation	Consensus
6. SLNB should be performed by an experienced or validated sentinel lymph node team (which may include a nuclear medicine specialist, pathologist, surgeon) to ensure accuracy of the procedure. If a sentinel lymph node team is not available, a standard ALND should be done.	III	A	Yes 93.3% Abstain 6.7%
7. The combined use of radiocolloid and blue dye for SLN identification is ideal; however, with adequate experience, the use of either modality alone has also shown equal success rates.	I	A	Yes 93.3% Abstain 6.7%
8. Permanent H and E evaluation of the SLNs is recommended and the routine use of immuno-histochemistry (IHC) is not indicated as metastasis shown by IHC would not change the management.	III	A	Yes 75.0% Abstain 25.0%
9. A standard ALND is indicated for all patients with a clinically positive axilla, tumors >5cm even if with a clinically negative axilla and inflammatory breast cancers. In a standard ALND, at least 10 lymph nodes should be removed to adequately stage the axilla.	I	A	Yes 93.3% Abstain 6.7%
10. The Philippine College of Surgeons (PCS) and the Philippine Society of General Surgeons (PSGS) should set up guidelines for sentinel lymph node biopsy and its validation process.	V		Yes 100%

B. Neoadjuvant Therapy for Early Invasive Breast Cancer

Preoperative or neoadjuvant chemotherapy is an option for patients with early stage breast cancer. Several studies were performed to evaluate the potential clinical benefits of neoadjuvant chemotherapy in early breast cancer. For patients who fulfill the criteria for breast conserving surgery except for tumor size, neoadjuvant chemotherapy may be given to downstage the primary tumor, resulting in an increase in breast conservation rates[54-56]. Unfortunately, neoadjuvant chemotherapy does not seem to offer an advantage over adjuvant systemic therapy in terms of survival and local control, as demonstrated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B18 and B27 trials and European Organization for Research and Treatment of Cancer Trial (EORTC) 10902[55-58]. It may, however, allow early assessment of tumor sensitivity to chemotherapy leading to modifications of treatment regimen in cases of poor response.

C. Adjuvant Treatment for Early Invasive Breast Cancer

Chemotherapy

Adjuvant chemotherapy is generally recommended by estimating an individual's risk for recurrence and expected benefit of therapy. Increasing tumor size and nodal involvement are well established adverse prognostic factors for patients who have early-stage breast cancer.[59]

Table 7. Neoadjuvant therapy for early invasive breast cancer.

Guideline Statements	LoE	Category of Recommendation	Consensus
11. Neoadjuvant chemotherapy may be given to patients who fulfill the criteria for breast conserving surgery except for tumor size, to downstage the primary tumor.	I	A	Yes 86.7% No 13.3%

Other factors that should be considered include tumor grade, hormone receptor status, HER-2 receptor status, lymphovascular invasion and molecular subtypes. It was emphasized during the Expert Panel discussion that no single prognostic factor is considered an absolute indication for adjuvant chemotherapy. All of the aforementioned factors should be taken into consideration to determine the need for chemotherapy.

In 2011, the St. Gallen International Expert Consensus proposed an intrinsic biological subtypes within the breast cancer spectrum based on expression of estrogen receptor (ER), progesterone receptor (PgR), HER-2/ neu (HER2) and Ki67.[50]

Tang, et al. identified the 5 distinct molecular subtypes[60]:

Molecular Subtype	Immunohistochemical Staining			
	ER	PgR	HER2	Ki67
Luminal A	+	+	-	Low (<14%)
Luminal B (HER2-negative)	+	+	-	High (>14%)
Luminal B (HER2-positive)	+	+	+	any
HER2-positive (non-luminal)	-	-	+	
Basal-like	-	-	-	

ER=estrogen receptor
PgR=progesterone receptor
Her2=human epidermal growth factor receptor 2

In an independent cohort of 4046 patients with breast cancer wherein 2847 had hormone receptor positive tumors, Cheang, et al. was able to classify tumors using HER2 immunohistochemistry and the Ki67 index for subtyping as follows: 1530 (59%, 95% confidence interval [CI] = 57% to 61%) as luminal A, 846 (33%, 95% CI = 31% to 34%) as luminal B, and 222 (9%, 95% CI = 7% to 10%) as luminal-HER2 positive. Luminal B and Luminal-HER2 positive breast cancer were statistically significantly associated with poor breast cancer recurrence free and disease- specific survival in all adjuvant systemic categories particularly women who received tamoxifen as their sole adjuvant systemic therapy, among whom the 10-year breast cancer-specific survival was 79%, 64% and 57% respectively for luminal A, luminal B and luminal-HER2 subtypes.[61]

Bonadonna and colleagues first evaluated the administration of polychemotherapy / multi-agent chemotherapy by administering a minimum of two agents in combination. Women with node positive breast cancer were randomized to 12 monthly cycles of cyclophosphamide, methotrexate and 5-Fluorouracil (CMF) chemotherapy or no further therapy after radical mastectomy. Twenty years of follow up showed significant improvement in relapse free survival (RFS), (relative risk 0.65) and overall survival (relative risk 0.76).[62-63]

An overview of 194 randomized clinical trials involving more than 145,000 women at 15 years follow up by the Early Breast Cancer Trialists Collaboration Group (EBCTCG) in 2005[64] demonstrated that 6 months of treatment with a multi-agent anthracycline containing regimen (FAC or FEC) is more efficacious than 6 months of treatment with the non-anthracycline regimen, CMF. The anthracycline-containing regimen reduced the annual breast cancer death rate by 38% for women less than 50 years of age and by about 20% for women 50-69 years of age at diagnosis.

The timing of the initiation of systemic therapy was reviewed in a retrospective analysis of 2,594 patients with early breast cancer.[65] Relapse-free survival (RFS) and overall survival (OS) were compared among patients grouped by time from definitive curative surgery to start of adjuvant chemotherapy (<4 weeks, >4 to 8 weeks, >8 to 12 weeks and >12 to 24 weeks). It was concluded that adjuvant chemotherapy is equally effective up to 12 weeks after definitive surgery but the RFS and OS appears to be compromised by delays of more than 12 weeks after definitive surgery. It was therefore recommended by the Panel that adjuvant systemic treatment should be ideally started 4 to 6 weeks after surgery. However, a category A recommendation was not achieved because some members of the Panel of Experts abstained from voting as the subject matter under discussion was not their specialty.

Targeted Therapy. Targeted therapy using trastuzumab should be highly considered as an integral part of adjuvant treatment for Her-2 positive early breast cancer in the following settings: a. node positive early breast cancer irrespective of pathologic tumor size; b. node negative breast cancer with more than 1 cm tumor size. Dahabreh et. al conducted a meta-analysis of randomized controlled trials which evaluated HER2 positive early breast cancer patients receiving adjuvant chemotherapy with or without trastuzumab[66]. The HERA, NCCTG N9831, NSABP B31, BCIRG 006 and FINHER trials were included in this meta-analysis. These trials involved patients with early invasive breast cancers, node positive or node negative high-risk patients with a tumor size greater than 1 cm.

The primary endpoint of these trials is disease-free survival (DFS) event defined as progression of disease or death from any cause. Secondary endpoints were mortality, locoregional recurrence, distant recurrence and central nervous system recurrence, Class III/IV congestive heart failure and significant decline in left ventricular ejection fraction (LVEF).

NSABP B-31, NCCTG N9831 and BCIRG 006 trials evaluated the combination of doxorubicin and cyclophosphamide followed by administration of a taxane with or without trastuzumab. The FinHer study randomized patients to receive vinorelbine or docetaxel and then randomized all patients with HER2 positive tumors to receive trastuzumab or observation. In the HERA trial, patients with HER2 positive breast cancer were randomized to receive one or two years Trastuzumab following any four cycles of an accepted chemotherapy regimen comparing it with chemotherapy and observation only.

Results of the meta-analysis showed an overall 38% lower relative risk for disease progression or death from any cause with the use or trastuzumab. In terms of overall survival, the combined results in these trials favor the use of trastuzumab in combination with chemotherapy with an overall 34% reduction in relative risk for death from any cause. This also resulted in a lower risk for developing locoregional and distant recurrence. Other secondary outcomes showed an increased risk for developing CNS disease as the first site of recurrence in patients receiving trastuzumab. A decline in cardiac function was also observed in these patients resulting in a higher risk for Class III/IV congestive heart failure and decreased left ventricular ejection fraction (LVEF). These secondary outcomes however were outweighed by the overall lower risk for distant recurrences (non-visceral disease) and superior improvement in overall survival.[66]

A meta-analysis of the six trials (BCIRG 006, FinHer, HERA, NCCTG N9831, NSABP B31 and PACS 04) was done by Wenjin, et al. to assess the benefits of concurrent or sequential trastuzumab with adjuvant chemotherapy for early breast cancer.[67] The NCCTG N9831 study was the only trial to directly compare the concurrent and sequential use of trastuzumab. Update on this study showed that HER2 positive breast cancer patients had improved DFS with concomitant trastuzumab rather than from the sequential administration. There is also a considerable reduction in mortality risk but a higher incidence of CNS recurrence relative to those without any trastuzumab treatment.[67] It is hypothesized that the increased incidence of CNS involvement may be due to a lower bioavailability of trastuzumab because of the poor penetration of the blood-brain barrier and its high effectiveness in preventing the development of non-CNS visceral disease.

In the HERA trial, one year treatment with trastuzumab after adjuvant chemotherapy significantly improved disease-free survival. The data that evaluated the administration of 2 years of trastuzumab has not been reported yet.[68]

International guidelines clearly recommend adjuvant targeted therapy in patients with node negative disease and tumor size is larger than 1 cm if HER-2 is overexpressed. However, its role in small node negative tumors less than 1 cm is still controversial. Two retrospective studies demonstrated an increase in recurrence for tumors less than 1 cm with her-2/neu overexpression, especially in patients who did not receive trastuzumab[69-70] and it was recommended that anti-HER2 therapy be administered. The panel believes however that the use of trastuzumab in these subsets of patients still lacks sufficient evidence to make a recommendation.

Hormonal therapy

Hormonal therapy is recommended as an adjuvant treatment for patients with hormone-sensitive early breast cancers, regardless of the patient's age, menopausal status, and type of surgery. Hormone-sensitive breast cancers are those that are positive for estrogen receptor (ER), for progesterone receptor (PR), or for both, regardless of intensity of staining or number of cells stained. Therefore, patients with ER-negative and PR-negative breast cancers should not be given hormonal therapy.

For many years, the selective estrogen-receptor modulator tamoxifen was the standard hormonal adjuvant therapy for early breast cancer. Tamoxifen's role in the adjuvant treatment of breast cancer was summarized in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 15-year update published in 2005[64]. In women with ER-positive disease, 5 years of tamoxifen reduced the annual breast cancer death rate by 31%, irrespective of age, administration of adjuvant chemotherapy, PR status, or other tumor characteristics. This reduction was evident during the first 15 years (i.e. from start of treatment up to years 6 to 15). Moreover, the rate of recurrence was also reduced, and this reduction similarly persisted beyond the 5-year treatment period up to the first decade.

Long-term tamoxifen therapy is associated with an increased risk for hot flashes, vaginal bleeding and discharge, endometrial cancer, hysterectomy, ischemic cerebrovascular events, and venous thromboembolic events. Despite this, only 5% of patients discontinue therapy.[71] It is clear that the benefits of tamoxifen as an adjuvant treatment in early invasive breast cancer far outweigh its risks, and therefore, tamoxifen remains a mainstay in the hormonal therapy of breast cancer.

The optimal duration of tamoxifen use was 5 years based on studies comparing the outcomes of patients who took tamoxifen for 2 and 5 years. A number of these studies extended the use for more than 5 years and noted there was no additional benefit from prolonged use of tamoxifen; in fact, patients who took tamoxifen for more than 5 years had a worse prognosis than those who discontinued therapy at 5 years.[72-74] Two recently concluded studies however showed that continuing

tamoxifen to 10 years further reduced mortality and recurrence rates.[75-76] The rationale for the contradicting conclusions may stem from two facts: first, the earlier studies that attempted to see the effect of extending tamoxifen to 10 years had a smaller population; and second, these trials were prematurely discontinued, after only a couple of years, when the preliminary results showed no further advantage and an increase in incidence of the side effects. The Panel recommends that hormonal therapy be given for a minimum of five years, whether monotherapy, switch or sequential strategy is used. Tamoxifen, given as a 20-mg tablet once daily, is the recommended hormonal therapy in the adjuvant setting for premenopausal patients. However, it may still be given to post-menopausal patients.

The third-generation aromatase inhibitors (AIs) anastrozole, letrozole, and exemestane were introduced after almost two decades of having tamoxifen as the sole hormonal therapy for breast cancer. Presently, it is recommended that adjuvant hormonal therapy for postmenopausal women include an AI. In comparison to 5 years of tamoxifen alone, the use of an AI in post menopausal women with hormone sensitive breast cancer as primary, sequential, or extended treatment improves disease-free survival and reduces the risk of breast cancer events, including distant recurrence, locoregional recurrence, and contralateral breast cancer.

Anastrozole, a non-steroidal AI, was compared to tamoxifen in 6241 postmenopausal women with early breast cancer in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial. It showed that anastrozole had a significant advantage over tamoxifen in terms of disease-free survival (DFS), time to recurrence (TTR), time to distant recurrence (TTDR), contralateral breast cancer (CLBC) at a median follow-up of 100 months.[77] Treatment with anastrozole significantly reduced the risk for distant metastases by 15% and contralateral breast cancer by 40% in the intent-to- treat population compared with tamoxifen (P = 0.003 and P = 0.004, respectively).

Letrozole, another non-steroidal AI, has been studied in a variety of adjuvant settings as well. The Breast International Group (BIG) 1-98 study which was published in 2005, enrolled 8010 postmenopausal women with early breast cancer and compared letrozole with

tamoxifen. Both drugs were used as monotherapy and in sequence with the other for a total of 5 years. At a median follow-up time of 51 months, BIG 1-98 showed that letrozole was superior to tamoxifen in terms of efficacy in the overall population, regardless of age and nodal status.[78-79] The hazard ratio for DFS was 0.82 (95% CI, 0.71 to 0.95; P= 0.007), and the 5-year DFS survival estimates were 84.0% and 81.1% for letrozole and tamoxifen, respectively.

In the National Cancer Institute of Canada (NCIC) MA.17 Trial conducted by the North American Breast Intergroup, about 5,000 postmenopausal women were randomized to either 5 years of letrozole therapy or placebo, following 5 years of tamoxifen therapy. The trial was closed after only 2.4 years of median follow-up when data analysis revealed the significant superiority of the results from the letrozole treatment arm. Those receiving letrozole showed an improvement in disease-free survival earlier than anticipated (p=0.00008 at the first interim analysis), with an estimated 4-year reduction in recurrence of 43% compared with placebo.[80]

Exemestane, a steroidal AI with an androgen structure, has been studied as sequential adjuvant therapy after several years of tamoxifen. The Intergroup Exemestane Study (IES) trial investigated the efficacy and safety of receiving exemestane therapy after 2–3 years of adjuvant tamoxifen.[81] At 91 months of follow-up, IES showed a significant improvement in disease-free survival for sequential therapy with tamoxifen followed by exemestane, compared with 5 years of tamoxifen alone (hazard ratio, 0.86; P = .04).[62] This significant 14% reduction in risk of death was observed regardless of nodal status and corresponded to an absolute benefit of 2.4% in disease-free survival with exemestane at 3 years post-randomization compared with the standard 5 years of tamoxifen treatment. Moreover, the reduction in the risk of relapse or death was maintained for at least 5 years post-treatment.

Use of hormonal therapy in patients who have breast cancers that are strongly hormone-sensitive is recommended since it has been found to be superior to chemotherapy in this subset of patients.[64,82-83] When the breast cancer profiles of these patients are favorable, hormonal therapy may be given as the sole systemic adjuvant treatment. This becomes even more important when the patient's medical status is a contraindication to chemotherapy. More commonly, both hormonal therapy and chemotherapy will be beneficial to patients with hormone-responsive early breast cancer, especially when the cancer is weakly hormone receptor-positive.[84] Other instances when combined chemohormonal therapy is recommended include: a) when patient is premenopausal or perimenopausal; b) when there is axillary lymph node involvement; or c) when the other biologic characteristics are unfavorable.

When both hormonal therapy and chemotherapy are required, it has been recommended to give the treatments sequentially rather than concurrently, completing chemotherapy first before starting hormonal therapy. Studies have shown that their antagonistic action is a consequence of chemotherapy being cytotoxic and hormone therapy being cytostatic; i.e. chemotherapy kills cells that are actively cycling while hormonal therapy prevents cells from cycling. In addition to this, simultaneous use of the two modalities enhances their toxicities, so that it would be prudent to avoid using them in combination.[85]

An alternative adjuvant treatment for premenopausal women with breast cancer is ovarian ablation. When having limited resources is a consideration during decision-making regarding adjuvant treatment, oophorectomy is cost-effective compared to five years of hormonal treatment. Ovarian ablation may also be offered in place of chemotherapy in premenopausal women with hormone responsive breast cancer who cannot receive chemotherapy for any number of reasons.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published a meta-analysis of 12 randomized controlled trials that reported the effects of ovarian ablation on recurrence and death among women under the age of 50 with early breast cancer.[86] The EBCTCG overview showed that premenopausal women with early invasive breast cancer, who underwent oophorectomy or ovarian irradiation, experienced approximately a 25% relative reduction in the risks of recurrence and mortality at 15 years of follow-up compared to those receiving no adjuvant therapy. This benefit was comparable to the benefit this same subset of patients received from chemotherapy, regardless of

axillary lymph node involvement. However, when premenopausal patients received both ovarian ablation and chemotherapy, the effect of the former on recurrence and mortality is lower.

On the other hand, the Oxford overview[87], published 2 years after the EBCTCG meta-analysis, reported that the use of polychemotherapy resulted in a 23.5% lower annual risk of recurrence and a 15.3% lower annual risk of death compared to ovarian ablation.

The Scottish Cancer Trials Breast Group published another study comparing ovarian ablation and polychemotherapy in women with axillary lymph node involvement but with no regard to hormone receptor status. This showed that the effects of these two treatments are comparable with regard to disease-free and overall survival rates.[88] However, when hormone receptor status was considered in the analysis, the study concluded that women whose breast cancers were hormone-responsive tended to have a longer survival with ovarian ablation, while women whose breast cancers were not hormone responsive tended to have a better outcome with chemotherapy.

One completed study that observed the effect of combining oophorectomy and tamoxifen, was conducted on premenopausal Vietnamese and Chinese women with operable breast cancer. Love, et al. showed that among the premenopausal Asian women with hormone responsive breast cancer, the 5-year disease free survival rate and the overall survival rate was statistically significantly higher in the group that was randomized to adjuvant oophorectomy and tamoxifen (20 mg orally every day) for 5 years compared to the observation group.[89]

To date, there are no published studies that substantiate the benefit of adding ovarian ablation to the present evidence-based practice of adjuvant chemotherapy followed by 5 years of hormonal therapy. The Adjuvant Breast Cancer Trials Collaborative Group randomly assigned premenopausal and perimenopausal women with early breast cancer who were receiving 5 years of tamoxifen with or without chemotherapy to ovarian ablation or suppression (by oophorectomy, ovarian irradiation, or treatment with luteinizing hormone–releasing hormone agonist) versus no ovarian ablation or suppression.[90]

The group concluded that adding ovarian ablation or suppression had no beneficial effect on relapse-free survival or overall survival of premenopausal women. They recommended that studies examining the effect of ovarian ablation or suppression on women who did not receive standard chemotherapy or hormonal therapy must be carried out in the future.

The American Society of Clinical Oncology stated in 2011 that they agreed with the Cancer Care Ontario (CCO) Practice Guideline on Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women With Early-Stage Invasive Breast Cancer.[91] According to the CCO, ovarian ablation or suppression should not be routinely added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy. Moreover, ovarian ablation or suppression cannot be considered the sole adjuvant treatment but may be added to either chemotherapy or hormonal therapy in patients who cannot receive either of these two standard systemic treatments.

It is not clear whether an aromatase inhibitor with ovarian ablation will be as good or better than tamoxifen with or without ovarian ablation as first line hormonal treatment for premenopausal women with endocrine-responsive breast cancers, although responses have been observed in premenopausal women with concomitant goserelin and AI treatment following tamoxifen failure.[92-93] The 2011 St. Gallen Consensus Conference on early breast cancer recommended the use of ovarian function suppression plus aromatase inhibitors as a therapeutic option in cases where tamoxifen is contraindicated.[94] Two ongoing trials, the Suppression of Ovarian Function Trial (SOFT)[95] and Tamoxifen and Exemestane Trial (TEXT)[96] may be able to provide additional evidence on the role of adjuvant aromatase inhibitors in premenopausal breast cancer patients.

Radiotherapy. Post-mastectomy radiation therapy (PMRT) used as a locoregional control of breast cancer has been shown to impact the survival of these patients.[97] Early studies[98-99] that were conducted to establish this survival advantage showed that there was a reduction in breast cancer mortality associated with adjuvant radiation therapy, but this was offset by increases in non-breast

cancer-related mortality. During these early studies, existing PMRT protocols translated to higher radiation doses delivered to the heart and lungs thus non-breast cancer related mortality was high. For instance, a meta-analysis published by Cuzick et al in 1994 established that PMRT improved breast cancer cause-specific survival but this was countered by an increase in non-breast cancer events in the same patient population.[100] Later, improvements in delivery of radiation therapy decreased the incidence of post-radiation therapy morbidity so that improvement in survival after PMRT became noticeable. A meta-analysis published by Whelan et al in 2000 showed that radiation reduced the risk of local recurrence (odds ratio=0.25; 95% CI=0.19–0.34) as well as overall mortality (odds ratio=0.83; 95% CI=0.74–0.94).[101] The landmark study of the Oxford Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published in 2005 showed a clear overall survival advantage conferred by PMRT in patients with node-positive disease. Specifically, the EBCTCG showed the five-year local recurrence risk was reduced from 22.8% to 5.8%, with 15-year breast cancer mortality risks of 54.7% vs 60.1% and overall mortality reduction of 4.4%.[102] In 2011, the EBCTCG published a metaanalysis on radiotherapy after breast conserving surgery involving both node-negative and node-positive patients. This study showed that radiotherapy reduced the 10-year risk of any (ie, locoregional or distant) first recurrence from 35.0% to 19.3% (absolute reduction 15.7%, 95% CI=13.7–17.7, 2p<0·00001) and reduced the 15-year risk of breast cancer death from 25.2% to 21.4% (absolute reduction 3.8%, 1.6–6.0, 2p=0.00005)[103]. Overall, about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10.

The indications for PMRT have been established and these have been included by several groups in their recommendations.[97,104-107] Patients with increased risk for local recurrence benefit from the addition of PMRT. These patients include those with large tumors (invasive cancers with diameters greater than or equal to 5 cm), with positive or close margins after mastectomy, and those with tumor metastasis to at least 4 ipsilateral axillary lymph nodes. There is still controversy regarding the use of PMRT in patients with breast cancers measuring less than 5 cm in diameter and with metastasis to 1 to 3 ipsilateral axillary lymph nodes. Risk of local recurrence in these patients is modified by other patient and tumor characteristics including age of patient at diagnosis, estrogen receptor negative tumors, and presence or absence of lymphovascular invasion.[108] Recommendations regarding PMRT in these patients should be individualized and discussed in a multidisciplinary conference.

Partial mastectomy is an established alternative to total mastectomy in the management of patients with early (stage I and II) breast cancer. However, when it is done as the only local treatment, local recurrence is the consequence. Local recurrence is related to young age, surgical margins, extensive intraductal component, high tumor nuclear grade, large tumor size, lymphovascular invasion, and axillary lymph node involvement.[109] Radiotherapy (RT) following partial mastectomy reduces the incidence of local recurrence, and in a pooled analysis of published randomized trials comparing partial mastectomy with or without RT, it was shown that post-operative RT confers a small survival advantage. Omission of RT was associated with an increased risk of ipsilateral breast tumor recurrence, whether or not patients received systemic treatment. Moreover, omission of RT also led to an increase of 8.6% in the relative risk of death.[110]

Several studies have been conducted to identify a low risk group of patients who, after completion of partial mastectomy, may not undergo RT. One such study published by Varghese, et al. in 2007 showed that it is possible to safely avoid radiotherapy in a selected subgroup of node-negative invasive breast cancers measuring 1 cm or less in diameter[111]; however, this proved to be the exception since the majority of studies with similar objectives did not find that any particular group was considered at low risk for locoregional recurrence.[109] In fact, Truong, et al.[112] in 2005 showed that omission of RT in the local treatment of elderly women with breast cancer treated with partial mastectomy was associated with reduced survival. Therefore, omission of RT after partial mastectomy in patients considered to be "low risk" for local recurrence should be recommended only after discussion in a multidisciplinary conference.

The proper timing of RT in patients with early breast cancer after undergoing partial mastectomy has not been clearly established. The decision regarding timing of RT may be influenced by the patient's need for adjuvant chemotherapy. A study by Olivotto, et al.[112] published in 2009 showed that a delay of up to 20 weeks in starting RT after partial mastectomy was acceptable when patients do not require chemotherapy; a delay of more than 20 weeks resulted in higher rates of local and distant recurrence and inferior breast cancer-specific survival. In patients who require chemotherapy, the sequencing of chemotherapy and RT was more impactful. Disease-free survival appeared to improve if chemotherapy was given first; conversely, local recurrence rates were improved if chemotherapy was given after radiotherapy. However, according to Benchalal and colleagues, there was no increase in the risk of local recurrence when RT was delayed to deliver the adjuvant chemotherapy.[111] In a review conducted by Tsoutsou, et al. it was found that the delivery of chemotherapy before RT does not compromise local control for as long as RT is delivered within 7 months after surgery.[108]

Table 8. Adjuvant therapy for early invasive breast cancer.

Guideline Statements	LoE	Category of Recommendation	Consensus
12. Adjuvant multi-agent chemotherapy is recommended for patients with an increased risk of relapse as determined by the following factors: tumor size, tumor grade, lymph node status, hormone receptor status, Her-2 receptor status, lymphovascular invasion and molecular subtype	I	B	Yes 60.0% Abstain 40.0%
13. Systemic treatment should be started ideally 4 to 6 weeks after surgery.	II	B	Yes 60.0% Abstain 40.0%
14. Targeted therapy using trastuzumab should be highly considered as an integral part of adjuvant treatment for Her-2 positive early breast cancer in the following settings:			
a) Node positive early breast cancer irrespective of pathologic tumor size	I	B	Yes 70.0% Abstain 30.0%
b) Node negative breast cancer with more than 1cm tumor size	I	B	Yes 60.0% Abstain 40.0%
15. Hormonal therapy is recommended as an adjuvant treatment for patients with hormone-sensitive early breast cancers regardless of age, menopausal status, and type of surgery.	I	A	Yes 90.0% No 10.0%
16. Hormonal therapy should be given for a minimum of five years, whether monotherapy, switch or sequential strategy is used.	I	A	Yes 100%
17. Hormonal therapy is best given after chemotherapy. Hormonal therapy may be given sequentially or concurrently with radiotherapy.	II	A	Yes 100%
18. Tamoxifen, given as a 20 mg tablet once a day for five years, is the recommended hormonal therapy in the adjuvant setting for premenopausal patients. However, it may still be given to postmenopausal patients.	I	A	Yes 100%
19. Aromatase inhibitors are recommended as the hormonal therapy of choice in the adjuvant setting for postmenopausal patients.	I	A	Yes 100%

Guideline Statements	LoE	Category of Recommendation	Consensus
20. Postmastectomy radiation therapy (PMRT) is recommended in patients with early breast cancer with increased risk for local recurrence, including those with the following characteristics: size of invasive component ≥5cm, surgical margins are positive or close to tumor, and tumors with metastasis to 4 or more ipsilateral axillary lymph nodes.	I	A	Yes 100%
21. Radiation therapy of the conserved breast is recommended for patients with early breast cancers who underwent breast conservation surgery (i.e. partial mastectomy), regardless of menopausal status and type of axillary surgery.	I	A	Yes 100%
22. In patients with early breast cancer who underwent partial mastectomy and will not be requiring chemotherapy, radiation therapy should be started not later than 20 weeks after surgery.	II	A	Yes 100%
23. In patients with early breast cancer who underwent partial mastectomy and will be requiring chemotherapy, radiotherapy may be started after completion of chemotherapy for as long as it is delivered within 7 months after surgery.	II	A	Yes 100%

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Part IV: Guidelines on Preoperative Work-up and Postoperative Surveillance for Early Breast Cancer

A. Preoperative Work-up for Early Invasive Breast Cancer

The committee retains the recommendation that intensive preoperative workup should not be routinely done in asymptomatic patients with early breast cancer[1]. At this point, there is no clear evidence that this increases survival. Several studies have reported a limited value of breast cancer baseline staging, as the probability of finding metastatic disease in this group of patients is very low and may only lead to false positive results and more examinations that may delay therapy[2-5].

B. Postoperative Surveillance for Early Invasive Breast Cancer

For women with early breast cancer who have undergone primary treatment and is asymptomatic, it is recommended that follow up should consist of careful history and physical examination and annual mammography of the contralateral and preserved breast. 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 used routinely.

The committee recommends no revision with regards to follow up of patients with breast cancer who have completed primary therapy with curative intent[1]. No evidence has been published recently that warrants such revision.

The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline update, after a systematic review of recent publications has likewise recommended regular history and physical examination be performed every 3-6 months for the first year and every 6-12 months for years 4 and 5 and annually thereafter[6]. Annual mammography starting from 1year after completion of radiation treatment is also recommended. The routine use of complete blood count (CBC), chemistry panels, bone scans, chest radiographs, liver ultrasound, CT scans, PET scans, MRI and tumor markers is not recommended for breast cancer follow up in an otherwise asymptomatic patient with no specific findings on clinical examination. Recommendation was also given with regards the need for further research, particularly RCT's to determine the comparative effectiveness of different modes of breast cancer surveillance and the ideal frequency and duration of follow up.

The 2013 National Comprehensive Cancer Network Guidelines for Surveillance after breast cancer treatment recommend history and physical examination every 4-6 months for 5 years and annual mammography[7]. Body imaging studies, labs or tumor markers are not routinely recommended in asymptomatic patients.

Table 9. Preoperative work-up for early invasive breast cancer.

Guideline Statements	LoE	Category of Recommendation	Consensus
1. In asymptomatic patients, it is recommended that history and physical examination, routine blood tests and mammography (if not yet done) be done preoperatively.	II	A	Yes 100%
2. The following studies may be considered in symptomatic patients:			
a. Bone scan in the presence of localized bone pain/elevated alkaline phosphatase			
b. Abdominal CT/MRI if with elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms or abnormal abdominal examination	II	A	Yes 100%
c. Chest CT in the presence of pulmonary symptoms			

Table 10. Post-operative surveillance for early invasive breast cancer.

Guideline Statements	LoE	Category of Recommendation	Consensus
3. For asymptomatic women, follow up consists of careful history and physical examination and annual mammography of both the contralateral and preserved breast.	II	A	Yes 100%
4. Routine use of intensive metastatic work up following treatment is not recommended.	II	A	Yes 100%

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Part V: Guidelines on Specimen Handling and Histopath Reporting for Breast Carcinoma

Effective cooperation and collaboration between the surgeons, pathologists and operating room (OR) staff is crucial to ensure that the specimen taken from the patient when process properly will truly reflect the histology, nature, and tumor markers of the disease. All pathology tests are adversely affected by a delay in fixation in 10% neutral buffered formalin (NBF) and this especially holds true for the HER-2 test.

With very few modifications, the Panel adapted the 2008 Consensus Guidelines for the Standardization of Histopathologic Reporting of the Philippine Society of Pathologists, Inc.

The status of the hormone receptors and HER-2/neu are independent predictive and prognostic factors for breast cancer; hence, their determination is paramount for all invasive cancers. The Panel recommends the Allred scoring for the reporting of the hormone receptor status to allow for easy communication between all the specialties who manage the disease.

The use of Trastuzumab for HER 2 neu positive breast cancer has become the standard of care worldwide; however, its use is associated with significant cardiac events. Considering the significant benefits coupled with the high cost and potential cardiotoxicity of Trastuzumab, accurate HER2 testing is essential. Equivocal results are inconclusive. Equivocal results require additional action for final determination.

Equivocal immunohistochemistry (IHC) samples must be confirmed by an in situ hybridization (ISH) evaluation. This may be in the form of fluorescence in situ hybridization (FISH), Silver enhanced in situ hybridization (SISH) or Chromogenic in situ hybridization (CISH). Equivocal ISH samples are confirmed by counting additional cells or repeating the ISH test.

All the recommendations in Tables 11 and 12 were unanimously approved by the Expert Panel. The Panel of Experts from Pathology believes that aside from the importance of time from excision to fixation equally important is the duration of fixation which should ideally be 6 to 48 hours.

Table 11. Guidelines on specimen handling.

Guideline Statements	LoE	Category of Recommendation	Consensus
1. Specimens should be provided to the laboratory fresh or in 10% neutral buffered formalin (NBF) and oriented using sutures and/or clips, or ink, to allow accurate pathological orientation and margin assessment.	III	A	Yes 100%
2. Time from tissue removal to fixation in an adequate volume (optimally 10-fold greater than volume of specimen) of ideally should be 20-30 minutes but no longer than 60 minutes. Adequate fixation time in 10% NBF is 6 to 48 hours.	III	A	Yes 100%
3. Documenting time from tissue removal to fixation is essential.	V		Yes 100%

Table 12. Histopath reporting of breast carcinoma.

Guideline Statements	LoE	Category of Recommendation	Consensus
1. The histopath report for invasive breast cancer should include: a) gross description; b) type of breast specimen/procedure (e.g. excision, lumpectomy, mastectomy); c) specimen laterality (left, right, bilateral, unspecified); d) tumor site, if known (upper/lower and inner/outer quadrant, axillary tail, subareolar or clock face orientation); e) histologic type of invasive carcinoma; f) histologic grade (using Nottingham score); g) greatest dimension of invasive component (tumor size); h) presence/absence of peritumoral/ perineural/ lymphovascular invasion; i) distance of surgical margins from tumor; j) lymph node status (number of lymph nodes harvested and number of lymph nodes involved); k) involvement of nipple, skin, chest wall and dermal lymphatics; l) most recent AJCC TNM stage. a. Features to report if present: multifocality/ multicentricity; in situ component (ductal or lobular); presence of microcalcifications; presence of atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH); extra-nodal involvement. b. Optional features to report: nuclear grade (Black's Grading System); microscopic description; presence of any benign proliferative lesions; presence of tumor necrosis; comments when warranted.	III	A	Yes 100%
2. Histopath report for in-situ breast carcinoma should include the following: a) gross description; b) type of breast specimen/procedure (excision, lumpectomy, mastectomy); c) specimen laterality (left, right, bilateral, unspecified); d) histologic subtype of ductal carcinoma-in-situ; e) tumor grade; f) tumor size; g) presence/absence of microinvasion ($\leq$ 1mm); h) distance of surgical margins from tumor. a. Features to report, if present: lymph node status; presence of microcalcifications; multifocality/multicentricity; presence of any benign proliferative lesions.	V		Yes 100%
3. ER, PR and HER-2/neu determination should be done for all invasive breast carcinoma. Reliable and reproducible ER, PR and HER2 testing and accurate interpretation is essential to ensure patients with breast cancer receive appropriate diagnosis and treatment.	III	A	Yes 100%

Guideline Statements	LoE	Category of Recommendation	Consensus
4. The hormone (Estrogen/Progesterone) receptor status should be reported using the Allred scoring or by proportion of tumor cells stained and by their stain intensity.	III	A	Yes 100%
5. Results of HER-2/neu testing by IHC should be reported as negative (0 and +1), equivocal (+2) and positive (+3).	III	A	Yes 100%
6. If the HER-2/neu status by IHC is equivocal, an in-situ hybridization test should be done (i.e. FISH, SISH, DISH or CISH).	III	A	Yes 100%

References

1. Philippine Society of Pathologist, Inc. Consensus Guidelines for the Standardization of Histopathologic Reporting of Breast Carcinoma 2008.
2. Hammond MEH, Hayes DF, Allred DC, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer. J Clin Oncol 2010; 28(16): 2784-95.
3. Wolff AC, Hammond MEH, Schwartz JN, Hagerty KL, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. J Clin Oncol 2007; 25(1):118-45.
4. Philippine Society of Pathologist, Inc. Philippine Consensus for HER-2/neu Testing Guidelines in Breast Cancer.