



# **BREAST CANCER NATIONAL CLINICAL PRACTICE GUIDELINES**



**NATIONAL INTEGRATED  
CANCER CONTROL PROGRAM**

## **Breast Cancer National Clinical Practice Guidelines**

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## Abbreviations and Acronyms

AC	doxorubicin + cyclophosphamide
ADH	atypical ductal hyperplasia
ALND	axillary lymph node dissection
APBI	accelerated partial breast irradiation
ASTRO	American Society for Radiation Oncology
CMF	cyclophosphamide + methotrexate + fluorouracil
CT	computed tomography
DCIS	ductal carcinoma in situ
DFS	disease-free survival
ER	estrogen receptor
FNA	fine needle aspiration
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IBTR	ipsilateral breast tumor recurrence
LRNI	locoregional lymph node irradiation
MIBT	minimally invasive biopsy technique
MRI	magnetic resonance imaging
NAC	neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
OS	overall survival
pCR	pathologic complete response
PET	positron emission tomography
PMRT	postmastectomy radiation therapy
PR	progesterone receptor
RT	radiation therapy
SLNB	sentinel lymph node biopsy
TAC	docetaxel + doxorubicin + cyclophosphamide
TC	docetaxel and cyclophosphamide
TCH	docetaxel + carboplatin + trastuzumab
TCHP	docetaxel + carboplatin + trastuzumab + pertuzumab
TNBC	triple negative breast cancer
US	ultrasonography
WBRT	whole breast radiation therapy

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- Philippine Society of Breast Surgeons (PSBS)
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- Philippine Society of Hospice and Palliative Medicine (PSHPM)
- Philippine Academy of Family Physicians (PAFP)
- Philippine Society of Pathologists (PSP)
- Philippine Society for Fertility Preservation (PSFP)
- Philippine Society of Nuclear Medicine (PSNM)
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- Surgical Oncology Society of the Philippines (SOSP)

## Contributors

These guidelines were a collaborative effort between various guideline committees, methodologists, and evidence synthesis experts. The consensus panel/committee included breast cancer advocates, surgeons, radiologists, pathologists, and primary healthcare givers. All contributors completed the declaration of interest form.

The Technical Advisory Group (TAG) consisted of the following individuals: Dr. Nilo C. de los Santos (EAMC), Dr. Clarito U. Cairo, Jr. (DOH), Ms. Alma B. Abainza-Sanchez (PhilHealth), Dr. Allan Troy D. Baquir (EAMC), and Dr. Samuel S. Duran (EAMC).

The Steering Committee led by Dr. Felicidad Claudia R. Ordoñez (EAMC) was composed of representatives, namely: Ms. Maria Dolores Manalastas (DOH), Dr. Marc Anthony Cepeda (PhilHealth), Dr. Jose Montoya (PSMO), Dr. Kathleen Baldivia (PROS), Dr. Joan Uy-Valdez (PCR), Dr. Shalimar Cortez (PSGS), Dr. Eillen Borje (PSGS), and Dr. Lorlyn Agatep (PSP).

With a background in clinical epidemiology, evidence-based medicine, medical informatics, and public health, Healthcare Practice and Policy Management, Inc. provided the technical guidance for the development of these national clinical practice guidelines. Dr. Ian Theodore Cabaluna and Dr. Jane Eflyn L. Lardizabal-Bunyi provided the oversight as methodologists, evidence review experts, and technical writers for the NCPG. Dr. Felicidad Claudia Ordoñez, the Project Lead and Steering Committee Chair provided her expertise as technical reviewer and subject matter expert. Ms. Maria Vanessa C. Villarruz-Sulit, Mr. Howell Henrian Bayona, Dr. Aldrich Ivan Lois Burog, and Ms. Myzelle Anne Infantado appraised the scoped national clinical practice guidelines. The project was made possible with the technical and administrative support, coordination, and review services provided by Mr. Teddy Dizon, Ms. Hygeia Agosto, and Ms. Jennel Pimentel.

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## Executive Summary

Breast cancer remains to be one of the most common causes of death among Filipino women. Management of this life-threatening condition continues to evolve as new evidence on the diagnosis and treatment are discovered and/or improved.

This 2022 National Clinical Practice Guidelines (NCPG) on breast cancer aims to provide quality evidence-based standard diagnosis and treatment guidelines for Filipino patients with breast cancer. It aims to provide them with the best available evidence and develop equitable and locally acceptable recommendations through consensus building.

The multisectoral GDG convened and agreed employing the ADAPTE process to develop these guidelines. The TAG provided the general population-intervention-professional-outcome-healthcare setting (PIPOH) framework. The SC developed, prioritized, and rationalized practice guideline questions based on the PIPOH. The ERE conducted evidence-gathering, appraisal, and synthesis to answer the priority practice guideline questions. The CP conducted eDelphi consensus-building to finalize the recommendations on each practice guideline question. A series of online CP meetings were held to finalize the recommendations.

14 guideline questions and 55 recommendations were developed. See summary of recommendations below. This NCPG hopes to guide and standardize the practice in the management of breast cancer for Filipinos.

## Breast Cancer NCPG Summary

The Guideline Development Group used the ADAPTE methodology to generate and finalize the recommendations for BRCA NCPG, covering diagnosis, clinical management, surveillance, and pathology reporting. The ADAPTE process results in the adoption and adaption of recommendations from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Breast Cancer and supplemented from American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), European Society for Medical Oncology (ESMO), The Malaysian Health Technology Assessment Section (MaHTAS), and The National Institute for Health and Care Excellence (NICE).

**Table 1.** Breast Cancer NCPG Summary

CLINICAL QUESTION	RECOMMENDATION	SoR	QoE
<b>Diagnosis</b>			
What is the recommended imaging workup for patients with suspicious breast symptoms/complaints?	We recommend breast ultrasound for those less than 30 years of age.	Strong	Low
	We recommend diagnostic mammogram with or without ultrasound for those greater than or equal to 30 years of age.	Strong	Low
	We recommend ultrasound as a complementary imaging tool in the presence of mammographic findings suspicious of breast cancer to document lesion characteristics and to guide biopsy.	Strong	Low
What is the recommended biopsy technique to establish diagnosis of suspicious breast lesions?	We recommend breast biopsy if diagnostic imaging findings or clinical findings are suspicious or highly suggestive of malignancy.	Strong	High
	We suggest minimally invasive biopsy technique (MIBT) with a core needle preferably image-guided in the tissue diagnosis of breast cancer for both palpable and non-palpable breast lesions.	Weak	High
	Among patients with suspicious clinical findings but with no ultrasonographic or mammographic abnormality detected, we suggest tissue biopsy preferably core needle biopsy.	Weak	High
	We recommend doing open biopsy (excision or incision) if the diagnosis by	Strong	High

	core needle biopsy is an indeterminate lesion, a benign lesion that is discordant with imaging, atypical ductal hyperplasia (ADH), or other specific histology that requires additional tissue.		
What is the recommended workup for patients with confirmed breast cancer?	We recommend the following workup for patients with breast cancer: <ul style="list-style-type: none"> <li>• History and physical exam</li> <li>• Bilateral diagnostic mammography</li> <li>• Breast ultrasonography, if necessary</li> <li>• Determination of tumor HR status (ER and PR determinations) and HER-2 receptor status</li> <li>• Pathology review</li> <li>• Psychosocial distress assessment</li> </ul>	Strong	Low
	We recommend the symptom-directed staging workup for patients with breast cancer.	Strong	Low
	We recommend using bone scan if plain radiography or computed tomography staging is negative among patients with early breast cancer and with localized bone pain, elevated alkaline phosphatase, or symptoms suggestive of bone metastases.	Strong	Low
	We recommend the following in staging patients presenting with recurrent or stage IV breast cancer: <ul style="list-style-type: none"> <li>• History and physical exam</li> <li>• Blood work up — complete blood count and metabolic panel (liver function test, BUN, creatinine, calcium)</li> <li>• CT scan of the chest and whole abdomen with contrast or MRI scan of the abdomen</li> <li>• Bone scan, and radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan</li> <li>• Biopsy documentation of first recurrence if possible</li> </ul>	Strong	Low



	<ul style="list-style-type: none"> <li>Repeat tumor HR status (ER and PR determinations) and HER2-receptor status of the recurrence</li> </ul>		
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<b>Clinical Management</b>			
What are the indications for neoadjuvant chemotherapy for patients with early breast and locally advanced cancer?	<p>We recommend neoadjuvant systemic chemotherapy among patients with operable breast cancer with the following:</p> <ul style="list-style-type: none"> <li>a. HER2-positive disease or TNBC, if cT greater than or equal to 2 or cN greater than or equal to 1 (<i>High quality of evidence</i>)</li> <li>b. Large primary tumor relative to breast size in a patient who desires breast conservation (<i>Low quality of evidence</i>)</li> <li>c. cN+ disease likely to become cN0 with neoadjuvant therapy (<i>Low quality of evidence</i>)</li> </ul>	Strong	See individual population
	<p>We recommend neoadjuvant chemotherapy among patients with inoperable locally advanced breast cancer including:</p> <ul style="list-style-type: none"> <li>a. Those with inflammatory breast cancer</li> <li>b. Those with cN2 and cN3 regional lymph nodal disease</li> <li>c. Those with cT4 tumors</li> </ul>	Strong	Low
	<p>We suggest neoadjuvant chemotherapy for whom a delay in surgery is preferable or unavoidable.</p>	Weak	Low
	<p>We do not recommend neoadjuvant chemotherapy in patients with the following:</p> <ul style="list-style-type: none"> <li>a. Extensive in situ disease when the extent of invasive disease cannot be defined</li> <li>b. Tumors that are not palpable or clinically assessable</li> </ul>	Strong	Low
What are the indications for adjuvant chemotherapy for patients with early and locally advanced	<p>We recommend adjuvant systemic chemotherapy after careful consideration of tumor breast panel results and patient's risk for disease recurrence and mortality. Tumor breast panel results:</p> <ul style="list-style-type: none"> <li>a. ER/PR</li> <li>b. HER2 tumor status</li> </ul>	Strong	High

breast cancer?	Prognostic factors for disease recurrence or mortality: a. Age b. Comorbidity c. Tumor size d. Tumor grade e. Number of involved ALNs		
What are the indications and recommended regimen for HER2-targeted treatment for patients with breast cancer?	We recommend neoadjuvant therapy with trastuzumab with or without pertuzumab with chemotherapy for patients with HER2-positive, node-positive (or high-risk node-negative) tumors.	Strong	High
	We suggest neoadjuvant trastuzumab and chemotherapy for patients with HER2-positive, node-negative cT1c and N1mi tumors.	Weak	Low
	We recommend adjuvant trastuzumab with chemotherapy to patients with HER2-positive breast cancer greater than 0.5 cm.	Strong	Low
	We recommend adjuvant T-DM1 among patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and anti-HER2 neu therapy.	Strong	High
What is the indication of adjuvant hormonal therapy for patients with breast cancer?	We recommend adjuvant hormonal therapy for all patients with ER/PR positive breast cancer.	Strong	High
	For premenopausal women, we recommend the following: a. Tamoxifen with or without ovarian suppression/ablation b. Aromatase inhibitor with ovarian suppression/ablation	Strong	High
	For postmenopausal women, we recommend aromatase inhibitor as first-line treatment.	Strong	High
What are the indications for bone-modifying agents for patients with breast cancer?	We recommend zoledronic acid or denosumab for the following: a. Postmenopausal women (with node- positive and negative) invasive breast cancer on aromatase inhibitor with high risk of recurrence ( <i>High quality of evidence</i> ) b. Osteoporotic patients ( <i>High quality of evidence</i> )	Strong	See individual population

	c. Stage IV breast cancer with bone metastases ( <i>High quality of evidence</i> )		
What are the indications of radiation therapy for patients with breast cancer?	We recommend adjuvant radiation therapy using whole breast RT with or without boost following breast conserving surgery for DCIS patients.	Strong	High
	Hypofractionated Whole Breast Irradiation (HF-WBI) may be used as an alternative to conventional fractionation (CF-WBI).	Weak	Low
	For patients with invasive breast cancer, we recommend adjuvant radiation therapy using whole breast radiation therapy with or without boost for women who received breast-conserving surgery with negative axillary nodes.	Strong	High
	For women with invasive breast cancer receiving whole breast irradiation with or without inclusion of low axilla, the preferred dose-fractionation scheme is hypofractionated WBI.	Strong	High
	We recommend WBRT with nodal irradiation for patients who had partial mastectomy with involvement of the lymph node, T3 or T4 primary lesion, and T2 lesion with at least 2 other high-risk features (fewer than 10 axillary nodes removed, high grade histology, ER negativity, lymphovascular invasion).	Strong	High
	We recommend chest wall with lymph node irradiation in patients who underwent total mastectomy with T3 or T4 primary lesion, involvement of the lymph node, T2 with 2 or more high-risk features (young age, triple negative, high grade histology, LVI), close margin.	Strong	High
	We recommend chest wall with or without lymph node irradiation, for postmastectomy patients with positive margin and re-excision is not feasible.	Strong	High
	We recommend adjuvant RT using whole breast radiation in patients who underwent breast-conserving surgery and neoadjuvant chemotherapy.	Strong	Low
	We recommend adjuvant RT in postmastectomy patients who underwent neoadjuvant chemotherapy AND presenting with the following: a. Residual nodal disease b. T3, T4, or node-positive disease regardless of response	Strong	Low
	For patients with no response to neoadjuvant chemotherapy and in whom the	Weak	Low

	tumor remains inoperable or who develop disease progression during neoadjuvant chemotherapy, additional systemic therapy with or without preoperative palliative radiation may be considered to enhance local control.		
	We recommend the use of HF-WBI over CF-WBI for any stage and chemotherapy	Strong	Low
	We suggest CF-WBI over HF-WBI when treating primary breast cancer with rare histological features that are commonly treated with conventional fractionation when arising in other parts of the body.	Weak	Low
	We suggest HF-WBI for patients with breast cancer, and with breast augmentation or collagen vascular disease.	Weak	Low
	<p>We recommend regional nodal irradiation among breast cancer patients with the following conditions:</p> <ol style="list-style-type: none"> <li>a. Patient who underwent breast conserving surgery with a positive axillary lymph node.</li> <li>b. Patient who underwent total mastectomy with 4 or more positive axillary nodes.</li> </ol>	Strong	High
	<p>We suggest comprehensive regional nodal irradiation among breast cancer patients with the following conditions:</p> <ul style="list-style-type: none"> <li>• Patients who underwent breast conserving surgery with a negative axillary lymph node but with any of the following: <ul style="list-style-type: none"> <li>○ With central/medial tumors</li> <li>○ pT3 tumors</li> <li>○ pT2 tumors, with less than 10 axillary nodes removed and one of the following high-risk features such as grade 3, extensive lymphovascular invasion [LVI], or ER-negative</li> </ul> </li> <li>• Patients who underwent total mastectomy and with any of the following: <ul style="list-style-type: none"> <li>○ 1-3 positive axillary nodes</li> <li>○ Negative axillary nodes and tumor less than or equal to 5 cm and</li> </ul> </li> </ul>	Weak	Low

	<p>negative margins but less than 1 mm with additional high-risk features such as central/medial tumors or tumors greater than or equal to 2 cm with less than 10 axillary nodes removed and at least one of the following: grade 3, ER-negative or lymphovascular invasion</p> <ul style="list-style-type: none"> <li>○ Negative axillary nodes and tumor greater than 5 cm</li> <li>○ Margins positive and when re-excision to negative is not feasible.</li> </ul>		
	For whole breast with nodal irradiation (with or without tumor bed boost) and chest wall with nodal irradiation (with or without scar boost), we recommend using conventional fractionation.	Strong	High
What is the role of genomic testing in breast cancer?	<p>We recommend 21-gene RT-PCR assay among HR-positive, HER-2 negative patients and:</p> <ul style="list-style-type: none"> <li>a. Premenopausal with tumor size greater than 0.5 cm and pN0 stage:</li> <li>b. Postmenopausal with tumor size greater than 0.5 cm, or pN1Mi or pN1 stage:</li> <li>c. If they are a candidate for chemotherapy.</li> </ul>	Strong	High
What are the recommended fertility preservation and birth control measures among premenopausal breast cancer patients?	We recommend that the cancer team discuss to all premenopausal patients the impact of cancer and its treatment such as chemotherapy, endocrine therapy and, radiotherapy on fertility and be asked about their desire for future pregnancies. Patients who may desire future pregnancies should be referred to fertility specialists before starting treatment to discuss options.	Strong	High
	We recommend that patients should not become pregnant during or within 1 year of treatment with radiotherapy, chemotherapy, endocrine therapy, or targeted therapy.	Strong	Low
	Fertility preservation options such as oocyte or embryo freezing should be offered to BRCA 1 and 2 mutation carriers due to risk of premature menopause or premature ovarian insufficiency.	Strong	Low

<b>Surgical Management</b>			
What is the recommended surgical management for patients with breast cancer?	<p><b>Non-invasive (DCIS)</b></p> <p>We recommend the following options:</p> <ul style="list-style-type: none"> <li>a. Partial mastectomy with whole breast radiation therapy (breast conserving therapy) OR total mastectomy.</li> <li>b. SLNB may be performed for patients undergoing total mastectomy and selected patients undergoing breast conserving surgery.</li> <li>c. We recommend further surgery (re-excision or mastectomy) after partial mastectomy for positive or less than 2 mm margins.</li> </ul>	Strong	High
	<p><b>Invasive</b></p> <p>We recommend the following options:</p> <ul style="list-style-type: none"> <li>a. Partial mastectomy with whole breast radiation therapy (breast conservation therapy) with surgical axillary staging; OR total mastectomy with surgical axillary staging among patients.</li> <li>b. Breast reconstruction should be offered to women undergoing mastectomy; including those who may need radiotherapy.</li> <li>c. We recommend further surgery (re-excision or mastectomy) after partial mastectomy for positive margins (tumor on ink).</li> </ul>	Strong	High
What is the recommended axillary staging for patients with invasive breast cancer?	<p><b>Clinically node negative</b></p> <p>We recommend performing axillary staging using SLNB as the preferred method among patients with early-stage breast cancer.</p>	Strong	High
	<p>We recommend performing ALND among patients with early-stage breast cancer when SLNB is not possible.</p>	Strong	Moderate
	<p>In elderly patients and with significant competing comorbidities with tumor size of 2cm or less, hormone receptor–positive and human epidermal growth factor receptor 2 (HER2)–negative tumor, for whom axillary staging will not alter course of treatment, SLNB (or ALND) may be omitted.</p>	Weak	Low

	<b>Clinically node positive</b> We suggest conducting US-guided needle biopsy of the axillary node among patients with clinically suspicious nodes.	Weak	Low
	We recommend performing ALND in patients with positive node biopsy.	Strong	Low

<b>Surveillance</b>			
What is the recommended post-treatment surveillance for breast cancer?	We recommend that the follow-up of women with breast cancer include interval history and physical examination every 3 to 6 months for 5 years and then annually, as well as yearly mammography. In patients treated with breast-conserving therapy, the first follow-up mammogram should be performed 6 to 12 months after the completion of breast-conserving radiation therapy.	Strong	Low
	We do not recommend screening for metastasis in the absence of clinical signs and symptoms suggestive of metastatic disease.	Strong	Low
	We do not recommend the routine use of "tumor markers" for surveillance of patients with breast cancer.	Strong	Low

## **Background**



## Introduction

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast, which primarily occurs in women older than 50 years. It can also affect men, but it is approximately 1/150 as frequent in men as in women (Jameson et al, 2018). According to Clemons & Goss (2001), non-modifiable risk factors like age, sex, genetics, family history of breast cancer, history of previous breast cancer and proliferative breast disease; and modifiable risk factors like physical activity, diet, obesity, use of alcohol and tobacco contribute to the development of breast cancer. Women without functioning ovaries, have early menopause, and have never received combination estrogen/progesterone replacement therapy, are much less likely to develop breast cancer than those who have a normal menstrual history.

Initially, the cancer is limited to a duct or lobule (*in situ*) with no potential for metastasis. However, as time passes, these *in situ* cancers may progress and spread in the breast tissue, lymph nodes, or other organs in the body causing the more advanced stages of the disease. The most common symptom is a painless lump or thickening of the breast, which may include changes in appearance, dimpling or redness in the skin, and abnormal nipple discharge (WHO, 2020).

Breast cancer risk is increased in women with early menarche, late first full-term pregnancy, and late menopause. These three factors account for 70-80% of the variation in breast cancer frequency in different countries. Virtually all breast cancer cases are diagnosed by biopsy of a nodule detected either on a mammogram or by palpation. Only 1 in every 5-10 breast biopsies lead to a diagnosis of cancer, although the rate of positive biopsies varies in different countries and clinical settings. Correct staging of breast cancer patients permits accurate prognosis and is the basis of therapeutic decision-making.

According to the Global Cancer Observatory, excluding for other cancers, breast cancer has the highest incidence among all cancers worldwide, with approximately 2,261,419 new cases in 2020, and ranks fifth in the causes of mortality, with 684,996 deaths globally. These figures were solely based on women, resulting to breast cancer as the leading cause of cancer deaths in females. In 2020 alone, a total of 684,996 women died of breast cancer, with a crude death rate of 17.7 per 100,000 population (WHO International Agency for Research on Cancer, 2020).

In the Philippines, breast cancer is responsible for 10.7% of all cancer deaths and is the third leading cause of cancer mortality in 2020, with a crude mortality rate of 18.2 per 100,000 population (GLOBOCAN, 2020).

In terms of breast cancer survival, the odds have increased dramatically over the last 35 years due to a combination of early detection and more effective therapies. After diagnosis, survival for at least 5 years is 90% for patients in high-income countries but

much lesser for those in lower-income areas, which ranges from 40-66%. The implementation of early detection and treatment has proven to be effective in these high-income countries, which is being suggested to be carried out to countries with limited resources but has the necessary standard tools (WHO, 2020).

# Guideline Development Process

## Phase 1 – Preparation Phase

### **Establishment of the Guideline Development Group**

The guideline development group was composed of policy makers, program managers, medical oncologist, surgical oncologists, radiation oncologists, radiologists, general and breast surgeons, pain and palliative specialists, primary care physicians and family medicine doctors, fertility preservation specialist, nuclear medicine specialists and advocacy group. The multidisciplinary and multispecialty professionals composed the relevant working groups of the BRCA NCPG, the Technical Advisory Group (TAG), the Steering Committee (SC), the Evidence Review Experts (ERE), and the Consensus Panel (CP).

The TAG and the SC comprised the lead NCPG developers. The TAG has the oversight function to ensure a quality and inclusive NCPG development process. Nominated members for the TAG included representatives from East Avenue Medical Center, the Department of Health, and the Philippine Health Insurance Corporation.

The multidisciplinary SC drafted the scope and target audience of the NCPG. They also identified, ranked, and finalized the clinical questions on screening, diagnosis, clinical management, surveillance, and pathology reporting of BRCA in the Philippines. The SC identified, invited, reviewed, and managed the COI of the relevant working groups, such as the steering committee, evidence reviewers, consensus panelists, and facilitators.

The ERE provided technical assistance in evidence review ranging from the development of the clinical questions, search and identification of evidence, appraisal of relevant literature to answer clinical questions, and synthesis of evidence summaries as the basis of recommendation statements. The ERE for this Guideline included consultants with backgrounds in clinical epidemiology, information specialists, medical informatics, and public health.

The CP was a wider group of BRCA stakeholders. Establishing a more open and diverse group of stakeholders for the CP — including multidisciplinary healthcare practitioners, patient advocates, DOH program managers, and other technical content experts — was aimed at promoting transparency, introducing different perspectives to BRCA management, and safeguarding against conflicts of interest. The CP reviewed and revised the recommendation statements and voted on adopting these statements into the Guideline.

## Declaration and Management of Conflicts of Interest

The BRCA NCPG Guideline Development Group utilized the PhP 2,000,000 DOH sub-allotment to develop the guideline. The stakeholder of the working groups that composed the Guideline Development Group (GDG) declared no true conflict interests related to this material. The stakeholders included in the guideline development groups were requested to provide a summary of their conflicts of interest (COI) related to BRCA. These COIs may be classified into financial and non-financial (or intellectual) COI. COIs were reviewed by the ERE, and admission of a stakeholder to the GDG was contingent on the stakeholder having no or minimal COI, following recommendations in the DOH CPG Manual (DOH [Philippines] 2018). Conflicts of interest(s) and how COIs were managed are presented in Annex A.

## Identification of the Scope of the NCPG

The PIPOH framework was used by the TAG and the SC in defining the scope of this Guideline, which refers to Population, Intervention, Professionals, Outcomes and Health Care Setting (ADAPTE Collaboration, 2009). These five items aided the selection and framing of clinical questions on Population; Intervention of interest – screening, diagnostics, and treatment/management; Professionals to whom the guideline will be targeted; specific Outcomes; and Health care setting and context that the guideline will be implemented.

## Generation of NCPG questions

The methodology of clinical question generation is based on frameworks of clinical practice guidelines (CPG), agenda-setting, and consensus-building (Murphy et al, 1998; The James Lind Alliance, 2020; WHO, 2014). For CPG question development guidelines, we specifically referred to guidance published by the WHO in 2014. Due to the COVID-19 pandemic and mobility restrictions at the time of guideline development, all methods of communication were virtual; no face-to-face, physical gatherings were conducted.

PIPOH framework was used by the TAG and the SC in defining the scope of this Guideline, which refers to Population, Intervention, Professionals, Outcomes, and Health Care Setting (ADAPTE Collaboration, 2009).

**Table 2.** PIPOH Framework for the Breast Cancer NCPG Development

Population	Adult breast cancer stages 0-3; all types
Intervention	Diagnosis and clinical and surgical management
Professionals	Physicians/medical doctors, allied health professionals, and health policy makers
Outcomes	Overall survival rate, disease-free survival, recurrence, remission, diagnostic accuracy

Health Care Setting	Secondary and tertiary level of care
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These guidelines included relevant questions on screening, diagnosis, treatment, and surveillance of breast cancer. The objectives are the following:

1. To present and synthesize the best available evidence on the diagnosis, treatment, and surveillance of breast cancer;
2. To standardize the diagnosis, treatment, and surveillance of breast cancer in the Philippines for the reduction of the burden of disease; and,
3. To complement the existing DOH program mandates on cancer control by providing evidence to its statements for policy implementation.

The generation of CPG questions is an essential early step in CPG development. These questions were used as the basis for the subsequent systematic review of the evidence base on BRCA (WHO, 2014). CPG questions generated by the SC were agreed to focus on evidence uncertainties, areas of controversy in the management of BRCA and known variations of clinical practice and care especially in the resources available in the Philippine setting. The SC was then convened in virtual workshops where the final questions were formulated in PICO (Population, Intervention, Comparator, and Outcome) format, reviewed, and prioritized according to a consensus. Technical working groups were assigned for further review and revision to reach the final PICO format of the clinical questions. The final list of PICO elements for each CPG question is located in Annex C.

## **Phase 2 – Evidence Synthesis**

### **Overview of Evidence Synthesis Methods**

Considering the time and resources to produce quality CPGs, it is recommended that existing guidelines be adapted to reduce duplication of effort and update existing guidelines in a shorter period of time. In this CPG development process, guideline adaptation by the ADAPTE method was considered to address specific health questions generated. Independent methodologists and reviewers determined if adaptation of any existing CPG was feasible and consequently created the evidence base and recommendation matrix.

The ERE utilized the ADAPTE method to review existing guidelines for inclusion in the evidence base and drafting of recommendation matrix. The ADAPTE collaboration has developed a systematic approach to aid in the adaptation of guidelines (ADAPTE Collaboration, 2009). The systematic approach aids in the use and modification of existing guidelines to customize an existing guideline to suit the local context while addressing relevant health questions. A systematic search of existing guidelines in multiple databases, including PubMed, Google Scholar and Scopus®. Search terms and limits are provided in Annex B. Updated versions of the guidelines were also searched to ensure currency of the recommendations.

Assessment of the guidelines yielded from the systemic search were then given consideration for adaptation by assessment if it meets the qualities of a high-quality guideline using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument as well as if it can address the specific clinical questions. The AGREE II instrument provides a framework for assessing the quality of CPGs (Brouwers et al, 2013). The 23 items in the AGREE instrument assess the methods used for developing the guideline and quality of reporting. Assessment is focused on the rigor and overall score. The domains and criteria for the AGREE II tool are shown in Annex B. The guidelines were assessed for guideline quality, currency, content, consistency, and applicability (ADAPTE Collaboration, 2009). The characteristics and contents of the source guidelines are summarized in Annex B.

### Phase 3 – Evidence to Recommendations

The ERE drafted the initial recommendation statements to include level of evidence based on the source guidelines and its references. All guidelines included utilized by recommended Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for evaluation of level of evidence (Schünemann et al, 2013). This is the tool developed by the GRADE working group in evaluating the quality of the evidence and is summarized and defined in Table 3 below.

**Table 3.** Quality of Evidence Grades (Schünemann et al, 2013)

<b>Grade</b>	<b>Definition</b>
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The recommendation matrix developed was for finalization of the CP who were provided by the ERE with a guide on determining the strengths of recommendation (Schünemann et al, 2013). Recommendations may either be *strong* or *weak*. *Strong* recommendations refer to issues where the guideline development group may be confident that the benefits outweigh the risks or costs of an intervention, or vice versa, whereas *weak* recommendations are those where there is appreciable uncertainty on the calculus of benefits and risks. A summary of the implication of recommendation strength on each type of guideline user based on WHO which is reproduced in full in Table 4.

**Table 4.** Implications of Strong and Weak Recommendations for Different Users of Guidelines (WHO, 2014)

	<b>Strong Recommendation</b>	<b>Weak Recommendation</b>
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

## Phase 4 – Consensus Development

The result of ADAPTE evidence evaluation and recommendation synthesis was presented to the CP, composed of BRCA management stakeholders, from health care practitioners to patient advocates to program implementers, for validation. The results of the systematic literature review and recommendation synthesis were forwarded to the members of the CP for review, either individually or together with their affiliated organizations. The suggested recommendations were also reiterated to the CP.

Nominal group techniques were applied to direct the discussions (Delbecq et al, 1986). After presentation of the evidence and recommendations, stakeholders were

requested one-by-one to provide their inputs on each recommendation within a set time limit. The CP was allowed to revise the recommendation statements for adaptation within reasonable limits as long as the revision did not alter the value of the underlying evidence. The content and strength of each recommendation was then put to a vote for finalization, consensus was set at 80% agreement on a specific recommendation. If the CP was unable to reach the consensus marker, the cycle of discussions then voting was repeated up to two times.

## **Patient Values, Preferences, and Other Considerations**

As there is advocacy group present within the GDG, results based on a systematic review of patient or family values, was assessed vis-à-vis the recommendations of the GDG after consensus made.

The SC and CP thoroughly discussed the applicability of the recommendations using several criteria, such as improvement of treatment outcomes, acceptability to local professional practice, public health impact, and healthcare cost based on lived experiences.

Ethics review was sought and approved by the DOH Single Joint Review Board.

External evaluation was sought by the guideline development group through a public forum with the general surgeons where feedbacks were documented and directly incorporated in the final manuscript.

The DOH as funding agency and EAMC as fund manager did not influence the editorial independence of the GDG.

## **Dissemination and Use of the Guideline**

The value of a CPG is fully appreciated when it is widely adopted, and adoption is contingent on access and distribution of the CPG to its target audience. This clinical practice guideline is available on the DOH website.

The GDG will work closely with DOH and other partners to ensure wide dissemination of the guideline through different events: (1) Presentation in professional society's scientific fora; (2) Distribution of the guideline will be done electronically through DOH and partner society websites; (3) Monitoring/assessment on the uptake of the guideline will be done through monitoring the number of downloads and request for distribution, and; (4) Health outcomes will be monitored during the first three years of guideline distribution specifically on number of cases identified, treated and surveillance for recurrence reported.

The NCPG recommendations are valid until new significant evidence emerges that would require a change in recommendation. The ERE recommends revisiting the Guidelines regularly every three years. The research recommendations may be



considered by policymakers and program managers for future research funding as part of the continuous quality improvement of healthcare services in the country.

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## **Clinical Practice Guidelines**

# Breast Cancer National Clinical Practice Guidelines Recommendations

## Diagnosis

Question 1: What is the recommended imaging work-up for patients with suspicious breast symptoms/complaints?

### Recommendation 1a.

We recommend breast ultrasound for those <30 years of age.

*Strong recommendation, Low quality of evidence*

### Recommendation 1b.

We recommend diagnostic mammogram with or without ultrasound for those ≥30 years of age.

*Strong recommendation, Low quality of evidence*

### Recommendation 1c.

We recommend ultrasound as a complementary imaging tool in the presence of mammographic findings suspicious of breast cancer to document lesion characteristics and to guide biopsy.

*Strong recommendation, Low quality of evidence*

## Consensus Issues

The Consensus Panel members adopted these recommendations, and pointed out that in local practice, 40 years old is being used as the cutoff age for recommending mammogram. Mammograms for 39-year-olds and below are for high-risk patients including those with a 1<sup>st</sup> degree relative diagnosed with breast cancer at age less than or equal to 49. The panel raised the issue on the use of MRI in patients with suspicious breast symptoms and is recommended to be tackled more in depth in the next update.

Based on the NCCN Guidelines section on Invasive Breast Cancer (2022), indications for MRI are as follows:

- May be used for staging evaluation to define extent of cancer or presence of multifocal or multicentric cancer in the ipsilateral breast, or as screening of the contralateral breast cancer at time of initial diagnosis (category 2B).

- May be helpful for breast cancer evaluation before and after preoperative systemic therapy to define extent of disease, response to treatment, and potential for breast-conservation therapy.
- May be useful in identifying otherwise clinically occult disease in patients presenting with axillary nodal metastases (cT0, cN+), with Paget disease, or with invasive lobular carcinoma poorly (or inadequately) defined on mammography, ultrasound, or physical examination.
- The utility of MRI in follow-up screening of patients with prior breast cancer is undefined. It should generally be considered only in those whose lifetime risk of a second primary breast cancer is >20% based on models largely dependent on family history, such as in those with the risk associated with inherited susceptibility to breast cancer.

### Summary of Evidence

These recommendations were adapted from the NCCN Guideline for Breast Cancer Screening and Diagnosis Version 1.2021. The recommendations were based on an accuracy study of breast ultrasound for primary imaging evaluation of symptomatic women 30-39 years of age and a review article discussing the evidence informing current imaging management of palpable breast abnormalities. The table below summarizes the performance of mammography and ultrasound in women aged 30-39 years old (Lehman et al, 2012).

**Table 5.** Performance of Mammography and Ultrasound in Women 30–39 Years Old at Site of Focal Clinical Concern (N=1208)

Performance Statistic	Mammography	Ultrasound
Sensitivity	60.9%	95.7%
Specificity	94Z%	89%
Positive Predictive Value	18.4%	15.1%
Negative Predictive Value	99.2%	99.9%

Source: Lehman, C. D., Lee, C. I., Loving, V. A., Portillo, M. S., Peacock, S., & DeMartini, W. B. (2012). Accuracy and value of breast ultrasound for primary imaging evaluation of symptomatic women 30-39 years of age. *American journal of roentgenology*, 199(5), 1169-1177.

The review article on imaging management of palpable breast abnormalities concluded the following:

- Breast ultrasound should be the primary imaging tool for women with palpable lumps who are pregnant, lactating, or younger than 30 years.
- For women 30–39 years old, ultrasound or mammography may be performed first at the discretion of the radiologist or referring provider.
- For women 40 years old and older, mammography, followed in most cases by

ultrasound, is recommended.

- There is little to no role for breast MRI or other advanced imaging technologies in the routine diagnostic evaluation of palpable breast abnormalities.

### Research Recommendation

The GDG recommended no additional research.



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Question 2: What is the recommended biopsy technique to establish diagnosis of suspicious breast lesions?

#### Recommendation 2a.

We recommend breast biopsy if diagnostic imaging findings or clinical findings are suspicious or highly suggestive of malignancy.

*Strong recommendation, High quality of evidence*

#### Recommendation 2b.

We suggest minimally invasive biopsy technique (MIBT) with a core needle preferably image-guided in the tissue diagnosis of breast cancer for both palpable and non-palpable breast lesions.

*Weak recommendation, High quality of evidence*

#### Recommendation 2c.

Among patients with suspicious clinical findings but with no ultrasonographic or mammographic abnormality detected, we suggest tissue biopsy preferably core needle biopsy.

*Weak recommendation, High quality of evidence*

#### Recommendation 2d.

We recommend doing open biopsy (excision or incision) if the diagnosis by core needle biopsy is an indeterminate lesion, a benign lesion that is discordant with imaging, atypical ductal hyperplasia (ADH) or other specific histology that requires additional tissue.

*Strong recommendation, High quality of evidence*

#### Consensus Issues

The Panel decided to adopt the recommendations and indicated that not all hospitals or physicians can perform MIBT; thus, accessibility is an issue.

#### Summary of Evidence

These recommendations were adapted from the Malaysian CPG for the Management of Breast Cancer (3<sup>rd</sup> edition) and the NCCN Guideline for Breast Cancer Screening and Diagnosis Version 1.2021.

The Malaysian CPG recommendations were based on the consensus guidelines of

the American Society of Breast Surgeons (ASBrS). The goals of MIBT are to accurately diagnose pre-malignant and malignant breast lesions and to avoid open surgery for patients with benign abnormalities. The choice of device depends on various factors, namely: target lesion, target location, intent to remove the entire lesion, and the surgeon's training and experience. Core needle biopsy (CNB) or vacuum-assisted technique is preferred over fine-needle aspiration cytology for all breast lesions due to its higher sensitivity for diagnosis of breast lesions (Wang et al, 2017). ASBrS recommends that concordance of clinical breast examination, imaging, and the biopsy results be determined and documented. A repeat percutaneous biopsy or surgical excision is indicated for discordant biopsy results.

In a study of 98 patients, each with a palpable breast mass, ultrasound-guided core needle biopsy was found to be 100% sensitive and 100% specific (Yeow et al, 2001). Ultrasound-guided core needle biopsy is therefore an accurate initial diagnostic test for palpable breast masses.

In a prospective study of 50 patients with suspicious palpable breast lump/mass, core needle biopsy (CNB) was found to have higher sensitivity, diagnostic accuracy, and negative predictive value compared to fine needle aspiration cytology (FNAC) (Saha et al, 2016). Table 6 shows the performance of CNB and FNAC in the diagnosis of breast carcinoma.

**Table 6.** Performance of CNB and FNAC in the Diagnosis of Breast Carcinoma (N=50)

<b>Performance Statistic</b>	<b>CNB</b>	<b>FNAC</b>
Sensitivity	88.3%	69%
Specificity	100%	100%
PPV	100%	100%
NPV	53.3%	38.1%
Diagnostic accuracy	86%	74%

Source: Saha, A., Mukhopadhyay, M., Das, C., Sarkar, K., Saha, A. K., & Sarkar, D. K. (2016). FNAC versus core needle biopsy: a comparative study in evaluation of palpable breast lump. *Journal of clinical and diagnostic research: JCDR*, 10(2), EC05.

Indeterminate breast lesions (B3) are a group of heterogenous lesions with uncertain malignant potential and are associated with invasive carcinoma or DCIS (Shaaban & Sharma, 2019). Indeterminate lesions are traditionally managed by diagnostic open biopsy to exclude malignancy. A retrospective analysis of 152 patients with B3 lesions including atypical papilloma, atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and radial scar/complex sclerosing lesions (RS/CSL) revealed a low (0.66%) malignancy upgrade rate. However, no statistically significant predictor of malignancy was identified. Therefore, open biopsy remains a standard of care for indeterminate lesions (Tan et al, 2021).

A discordant benign lesion has imaging features suspicious for malignancy (i.e., BI-RADS category 4 or 5), but demonstrates benign pathology on percutaneous breast biopsy (Park et al, 2018). In a retrospective observational cohort study of 81 patients with benign discordant lesions, the overall rate of malignancy after excisional biopsy was 7.4% (Poole et al, 2015). This study concluded that discordant lesions still warrant excisional biopsy.

### Research Recommendation

The GDG recommended to conduct a costing study for minimally invasive techniques for the diagnosis of breast lesions.

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Question 3: What is the recommended work-up for patients with confirmed breast cancer?

#### Recommendation 3a.

We recommend the following workup for patients with breast cancer:

- History and physical exam
- Bilateral diagnostic mammography
- Breast ultrasonography, if necessary
- Determination of tumor HR status (ER and PR determinations) and HER2-receptor status
- Pathology review
- Psychosocial distress assessment

*Strong recommendation, Low quality of evidence*

#### Recommendation 3b.

We recommend the symptom-directed staging workup for patients with breast cancer.

*Strong recommendation, Low quality of evidence*

#### Recommendation 3c.

We recommend using bone scan if plain radiography or computed tomography staging is negative among patients with early breast cancer and with localized bone pain, elevated alkaline phosphatase, or symptoms suggestive of bone metastases.

*Strong recommendation, Low quality of evidence*

#### Recommendation 3d.

We recommend the following in staging patients presenting with recurrent or stage IV breast cancer:

- History and physical exam
- Blood work-up — complete blood count and metabolic panel (liver function test, BUN, creatinine, calcium)
- CT scan of the chest and whole abdomen with contrast or MRI scan of the abdomen.
- Bone scan, and radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan
- Biopsy documentation of first recurrence if possible
- Repeat tumor HR status (ER and PR determinations) and HER2-receptor status of the recurrence

*Strong recommendation, Low quality of evidence*

## Consensus Issues

The Panel voted to adopt the recommendations and noted that some tumors with unfavorable biology like TNBC may benefit from early metastatic workup. However, diagnostic workup MRI is costly and not available in some areas but is important to obtain prior to treatment. Patients with locally advanced disease should then be screened for possible distant metastasis. Baseline comprehensive laboratory testing (CBC, renal function test, liver enzymes) must be done at diagnosis, and the cost of these procedures should also be considered for the patients.

## Summary of Evidence

These recommendations were adapted from the Malaysian CPG for the Management of Breast Cancer (3<sup>rd</sup> edition), the NCCN Guideline for Breast Cancer Version 8.2021, 2019 ESMO CPG for diagnosis, treatment, and follow-up of early breast cancer, and Pan-Asian adapted ESMO CPG for the management of patients with early breast cancer.

The recommendations from the Malaysian CPG were retained from its previous version published in 2010. Similar recommendations were found in the NICE's guideline for early and locally advanced breast cancer and NCCN's 2019 Breast Cancer guideline Version 1.

The NCCN recommendations were based on a single institution retrospective chart review of asymptomatic women with early-stage breast cancer (Stage I/II) which found that pretreatment CBCs, LFTs, and chest x-rays did not improve detection of occult metastatic disease but resulted in additional financial costs (Louie et al, 2015).

The Pan-Asian recommendation was adapted from the 2019 ESMO CPG for diagnosis, treatment and follow-up of early breast cancer. The Korean experts added HBV testing based on the 8<sup>th</sup> Korean Clinical Practice Guideline for Breast Cancer and an article highlighting the importance of HBV screening and prevention in cancer patients undergoing chemotherapy.

Based on NCCN, additional workup procedures include the following:

### Distress Assessment

1. Levels of distress may vary in patients and should be addressed individually.
2. We recommend assessing for distress in patients newly diagnosed with breast cancer using a validated assessment tool

### Others

1. CBC, comprehensive metabolic panel, liver function, and alkaline phosphatase



tests should be considered only if the patient is a candidate for preoperative or adjuvant systemic therapy. (MS-12)

2. Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer and for patients with the following characteristics (NCCN, 2022):
  - a. Equal or less than 45 years of age
  - b. 46 to 59 years of age with ANY:
    - i. Unknown or limited family history
    - ii. Multiple primary breast cancers
    - iii. Greater than or equal to close blood relative with breast, ovarian, pancreatic, or prostate cancer at any age
  - c. Greater than or equal to 51 years of age
    - i. Greater than or equal to one blood relative with ANY:
      1. Breast cancer at age of less than or equal to 50 or male breast cancer at any age
      2. Ovarian cancer at any age
      3. Pancreatic cancer at any age
      4. Metastatic, intraductal/cribriform histology, or high- or very high-risk group prostate cancer at any age
      5. Greater than or equal to 3 total diagnoses of breast cancer in patient and/or close blood relatives
      6. Greater than or equal to 2 close blood relatives with either breast or prostate cancer (any grade) at any age
  - d. Any age
    - i. To aid in adjuvant decisions with Olaparib for high-risk, HER-2 negative breast cancer
    - ii. TNBC
    - iii. Lobular breast cancer with personal or family history of diffuse gastric cancer
    - iv. Male breast cancer
    - v. Greater than or equal to close relative with male breast cancer

### Research Recommendation

The GDG recommended no additional research.

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## Treatment (Chemotherapy and Radiotherapy)

Question 4: What are the indications for neoadjuvant chemotherapy for patients with early breast and locally advanced cancer?

### Recommendation 4a.

We recommend neoadjuvant systemic chemotherapy among patients with operable breast cancer with the following:

- HER2-positive disease or TNBC, if cT $\geq$ 2 or cN $\geq$ 1 (*High quality of evidence*)
- Large primary tumor relative to breast size in a patient who desires breast conservation (*Low quality of evidence*)
- cN+ disease likely to become cN0 with neoadjuvant therapy (*Low quality of evidence*)

*Strong recommendation*

### Recommendation 4b.

We recommend neoadjuvant chemotherapy among patients with inoperable locally advanced breast cancer including:

- those with inflammatory breast cancer
- those with cN2 and cN3 regional lymph nodal disease
- those with cT4 tumors

*Strong recommendation, Low quality of evidence*

### Recommendation 4c.

We suggest neoadjuvant chemotherapy for whom a delay in surgery is preferable or unavoidable.

*Weak recommendation, Low quality of evidence*

### Recommendation 4d.

We do not recommend neoadjuvant chemotherapy in patients with the following:

- Extensive in situ disease when the extent of invasive disease cannot be defined
- Tumors that are not palpable or clinically assessable

*Strong recommendation, Low quality of evidence*

## Consensus Issues

The Consensus Panel members adopted these recommendations on neoadjuvant treatment. The consensus panel emphasizes the importance of considering the clinical profile and the response to treatment of patients when considering use of neoadjuvant treatment.

## Summary of Evidence

Neoadjuvant therapy has shown benefits on surgical outcomes and among patients with pathologic complete response.

The use of neoadjuvant compared to adjuvant therapy did not show any difference in long-term outcomes such as overall survival. In a meta-analysis on nine randomized controlled trials (N = 3946) comparing neoadjuvant versus adjuvant treatment among breast cancer patients, there were no difference noted on the outcomes of death (RR = 1.00, 95% CI: 0.90 to 1.12), disease progression (RR = 0.99, 95%CI: 0.91 to 1.07), and distant recurrence (RR = 0.94, 95% CI: 0.83 to 1.06) (Mauri et al, 2005). A later randomized clinical trial (N=1,523) showed the same results where there were no differences between giving neoadjuvant and adjuvant chemotherapy on disease free survival (HR = 0.93) and overall survival (0.99) (Rastogi et al, 2008).

Despite that, neoadjuvant treatment still offers other benefits including improvement of surgical outcomes by rendering inoperable tumors resectable and downstaging patients with operable breast cancer (NCCN, 2021). Several trials have observed that the use of neoadjuvant chemotherapy have shown higher rates of lumpectomies and/or higher rates of downstaging of patients (Gralow et al, 2008; Gianni et al, 2005; Wolmark et al, 2001; Fisher et al 1998; van der Hage et al, 2001). Same findings were observed in a retrospective review of the US National Cancer Database involving 354,204 patients. Patients with tumor larger than 3 cm who underwent neoadjuvant chemotherapy had higher chances of receiving breast conservation surgery (OR = 1.7, 95% CI: 1.6 to 1.8) (Kilelea et al, 2015).

Giving of neoadjuvant therapy may also provide important prognostic information to the response of patients on their management. Pathologic complete response (pCR) after neoadjuvant therapy was found useful in prognosticating breast cancer patients. A systematic review on 12 trials involving 11,955 patients showed that patients who achieved pathologic complete response (pCR) after neoadjuvant therapy were associated with higher overall survival. These were observed among triple negative (HR = 0.24, 95% CI: 0.18 to 0.33), HER 2-positive (HR = 0.39, 95%CI: 0.31 to 0.50), and hormone positive breast cancer patients (HR = 0.39, 95%CI 0.33 to 0.71) (Cortazar P et al, 2014). A pooled analysis on 6,377 patients from seven randomized trials showed the same result (von Minckwitz et al, 2012).

In an analysis of a clinical database involving 1,118 patients, patients with triple negative breast cancer who had neoadjuvant treatment had a higher pathologic complete response (pCR) rate, and those with pCR had higher survival rate. On the other hand, those with residual disease had poorer overall survival (Liedtke C., 2008 et al). NCCN suggests identifying these patients as candidates for RCT on novel agents postoperatively (NCCN, 2021).

NCCN also mentioned that giving neoadjuvant therapy allows time for appropriate genetic testing and planning breast reconstruction in patients proceeding with mastectomy (NCCN, 2021).

### Systemic Treatment Options

- Chemotherapy

The regimens recommended in the adjuvant setting may be considered in the preoperative setting. In both settings, the goal is to eradicate or control undiscovered distant metastases (NCCN, 2022).

In patients with TNBC who have clinically node-positive and/or at least T1c disease, ASCO and NICE recommended that they should be offered an anthracycline- and taxane-containing regimen in the neoadjuvant setting (ASCO, 2021; NICE, 2018).

The inclusion of platinum agents as neoadjuvant chemotherapy for TNBC remains controversial (NCCN, 2022). Several studies have shown improved pCR rates with incorporation of platinum (Von Minckwitz et al, 2014; He et al, 2021). However, long-term outcomes remain unknown. The routine use of platinum agents as part of neoadjuvant therapy for TNBC is not recommended for most patients (including BRCA mutation carriers), but it may be considered in select patients (such as those for whom achieving better local control is necessary). The use of platinum agents in the adjuvant setting is not recommended (NCCN, 2022).

- Endocrine Therapy

Neoadjuvant endocrine therapy alone may be offered to those with strongly HR-positive tumors (Ellis et al, 2011; Masuda et al, 2012; Torrisi et al, 2011; Fontein et al, 2014). The endocrine therapy options include an aromatase inhibitor (with ovarian suppression for premenopausal patients) or tamoxifen. The preferred endocrine therapy option for postmenopausal patients is an aromatase inhibitor (NCCN, 2022).

- HER2 Targeted Therapy

For patients with HER2-positive breast cancer who are candidates for preoperative systemic therapy, chemotherapy and trastuzumab-based therapy

is recommended (Petrelli et al, 2011).

The recommended therapy for the different subtypes of luminal breast cancer is depicted in Table 7.

**Table 7.** Recommended Therapy for Luminal Breast Cancer

<b>Subtype</b>	<b>Recommended Therapy</b>	<b>Comments</b>
Luminal A-like	Endocrine therapy (ET) alone in the majority of cases	Consider chemotherapy if high tumor burden ( $\geq 4$ lymph nodes, T3 or higher)
Luminal B-like (HER2-negative)	Chemotherapy followed by ET for the majority of cases	
Luminal B-like (HER2-positive)	Chemotherapy + anti-HER2 followed by ET for all patients	If contraindicated to chemotherapy, ET + anti-HER2 therapy may be considered, although no randomized data exist

Adapted from: Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Annals of oncology*. 2019 Aug 1;30(8):1194-220.

### Research Recommendation

The GDG recommended no additional research.

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Question 5: What are the indications for adjuvant chemotherapy for patients with early and locally advanced breast cancer?

#### Recommendation 5a.

We recommend adjuvant systemic chemotherapy after careful consideration of tumor breast panel results and patient's risk for disease recurrence and mortality.

Tumor breast panel results:

- ER/PR
- HER2 tumor status

Prognostic factors for disease recurrence/mortality:

- Age
- Comorbidity
- Tumor size
- Tumor grade
- Number of involved ALNs

*Strong Recommendation, High quality of evidence*

#### Consensus Issues

The Consensus Panel adopted the recommendations and suggested to consider the local availability and cost of the regimens.

#### Summary of Evidence

According to NCCN, adjuvant systemic therapy should be considered after surgical treatment. This decision, which must be done by the health care team together with the patient, is usually based on individual risk of relapse and predicted sensitivity to a particular treatment (e.g., ER/PR and HER2 status). It is also needed to consider and balance the risk for disease recurrence with local therapy alone, the magnitude of benefit from using adjuvant therapy, toxicity of the therapy, and comorbidity.

Recommendations for the favorable histology of invasive breast cancers, such as tubular and mucinous cancers, are outlined by NCCN based on tumor size and ALN status. The treatment options for endocrine therapy, chemotherapy, and sequencing of treatment with other modalities are similar to those of the usual histology of breast cancers. Majority of tubular breast cancers are both ER-positive and HER2-negative. As such, the pathology evaluation and accuracy of the ER and/or HER2 determination should be reviewed if a tubular cancer is ER-negative and/or HER2-positive, or if a tumor with an ER- and PR-negative status is grade 1 (Allred et al, 2009). If a case is

histologically identified as a tubular or mucinous breast cancer and be confirmed as ER-negative, then the tumor should be treated according to the guideline for the usual histology, ER-negative breast cancers. Prospective data are insufficient for systemic adjuvant therapy of tubular and mucinous histologies.

Based on the NCCN guidelines also, chemotherapy regimens used in the adjuvant setting can be given in preoperative cases since the sole objective is to eradicate or control undiscovered distant metastases. Moreover, the guidelines involving adjuvant chemotherapy cover specific representative doses and schedules with regimens categorized as “preferred” or “other.” The NCCN panel used the said categorization to indicate the relative efficacy, toxicity, and treatment schedules of the regimens (Erban & Lau, 2006).

The preferred regimens include dose-dense doxorubicin and cyclophosphamide (AC) with dose-dense sequential paclitaxel, dose-dense AC followed by sequential weekly paclitaxel, and docetaxel plus cyclophosphamide (TC). As seen in randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy, there were better disease-free rates among patients with axillary node-positive breast cancer, and in one trial, there was improvement in OS, when paclitaxel was given (Henderson et al, 2003; Mamounas et al, 2005).

While in a retrospective study, the paclitaxel-containing regimen seems to have more benefit in ER-negative patients; a randomized trial comparing the use of concurrent and sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide VS. doxorubicin plus cyclophosphamide followed by paclitaxel) given either every 2 weeks with filgrastim support or every 3 weeks showed a 26% reduction in hazard of recurrence ( $P=0.01$ ) and a 31% reduction in the hazard of death ( $P=0.013$ ) for the dose-dense regimens (Citron et al, 2003).

In another trial that assessed combination TC versus AC chemotherapy in stage I to III breast cancer patients ( $n=1,016$ ), overall DFS (81% versus 75%; HR, 0.74; 95% CI, 0.56–0.98;  $P=0.033$ ) and OS (87% versus 82%; HR, 0.69; 95% CI, 0.50–0.97;  $P=0.032$ ) were significantly improved with TC compared with AC, at a median follow-up of 7 years (Jones et al, 2009).

Meanwhile, the regimens listed as other in the guidelines are AC; epirubicin and cyclophosphamide (EC); CMF; AC with sequential docetaxel administered every 3 weeks; AC with sequential weekly paclitaxel; FEC/CEF followed by docetaxel or weekly paclitaxel; FAC followed by weekly paclitaxel; and docetaxel, doxorubicin, and cyclophosphamide (TAC).

Multiple randomized trials have demonstrated that the AC regimen for four cycles result in relapse-free survival and OS equivalent to CMF chemotherapy (Bang et al, 2000; Fisher et al, 1990). In addition, studies of CMF chemotherapy compared with no

chemotherapy have denoted DFS and OS advantages with CMF chemotherapy (Lancet, 1998; Lancet, 2005). In the EBCTCG overview of polychemotherapy, the annual odds of recurrence decreased by 12% ( $P=0.006$ ) and the annual odds of death was reduced by 11% ( $P=0.02$ ) with anthracycline-containing regimens (Lancet, 1998). And in a trial that evaluated 2 dose levels of EC chemotherapy with CMF chemotherapy in patients with node-positive breast cancer, the higher-dose EC chemotherapy was equivalent to CMF chemotherapy and superior to moderate-dose EC in event-free survival and OS (Piccart et al, 2001).

Nevertheless, the NCCN Panel has excluded the FEC/CEF and FAC/CAF regimens for adjuvant therapy due to the results of the NSABP B-36 phase III trial, which reported that DFS after eight years was lower for patients on the longer FEC treatment and that the patients given FEC experienced more side effects (Samuel et al, 2015). Also, FEC patients had a worse quality of life at six months and higher rate of post-chemotherapy amenorrhea (Ganz et al, 2015).

For premenopausal patients with node-positive breast cancer, a trial was conducted wherein they were randomized to receive classic CMF therapy or FEC chemotherapy using high-dose epirubicin. The 10-year relapse-free survival (52% versus 45%;  $P=0.007$ ) and OS (62% versus 58%;  $P=0.085$ ) were preferable in the FEC groups (Levine et al, 2005). Another trial that was done in premenopausal and postmenopausal patients with node-positive breast cancer compared FEC given intravenously every 3 weeks at 2 dose levels of epirubicin (50 mg/m<sup>2</sup> versus 100 mg/m<sup>2</sup>), with results of five-year DFS (55% versus 66%;  $P=0.03$ ) and OS (65% versus 76%;  $P=0.007$ ) favoring the epirubicin 100 mg/m<sup>2</sup> arm (French Adjuvant Study Group 05 Randomized Trial, 2001). In the study by Roche et al (2006) among patients with ALN-positive breast cancer, five-year DFS (78.4% versus 73.2%; adjusted  $P=0.012$ ) and OS (90.7% versus 86.7%;  $P=0.017$ ) were superior with sequential FEC followed by docetaxel.

In the trial of Martin et al (2008), the addition of weekly paclitaxel after FEC demonstrated to be superior to FEC alone in patients with early-stage breast cancer ( $n=1,246$ ). The regimen with weekly paclitaxel was associated with a 23% reduction in the risk of relapse versus with FEC (HR, 0.77; 95% CI, 0.62–0.95;  $P=0.022$ ), but there was no significant difference in OS at a median follow-up of 66 months. While in the phase III E1199 trial, the 10-year updated results support the regimen of weekly paclitaxel and docetaxel every 3 weeks since it was associated with significant improvements in DFS, and marginal improvements in OS, rather than giving paclitaxel every 3 weeks. For patients with triple-negative disease, the 10-year DFS rate with weekly paclitaxel was 69% and the 10-year OS rate was 75% (Sparano et al, 2014).

In investigating TAC versus FAC chemotherapy in ALN-positive breast cancer patients, the study by Martin et al (2005) presented an estimated 5-year DFS of 75% with TAC and 68% with FAC (HR, 0.72; 95% CI, 0.59–0.88;  $P=0.001$ ), survival was

87% with TAC and 81% with FAC (HR, 0.70; 95% CI, 0.53–0.91; P=0.008), and DFS favored TAC in both ER-positive and ER-negative tumors. In the 3-arm randomized NSABP B-30 trial comparing TAC versus AT versus AC followed by docetaxel (AC followed by T) at a median follow-up of 73 months, findings reveal that AC followed by T had a significant advantage in DFS (HR, 0.83; P=0.006) but not in OS (HR, 0.86; P=0.086) when compared with TAC. Both DFS (HR, 0.080; P=0.001) and OS (HR, 0.83; P=0.034) were also significantly higher when AC followed by T was examined with AT, with AT showing non-inferiority compared with TAC (Swain et al, 2009).

### Research Recommendation

The GDG recommended no additional research.

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Question 6: What are the indications and recommended regimen for HER2-targeted treatment for patients with breast cancer?

Recommendation 6a.

We recommend neoadjuvant therapy with trastuzumab +/- pertuzumab with chemotherapy for patients with HER2-positive, node-positive (or high-risk node-negative) tumors.

*Strong recommendation, High quality of evidence*

Recommendation 6b.

We suggest neoadjuvant trastuzumab and chemotherapy for patients with HER2-positive, node-negative cT1c and N1mi tumors.

*Weak recommendation, Low quality of evidence*

Recommendation 6c.

We recommend adjuvant trastuzumab with chemotherapy to patients with HER2-positive breast cancer greater than 0.5 cm.

*Strong recommendation, Low quality of evidence*

Recommendation 6d.

We recommend adjuvant T-DM1 among patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and anti-HER2 neu therapy.

*Strong recommendation, High quality of evidence*

Consensus Issues

The Panel adopted these recommendations for HER2-targeted regimens and recognized that T-DM1 is costly.

Summary of Evidence

Neoadjuvant Therapy (HER2-positive, node-positive; HER2-positive, node-negative) and Adjuvant Therapy (HER2-positive)

It is also advocated that a pertuzumab-containing regimen be provided preoperatively to patients with greater than or equal to T2, or greater than or equal to N1, HER2-positive, early-stage breast cancer.

In a pooled analysis of randomized trials done by Petrelli et al (2011), it was concluded that chemotherapy and trastuzumab-based therapy should be given to patients with HER2-positive breast cancer, who will possibly undergo preoperative systemic therapy. Studies have shown that chemotherapy and dual anti-HER2 blockade related with trastuzumab and pertuzumab yield significant improvements in the pCR rate versus chemotherapy and an anti-HER2 agent in the preoperative setting (Piccart-Gebhart et al, 2011; Gianni et al, 2012, 2015).

While in the NeoSphere trial of Gianni et al (2015), findings indicate that the addition of pertuzumab to trastuzumab and docetaxel preoperatively had a statistically significant increase in pCR in the breast (16.8% increase; 95% CI, 3.5–30.1; P=0.0141). In the TRYPHAENA trial, preoperative therapy with pertuzumab and trastuzumab together with anthracycline-containing or anthracycline-free standard chemotherapy regimens to patients with operable, locally advanced, or inflammatory HER2-positive breast cancer had pCR rates of 57-66% in all treatment groups (Schneeweiss et al, 2013).

Moreover, NCCN proposes adjuvant chemotherapy with trastuzumab and endocrine therapy for patients with tumor 0.6 to <1.0 cm. Several randomized trials have reported the use of trastuzumab as adjuvant therapy in patients with HER2-positive tumors (Joensuu et al, 2006, 2009; Piccart-Gebhart et al, 2005; Goldhirsch et al, 2012; Romond et al, 2005, 2012; Slamon et al, 2011; Perez et al, 2011; Gianni et al, 2011).

In the NSABP B-31 study, HER2-positive, node-positive breast cancer patients were randomly assigned to 4 cycles of AC every 3 weeks followed by paclitaxel for 4 cycles every 3 weeks, or the same regimen with 52 weeks of trastuzumab starting with paclitaxel. And in the NCCTG N9831 trial, patients with HER2-positive breast cancer that was node-positive, or node-negative, with primary tumors >1.0 cm in size if ER- and PR-negative or >2.0 cm in size if ER- or PR-positive, were randomized wherein paclitaxel was given in a low-dose weekly schedule for 12 weeks and a third arm delayed trastuzumab until paclitaxel ended.

A joint analysis of the B-31 and NCCTG N9831 trials (n=4,045) was conducted comparing the merged control groups and merged groups using trastuzumab initiated together with paclitaxel. At 3.9 years median follow-up, there was a 48% reduction in the risk of recurrence (HR, 0.52; 95% CI, 0.45–0.60; P<0.001) and a 39% reduction in the risk of death (HR, 0.61; 95% CI, 0.50–0.75; log-rank P=0.001) (Perez et al, 2011). However, elevated cardiac toxicity was observed in patients given trastuzumab (Romond et al, 2005; Perez et al, 2008; Tan-Chiu et al, 2005). The acceptable rate of significant cardiac toxicity seen in the trastuzumab adjuvant trials demonstrates rigorous monitoring for cardiac dysfunction.

The HERA trial (n=5,081) assessed trastuzumab for 1 or 2 years compared to none following all local therapy and standard chemotherapy regimens in patients with node-

positive disease or node-negative disease with tumor  $\geq 1.0$  cm (Piccart-Gebhart et al, 2005). At a median follow-up of 1 year, there was 46% reduction in the risk of recurrence in those treated with trastuzumab versus those who did not (HR, 0.54; 95% CI, 0.43–0.67;  $P < 0.0001$ ), and there was acceptable cardiac toxicity, and no difference in OS. The 2-year data illustrate that 1 year of trastuzumab therapy is associated with an OS benefit when compared with observation (HR for risk of death = 0.66; 95% CI, 0.47–0.91;  $P = 0.0115$ ) (Smith et al, 2007). After this initial analysis, patients given chemotherapy alone crossed over to receive trastuzumab. The primary endpoint of DFS remained to be significantly higher in the trastuzumab arm (78.6%) compared to the observation group (72.2; HR, 0.76; 95% CI, 0.66–0.87;  $P < 0.0001$ ).

The adjuvant trials of trastuzumab presented clinically significant improvements in DFS, and the analysis from the NSABP B31 and NCCTG N9831 trials, and the HERA trial, denoted significant improvement in OS among trastuzumab-treated high-risk, HER2-positive breast cancer patients. NCCN suggests 12 months of adjuvant trastuzumab as the standard of care, since a shorter period is not effective and longer durations have no added benefit (Pivot et al, 2013; Goldhirsch et al, 2013).

For patients with HER2-positive, node-negative tumors  $\leq 3.0$  cm, a single-arm, multicenter trial studied the benefit of trastuzumab-based chemotherapy, wherein they received trastuzumab and weekly paclitaxel for 12 weeks, followed by completion of a year of trastuzumab monotherapy (Tolaney et al, 2013). Half of the patients had tumors  $\leq 1.0$  cm and 9% of patients had tumors 2.0-3.0 cm. Results showed that the 3-year DFS rate in the overall population was 98.7% (95% CI, 97.6–99.8;  $P < 0.0001$ ). Dual anti-HER2 blockade (trastuzumab plus lapatinib and trastuzumab plus pertuzumab) have significant improvements in the pCR rate when compared with chemotherapy associated with an anti-HER2 agent in the neoadjuvant setting (Piccart-Gebhart et al; 2013, Gianni et al, 2012; Schneeweiss et al, 2013).

The NCCN Panel has identified the combination of trastuzumab with chemotherapy as a recommendation with high-level evidence for patients with HER2-positive tumors  $> 1.0$  cm. It was prescribed that trastuzumab and chemotherapy be given to patients with HER2-positive, node-negative tumors measuring 0.6-1.0 cm (i.e., T1b) and for smaller tumors  $\leq 2.0$  mm axillary node metastases (pN1mi). This recommendation is supported by studies that had a higher risk of recurrence for patients with HER2-positive, node-negative tumors  $< 1.0$  cm compared to those with HER2-negative tumors of the same size (Chia et al, 2008). In addition, the Panel recommends AC followed by paclitaxel with trastuzumab for 1 year beginning with the first dose of paclitaxel as a preferred HER2-targeting adjuvant regimen.

### Adjuvant T-DM1 (HER2-positive)

In HER-2 positive cases, ado-trastuzumab emtansine (T-DM1) is recommended by NCCN, with a dosage of 3.6mg/kg IV day 1, coursed every 21 days for 17 cycles (NCCN, 2022).

### Research Recommendation

The GDG recommended to conduct a costing study on T-DM1.

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Question 7: What is the indication of adjuvant hormonal therapy for patients with breast cancer?

#### Recommendation 7a.

We recommend adjuvant hormonal therapy for all patients with ER/PR positive breast cancer.

*Strong recommendation, High quality of evidence*

#### Recommendation 7b.

For premenopausal women, we recommend the following:

- Tamoxifen with or without ovarian suppression/ablation
- Aromatase inhibitor with ovarian suppression/ablation

*Strong recommendation, High quality of evidence*

#### Recommendation 7c.

For postmenopausal women, we recommend aromatase inhibitor as first line treatment.

*Strong recommendation, High quality of evidence*

#### Consensus Issues

The Consensus Panel adopted the recommendations, and no other issues were raised.

#### Summary of Evidence

The panel recommends endocrine therapy for ER/PR positive premenopausal and postmenopausal women based on the recommendations of NCCN and MAHTAS. The options include tamoxifen or aromatase inhibitor (with ovarian suppression) for premenopausal women, while aromatase inhibitor is preferred among postmenopausal women.

#### Neoadjuvant Endocrine Therapy

The role of endocrine therapy in the management of breast cancer in the neoadjuvant setting still remains unclear due to concern of delayed time to clinical response (MaHTAS, 2019). Thus, its use is generally reserved for patients who are unsuitable for chemotherapy or surgery.

#### Adjuvant Endocrine Therapy - Premenopausal Period

In women who are premenopausal at diagnosis, tamoxifen may be given with or

without ovarian ablation/suppression. Ovarian ablation may be accomplished by surgical oophorectomy or by ovarian irradiation while ovarian suppression may be accomplished by utilizing luteinizing hormone-releasing hormone (LHRH) agonists (i.e., goserelin, leuprolide) dosed monthly or every 3 months.

There is insufficient data that supports the routine addition of ovarian suppression/ablation to tamoxifen. In SOFT, a randomized, phase 3 trial conducted by Francis et al (2015), which studied ovarian suppression with either tamoxifen or exemestane among premenopausal women who have undergone surgery for HR-positive breast cancer, analysis of 281 women demonstrated no significant difference was observed in DFS rate between tamoxifen with ovarian suppression (86.6%) and tamoxifen alone (84.7%) (HR 0.83; 95% CI, 0.66–1.04; P = 0.10).

The use of aromatase inhibitor with or without ovarian suppression was studied in two randomized trials (TEXT and SOFT), where premenopausal women with HR-positive early-stage breast cancer were assigned to either exemestane or tamoxifen, with ovarian suppression for a period of 5 years. Exemestane with ovarian suppression demonstrated a significantly prolonged DFS (92.8%) when compared with tamoxifen with ovarian suppression (88.8%) (HR for recurrence, 0.66; 95% CI, 0.55–0.80 P < .001) while no significant difference was observed in the OS between the two groups (HR for death in the exemestane group, 1.14; 95% CI, 0.86–1.51; P = 0.37) (Pagani et al, 2014). Based on the results of the SOFT and TEXT trials, the use of tamoxifen alone, and aromatase inhibitor with ovarian suppression are recommended for premenopausal with ER/PR positive invasive breast cancer patients.

### Postmenopausal Period

According to NCCN, evidence from ATAC, a randomized trial that enrolled postmenopausal patients with invasive operable breast cancer who had completed primary therapy and were eligible to receive adjuvant hormonal therapy, demonstrated that in 5216 postmenopausal women analyzed, the aromatase inhibitor anastrozole significantly reduced recurrences (HR for DFS, 0.85; 95% CI, 0.76–0.94; p = 0.003) when compared with tamoxifen after a median of 100 months follow-up. In the same study, anastrozole was found to be associated with lesser effects on endometrial tissue, and both anastrozole and tamoxifen have similar effects on quality of life, which was reported as not significantly impaired.

A superior effect was also observed from another aromatase inhibitor, letrozole, over tamoxifen in the BIG 1-98, a randomized, phase 3, double-blind trial that compared various adjuvant regimens of letrozole and tamoxifen in postmenopausal women with HR-positive breast cancer. A significantly prolonged disease-free survival (HR, 0.81; 95% CI, 0.70–0.93; log rank P = 0.003) was demonstrated by letrozole over tamoxifen in an early analysis among 8010 women after 2 years of treatment. Overall incidence of cardiac adverse events was similar in both letrozole (4.8%) and tamoxifen (4.7%) in the said trial.

## Research Recommendation

The GDG recommended to conduct a costing study on adjuvant hormonal therapy as part of the standard breast cancer management.

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Question 8: What are the indications for bone-modifying agents for patients with breast cancer?

#### Recommendation 8a.

<p>We recommend zoledronic acid or denosumab for the following:</p> <ul style="list-style-type: none"><li>• Postmenopausal women invasive breast cancer on aromatase inhibitor with high risk of recurrence (<i>High quality of evidence</i>)</li><li>• Osteoporotic patients (<i>High quality of evidence</i>)</li><li>• Stage IV breast cancer with bone metastases (<i>High quality of evidence</i>)</li></ul> <p style="text-align: right;"><i>Strong recommendations</i></p>
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#### Consensus Issues

While a panelist raised the issue of cost, the panel still decided to give a strong recommendation due to high quality of evidence. As with all medications, potential adverse effects must also be discussed thoroughly with the patient.

#### Summary of Evidence

##### Bisphosphonates

In the Austrian Breast and Colorectal Study Group trial-12 (ABCSG-12) trial for patients older than 40 years, zoledronic acid significantly reduced the risk of recurrence by 34% and the risk of death by 49%. However, no improvement was seen in either DFS or OS in this post hoc analysis among patients younger than 40 years. In a planned subgroup analysis of the AZURE trial, zoledronic acid improved DFS in patients who were more than 5 years since menopause at trial entry. A meta-analysis of data from seven adjuvant bisphosphonate trials (AZURE, ABCSG-12, ZO-FAST, Z-FAST, EZO-FAST, NSABP-B34, GAIN), including only those known to be aged 50 years or older, postmenopausal, or with ovarian suppression, showed a significant benefit for the use of adjuvant bisphosphonates in patients with a low-estrogen state and early-stage breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBTCG) conducted a meta-analysis of 26 randomized adjuvant bisphosphonate studies and reported evidence that adjuvant bisphosphonates provide benefits to postmenopausal (natural or induced) patients with breast cancer. With bisphosphonate therapy, the greatest improvement was seen in bone recurrence and bone fractures. No effect was seen on distant recurrence outside bone. In premenopausal patients, bisphosphonate therapy did not seem to have a significant effect on bone recurrence. However, in postmenopausal patients, zoledronic acid significantly reduced bone recurrence; the difference in breast cancer mortality was not statistically significant. The suggested dosage is 4 mg intravenously every 6 months for 3 years (Gnant et al, 2011).

## Denosumab

In the adjuvant setting, the ABCSG-18 trial studied the effect of denosumab in postmenopausal patients treated with adjuvant aromatase inhibitors (AIs) and showed a reduction in clinical fractures. Subsequently in an interim analysis, an improvement in DFS was reported yet there is no available data showing an OS benefit with denosumab. The dosage is set at 60 mg administered subcutaneously every 6 months (Gnant et al, 2015).

The optimal duration of either therapy has not been established. Patients on an adjuvant aromatase inhibitor should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter.

## Research Recommendation

The GDG recommended no additional research.



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Question 9: What are the indications for radiation therapy for patients with breast cancer?

Recommendation 9a.

We recommend adjuvant radiation therapy using whole breast RT with or without boost following breast conserving surgery for DCIS patients.

*Strong recommendation, High quality of evidence*

Recommendation 9b.

Hypofractionated Whole Breast Irradiation (HF-WBI) may be used as an alternative to conventional fractionation (CF-WBI).

*Weak recommendation, Low quality of evidence*

Recommendation 9c.

For patients with invasive breast cancer, we recommend adjuvant radiation therapy using whole breast radiation therapy with or without boost for women who received breast conserving surgery with negative axillary nodes.

*Strong recommendation, High quality of evidence*

Recommendation 9d.

For women with invasive breast cancer receiving whole breast irradiation with or without inclusion of low axilla, the preferred dose-fractionation scheme is hypofractionated WBI.

*Strong recommendation, High quality of evidence*

Recommendation 9e.

We recommend WBRT with nodal irradiation for patients who had partial mastectomy with involvement of the lymph node; T3 or T4 primary lesion; and T2 lesion with at least 2 other high-risk features (fewer than 10 axillary nodes removed, high grade histology, ER negativity, lymphovascular invasion).

*Strong recommendation, High quality of evidence*

Recommendation 9f.

We recommend chest wall with lymph node irradiation in patients who underwent total mastectomy with T3 or T4 primary lesion; involvement

of the lymph node; T2 with 2 or more high-risk features (young age, triple negative, high grade histology, LVI); close margin.

*Strong recommendation, High quality of evidence*

#### Recommendation 9g.

We recommend chest wall with or without lymph node irradiation, for postmastectomy patients with positive margin and re-excision is not feasible.

*Strong recommendation, High quality of evidence*

#### Recommendation 9h.

We recommend adjuvant RT using whole breast radiation in patients who underwent breast conserving surgery and neoadjuvant chemotherapy.

*Strong recommendation, Low quality of evidence*

#### Recommendation 9i.

We recommend adjuvant RT in postmastectomy patients who underwent neoadjuvant chemotherapy AND presenting with the following:

- residual nodal disease
- T3, T4, or node-positive disease regardless of response

*Strong recommendation, Low quality of evidence*

#### Recommendation 9j.

For patients with no response to neoadjuvant chemotherapy and in whom the tumor remains inoperable or who develop disease progression during neoadjuvant chemotherapy, additional systemic therapy with or without preoperative palliative radiation may be considered in an attempt to enhance local control.

*Weak recommendation, Low quality of evidence*

#### Recommendation 9k.

We recommend the use of HF-WBI over CF-WBI for any age, stage and chemotherapy.

*Strong recommendation, Low quality of evidence*

#### Recommendation 9l.

We suggest CF-WBI over HF-WBI when treating primary breast cancer with rare histologies that are most commonly treated with conventional fractionation when arising in other parts of the body.

*Weak recommendation, Low quality of evidence*

#### Recommendation 9m.

We suggest HF-WBI for patients with breast cancer, and with breast augmentation or collagen vascular disease.

*Weak recommendation, Low quality of evidence*

#### Recommendation 9n.

We recommend regional nodal irradiation among breast cancer patient with the following conditions:

- a. Patient who underwent breast conserving surgery with a positive axillary lymph node.
- b. Patient who underwent total mastectomy with 4 or more positive axillary nodes.

*Strong recommendation, High quality of evidence*

#### Recommendation 9o.

We suggest comprehensive regional nodal irradiation among breast cancer patient with the following conditions:

- a. Patient who underwent breast conserving surgery with a negative axillary lymph node but with any of the following:
  - with central/medial tumors
  - pT3 tumors
  - pT2 tumors, with <10 axillary nodes removed and one of the following high-risk features: grade 3, extensive lymphovascular invasion [LVI], or ER-negative
- b. Patient who underwent total mastectomy and with any of the following:
  - 1-3 positive axillary nodes
  - Negative axillary nodes and tumor ≤ 5cm and negative margins but <1 mm with additional high-risk features (central/medial tumors or tumor ≥ 2cm with <10 axillary nodes removed and at least one of the following: grade 3, ER-negative or

lymphovascular invasion)

- Negative axillary nodes and tumor >5 cm
- Margins positive and when re-excision to negative is not feasible.

*Weak recommendation, Low quality of evidence*

#### Recommendation 9p.

For whole breast with nodal irradiation ( $\pm$  tumor bed boost) and chest wall with nodal irradiation ( $\pm$  scar boost), we recommend using conventional fractionation.

*Strong recommendation, High quality of evidence*

#### Consensus Issues

The Panel members adopted these recommendations regarding radiation therapy. However, they have noted that availability, accessibility, and affordability are all important considerations that must be discussed with all patients.

It was suggested as well to use APBI as an alternative after partial mastectomy for patients with screen-detected DCIS, low to intermediate nuclear grade, tumor size  $\leq$  2.5cm and resected with margins negative at  $\geq$  3mm. Additionally, it can be an alternative to whole breast radiation therapy for patients with invasive ductal carcinoma, age  $\geq$  50y/o, tumor measuring  $\leq$  2cm (pT1 disease) with negative margin widths of  $\geq$ 2mm, no LVI, ER-positive and BRCA negative.

The Panel noted that for patients who require limited number of treatment visits for WBRT delivery, ultra-hypofractionated WBRT of 28.5Gy should be delivered as 5 (once-a-week) fractions, in selected patients aged  $\geq$ 50 years following BCS with pTis/T1/T2/N0 tumors. And in patients >70 years of age, with ER-positive, cN0, T1 tumors who receive adjuvant endocrine therapy, breast irradiation should be omitted.

For DCIS patients, postmastectomy radiation therapy should not be routinely given. Its consideration should be based on an individualized risk for local recurrence such as proximity of lesion to margins of resection or on the basis of a positive margin upon pathologic review of the surgical specimen.

On the other hand, the decision to offer hypofractionated therapy should be independent of the following factors: tumor grade, whether the tumor is in the left or right breast, prior chemotherapy, prior or concurrent trastuzumab or endocrine therapy, and breast size provided that homogenous dosing can be achieved. It may then be independent of the following factors: hormone receptor status, HER2 receptor

status, margin status following surgical resection, and age.

The Panel pointed out that some radiation oncologists already use hypofractionated RT in some patients. The use of conventional fractionated radiotherapy is still the standard of care in radiotherapy to chest wall and RNI but recent studies show promising results with the use of hypofractionated RT. In a randomized phase III trial in 2019 by Wang et al, comparing postmastectomy hypofractionated radiotherapy (43.5 Gy in 15 fractions over 3 weeks) with conventional fractionated radiotherapy (50 Gy in 25 fractions over 5 weeks) in 820 patients with high-risk breast cancer, it was found that hypofractionated radiotherapy is non-inferior to conventional fractionated radiotherapy in terms of 5-year locoregional recurrence. Overall survival and disease-free survival are similar in both arms.

## Summary of Evidence

### Adjuvant RT using WBRT (with or without boost)

#### *RT after Breast-Conserving Surgery for DCIS and Invasive Breast Cancer*

Breast conserving therapy (BCT) includes lumpectomy to remove the tumor with negative surgical margins followed by WBRT to eradicate any residual microscopic disease. Several studies showed that the addition of WBRT after lumpectomy decreases the rate of in-breast disease recurrence (Fisher et al, 1998, Houghton et al; 2003; Julien et al, 2000; Cuzick et al, 2011; Wapnir et al, 2011; McCormick et al, 2015; Holmberg et al, 2008; Goodwin et al, 2009) and ipsilateral breast events (Sagara et al, 2016) both for DCIS and invasive breast cancer. Among patients with higher-risk DCIS (e.g., higher nuclear grade, younger age, and larger tumor size), a statistically significant improvement in survival was demonstrated (Bartelink et al, 2007). However, most studies fail to demonstrate this beneficial effect on overall survival and mortality (all-cause and breast cancer-specific) of DCIS patients in most studies (Holmberg et al, 2008; Goodwin et al, 2009; Sagara et al, 2016; Bartelink et al, 2007; Giannakeas et al, 2018).

Both MaHTAS and NCCN recommend adjuvant WBRT among patients with invasive breast cancer who had BCS with clear margin or negative axillary nodes. With WBRT offering a reduction in the risk of local recurrence, the benefit of reducing breast cancer death was also demonstrated in a meta-analysis conducted by EBCTCG (absolute reduction 3.8%, 1.6-6.0, 2p=0.00005) among this group of patients. (Ben-Aharon et al, 2013; Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2011; Darby et al, 2011; NCCN, 2022; MaHTAS, 2019)

#### *RT After Preoperative Therapy and BCS or Mastectomy:*

With the key evidence available, NCCN recommends that adjuvant WBRT be given to

those who have clinically negative nodes at diagnosis, that remain pathologically node-negative at definitive surgery with neoadjuvant therapy; and to those who have clinically positive nodes at diagnosis that respond to neoadjuvant therapy and become node-negative.

### RT Boost

The use of RT boost has been demonstrated to provide a small but statistically significant reduction in IBTR risk (4% at 20 years) and rate of local relapse in all age groups for invasive breast cancers (Bartelink et al, 1997, 2015; Romestaing et al, 1997; Polgar et al, 2002; Moran et al, 2017). Randomized trials have demonstrated decreased in-breast recurrences with an additional boost dose of radiation (by photons, brachytherapy, or electron beam) to the tumor bed. The panel recommends whole breast irradiation to include breast tissue in entirety.

### Accelerated Partial Breast Irradiation (APBI)

Randomized clinical trials (Coles et al, 2017; Livi et al, 2015; Meattini et al, 2020; Olivotto et al, 2013; Polgar et al, 2021; Strnad et al, 2016; Vicini et al, 2019; Whelan et al, 2019) comparing APBI with standard WBRT suggest that rates of local control in selected low-risk patients with early-stage breast cancer in both groups are comparable. However, some studies (Olivotto et al, 2013; Whelan et al, 2019) showed increased rates of adverse cosmesis and late radiation toxicity with external beam delivery methods of APBI compared to standard WBRT.

**Table 8.** RT Dosing (Adapted from NCCN, 2022)

<b>Regimen</b>	<b>Method</b>	<b>Reference</b>
30 Gy/5 fractions QOD (preferred)	External Beam RT (EBRT)	Livi, L., Meattini, I., Marrazzo, L., Simontacchi, G., Pallotta, S., Saieva, C., ... & Bianchi, S. (2015). Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. <i>European journal of cancer</i> , 51(4), 451-463.  Meattini, I., Marrazzo, L., Saieva, C., Desideri, I., Scotti, V., Simontacchi, G., ... & Livi, L. (2020). Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-Florence trial. <i>Journal of Clinical Oncology</i> , 38(35), 4175-4183.
40 Gy/15	EBRT	Coles, C. E., Griffin, C. L., Kirby, A. M., Titley, J.,

fractions		Agrawal, R. K., Alhasso, A., ... & Thompson, A. (2017). Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. <i>The Lancet</i> , 390(10099), 1048-1060.
34 Gy/10 fractions BID	Balloon /Interstitial	Vicini, F. A., Cecchini, R. S., White, J. R., Arthur, D. W., Julian, T. B., Rabinovitch, R. A., ... & Wolmark, N. (2019). Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. <i>The Lancet</i> , 394(10215), 2155-2164.
38.5 Gy/10 fractions BID	EBRT	Whelan, T. J., Julian, J. A., Berrang, T. S., Kim, D. H., Germain, I., Nichol, A. M., ... & El-Sayed, S. (2019). External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. <i>The Lancet</i> , 394(10215), 2165-2172.

### *Intraoperative Radiation Therapy (IORT)*

In TARGIT-A randomized clinical trial, eligible patients for intraoperative radiation therapy (IORT) are age 45y/o and above, diagnosis established by needle biopsy, unifocal invasive ductal carcinoma preferable  $\leq 3.5\text{cm}$ , cN0-1, and breast conserving surgery feasible (Vaidya et al, 2020). If high risk factors are found on final pathology, supplemental EBRT is recommended. Radiation is delivered using 50kv energy x-ray. The prescribed dose delivered is 20Gy at the surface of the tumor bed. This dose attenuates 5-7Gy at 1cm depth.

### Hypofractionated Whole Breast Irradiation (HF-WBI)

Observational, case series and population-based studies showed that HF-WBI demonstrated excellent local control outcomes among DCIS patients (Romestaing et al, 1997; Polgar et al, 2002; Moran et al, 2017; Di Saverio et al, 2008). In a population-based study among DCIS treated with lumpectomy and CF-WBI or HF-WBI, HF-WBI was not associated with increased risk of local recurrence compared to CF-WBI (HR=0.8, 95% 0.5-1.2) (King et al, 2020). In TROG 07.01, a phase-3 clinical trial, a better body image and sexuality was also reported by HF-WBI patients ( $-1.10$  [95% CI  $-1.79$  to  $-0.42$ ],  $p=0.0016$  when effects of HF-WBI and CF-WBI were compared (Group et al, 2008).



Among patients with invasive breast cancer receiving WBRT, HF-WBI is the dose scheme recommended. Randomized clinical trials have investigated HF-WBI schedules (39–42.9 Gy in single fractions of 2.6–3.3 Gy) compared to standard 50 Gy in single fractions of 2 Gy (Group et al, 2008; Owen et al, 2006; Whelan et al, 2010; Haviland et al, 2013). Results demonstrated that the local tumor control and breast cosmesis were similar between the two. The START trials reported radiation-related effects to normal breast tissue such as breast shrinkage, telangiectasia, and breast edema as less common with the hypofractionated fraction regimen (Haviland et al, 2013). The NCCN Panel recommends for whole breast irradiation, a dose of 46–50 Gy in 23-25 fractions or 40–42.5 Gy in 15–16 fractions with (40–42.5 Gy in 15–16 fractions) as the preferred option (NCCN, 2022).

#### *Recommendation for boost dose following hypofractionation*

In the absence of strong risk factors for local recurrence, 10 Gy in 4-5 fractions is suggested as standard tumor bed boost dose-fractionation, regardless of whole breast dose-fractionation, stage, or histology (Smith et al, 2018).

#### Conventional fractionation (CF-WBI).

Before hypofractionated radiation treatment became an option, most women with breast CA have received conventionally fractionated whole breast irradiation (CF-WBI), with a total dose of 45 to 50 Gy in daily fractions of 1.8 to 2.0 Gy over 25-28 fractions to the whole breast (Sherriff, 2021).

The NCCN recommends considering the use of a conventionally fractionated dosing in selected cases, as an alternative to the hypofractionated dose of 40.0-42.5 Gy (National Comprehensive Cancer Network, 2021). Following breast conserving therapy, WBRT lowers the rate of locoregional recurrence and the risk of death from breast cancer. The 2011 meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) that included around 10,000 women who were known to be pathologically node -negative or -positive in 17 trials demonstrated the benefits of WBRT. In comparison to breast-conserving surgery alone, the 10-year risk of any first recurrence is reduced by about 50% (19% versus 35%, respectively; RR 0.52, 95% CI 0.48-0.56). The drop in the recurrence rate linked with RT was attributable to a decline in locoregional recurrences rather than distant recurrences. There was also a reduction in the 15-year risk of breast cancer death (21% versus 25%; RR 0.82, 95% CI 0.75-0.90) (Darby et al, 2011).

A meta-analysis of data from a ten-year follow-up of START-A and START-B trials suggests that there was no significant difference between the shorter fractionation and conventionally dosed RT schedules. Specifically, the proportion of patients with a 10-year local-regional relapse had no significant difference between the 40 Gy group

(4.3%, 95% CI 3.2-5.9) and the 50 Gy group (5.5%, 95% CI 4.2-7.2; HR 0.77, 95% CI 0.51-1.16;  $p=0.21$ ), irrespective of the patient's age, type of primary surgery, axillary node status, tumor grade, administration of adjuvant chemotherapy, or the use of a tumor-bed boost RT (Haviland et al, 2013).

### Chest wall with lymph node irradiation

According to NCCN, for patients with positive margins and other risk factors, radiation is given to chest wall + RNI. For patients wherein positive margins are the only risk factor, radiation may be given to chest wall only.

Chest wall irradiation targets the ipsilateral chest wall, mastectomy scar, and drain sites if indicated. The recommended dose is 45.0 to 50.4 Gy in 25 to 28 fractions to the chest wall (with or without scar boost) at 1.8 to 2.0 Gy per fraction. This has a total dose of around 60 to 68 Gy (National Comprehensive Cancer Network, 2021).

In at least two studies, regional node and chest wall irradiation are associated with reduced rates of locoregional recurrence and improved long-term survival rates among high-risk breast cancer patients. In the 20-year British Columbia Randomized Radiation Trial, postmastectomy chemotherapy plus radiation therapy including all regional lymph nodes and the chest wall had a statistically significant improvement in all study end points, including survival free of isolated locoregional recurrences (74% versus 90%, respectively; RR = 0.36, 95% CI = 0.18 to 0.71;  $P = .002$ ), systemic relapse-free survival (31% versus 48%; RR = 0.66, 95% CI = 0.49 to 0.88;  $P = .004$ ), breast cancer-free survival (48% versus 30%; RR = 0.63, 95% CI = 0.47 to 0.83;  $P = .001$ ), event-free survival (35% versus 25%; RR = 0.70, 95% CI = 0.54 to 0.92;  $P = .009$ ), breast cancer-specific survival (53% versus 38%; RR = 0.67, 95% CI = 0.49 to 0.90;  $P = .008$ ), and, in contrast to the 15-year follow-up results, overall survival (47% versus 37%; RR = 0.73, 95% CI = 0.55 to 0.98;  $P = .03$ ). Long-term toxicities, including cardiac deaths (1.8% versus 0.6%), were minimal for both arms. Survival outcomes were significantly improved as well, with a statistically significant 32% reduction in breast cancer mortality in the chemotherapy plus radiation therapy group over the chemotherapy-alone group and a 27% reduction in overall mortality (Ragaz et al, 2005). A study about the failure pattern among high-risk breast cancer patients from the Danish Breast Cancer Cooperative Group DBCG 82 b and c showed that the 18-year probability of any first breast cancer event was 73% for no radiotherapy (RT) and 59% for those with RT ( $P < 0.001$ ), respectively (RR, 0.68; 95% CI, 0.63 to 0.75). For the 18-year probability of locoregional recurrences with or without distant metastases was 49% for no RT and 14% ( $P < 0.001$ ), respectively (RR, 0.23; 95% CI, 0.19 to 0.27). Also, the 18-year probability of distant metastases after locoregional recurrences was 35% after no RT and 6% after RT ( $P < .001$ ) (RR, 0.15; 95% CI, 0.11 to 0.20), whereas the probability of any distant metastases was 64% after no RT, and 53% after RT ( $P < .001$ ) (RR, 0.78; 95% CI, 0.71 to 0.86). It is important to note that the RT in this study was intended to cover the chest wall and regional lymph nodes,

which include the axillary, supra/infraclavicular, and ipsilateral mammary nodes (Nielsen et al, 2006).

A large meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) pooled data from 22 randomized trials comparing mastectomy with or without adjuvant radiation therapy. The result showed that among patients with four or more positive nodes, post-mastectomy RT (directed at the chest wall and regional lymph nodes) had a 19% reduction in locoregional recurrence and a 9% decrease in breast cancer mortality (McGale et al, 2014).

### Regional nodal irradiation

Several studies, such as the MA.20 and EORTC 22922/10925 trials have assessed the benefit of regional nodal irradiation (RNI) to the internal mammary nodes and the upper axillary nodes including the supraclavicular region, in addition to WBRT or chest wall irradiation after BCS or mastectomy, respectively. In the MA.20 study, regional recurrences decreased from 2.7% with breast irradiation only to 0.7% when nodal irradiation was added, while distant recurrences lessened from 17.3% to 13.4%. DFS also improved from 77% to 82% at 10 years for patients who were given RNI (Whelan et al, 2015).

For the EORTC 22922/10925 trial, regional RT aided in reducing the incidence of regional recurrences from 4.2% to 2.7% and rate of distant metastases from 19.6% to 15.9% at a median follow-up of 10.9 years (Poortmans et al, 2015). At 15.7 years follow-up, breast cancer mortality (19.8% versus 16%; 95% CI, 0.70–0.94) and breast cancer recurrence (27.1% versus 24.5%; 95% CI, 0.77%–0.98%) decreased with internal mammary and medial supraclavicular RT (Poortmans et al, 2020). However, routine inclusion of the internal mammary nodes as a component of RNI is somewhat disputed due to a higher risk of cardiac and lung toxicity, and data are inconsistent on its advantages.

In a Korean trial labelled KROG 08-06, patients were assigned to RNI with internal mammary RT and RNI without internal mammary RT, in order to evaluate the independent effect on DFS of RT to internal mammary nodes after BCS or mastectomy for node-positive disease. Radiation to the internal mammary nodes showed a statistically significant benefit in patients with medially or centrally located tumors (Kim et al, 2022). In the Danish Breast Cancer Cooperative Group study among cases with positive nodes and early-stage breast cancer, RT to the internal mammary nodes was delivered to right-sided patients (n=1,491), and no RT to internal mammary nodes for left-sided patients (n=1,598). Results indicated a 15-year improved OS rate of 60.1% with RT to internal mammary nodes versus 55.4% with no RT to internal mammary nodes. There were also benefits seen in terms of risk of developing distant recurrence and breast cancer-specific mortality favoring RT to internal mammary nodes (Thorben et al, 2022).

Nevertheless, clinical judgment is necessary when determining inclusion of the internal mammary nodes in RNI. The NCCN Panel noted that patient selection must evaluate risks and benefits involving long-term organ (cardiac and lung) toxicities, comorbidities of the patient, age, and life expectancy. In including RT to the internal mammary nodes, it is required to conduct meticulous treatment planning with normal tissue dose constraints. It was also advocated to consider comprehensive RNI in patients with central/medial tumors (in compliance with EORTC 22922 trial criteria) and in accordance with the MA.20 criteria: 3 tumors, patients with T2 tumors who have undergone limited axillary dissection (<10 lymph nodes) and have other risk factors, i.e., high-grade histology, ER-negative disease, or LVI (Whelan et al, 2015).

**Table 9.** Indications for RT in Patients who Underwent Neoadjuvant Therapy and BCS (Adapted from NCCN, 2022)

Subset of patients	Post-lumpectomy RT
cN+ and ypN0	WBRT ± RT boost <sup>a</sup> ; strongly consider RNI
Any ypN+	WBRT ± RT boost <sup>a</sup> ; RNI
Any cN0, ypN0	WBRT ± RT boost

<sup>a</sup> Strongly consider RT boost for high-risk features (e.g., high-grade disease, age <50 years)

**Table 10.** Indications for RT in Patients who Underwent Neoadjuvant Therapy and Mastectomy (Adapted from NCCN, 2022)

Subset of patients	Management
cN+ and ypN0 <sup>a</sup>	Adjuvant systemic therapy; strongly consider RT to the chest wall and RNI
Any ypN+	Adjuvant systemic therapy; RT is indicated to the chest wall + RNI
Any cN0, ypN0 <sup>a, b</sup>	Adjuvant systemic therapy without adjuvant RT

<sup>a</sup> ypN0 patients with TNBC and additional high-risk features (i.e., residual invasive breast disease, young age, and lymphovascular space invasion) may still benefit from regional nodal irradiation

<sup>b</sup> if axilla was assessed by SLNB or axillary node dissection

NCCN mentioned that in the case of a micrometastasis (>0.2 to ≤2.0 mm), and no axillary dissection, other patient risk factors should be evaluated when considering RT for patients with 1-3 positive axillary nodes after completion of mastectomy and axillary staging.

### Sequencing of RT and Systemic Therapy

Adjuvant radiotherapy is typically administered after the completion of chemotherapy (NCCN, 2022). The basis for this recommendation is a randomized trial of 244 patients

with Stage I or II breast cancer who have undergone breast-conserving surgery randomly assigned to receive chemotherapy either before or after radiation therapy (Recht et al, 1996). The median length of follow-up was 58 months. The chemotherapy-first regimen was associated with higher rates of overall survival and lower rates of distant metastases compared with the RT-first regimen. However, the local recurrence was higher in the chemotherapy-first regimen.

In an updated analysis of the same randomized trial, with a median follow-up of 135 months, there were no significant differences between the CT-first and the RT-first arms in time to any event (e.g., breast cancer recurrence, contralateral breast cancer, second malignancy), distant metastasis, or death (Bellon et al, 2005).

The SECRAB trial randomized 2,297 patients with invasive, early-stage breast cancer to sequential treatment (chemotherapy followed by RT) or synchronous treatment (RT given concurrently with chemotherapy) (Fernando et al, 2020). Chemotherapy regimens included CMF and anthracycline-CMF. After 10.2 years of median follow-up, statistical analysis showed significantly improved local recurrence rates associated with synchronous chemo-RT compared to sequential treatment. The greatest benefit was seen in patients treated with the anthracycline-CMF regimen.

The results of multiple studies (i.e., Ahn et al, 2005; Harris et al, 2005; Li et al, 2016; Pierce et al, 2005) show that there is no difference in outcomes or toxicity in breast cancer patients treated with endocrine therapy either before, during, or after RT. According to NCCN, sequential or concurrent endocrine therapy with RT may be administered. However, endocrine therapy after RT may be preferred to avoid compounding side effects.

According to NCCN, adjuvant capecitabine, when indicated, should be given after adjuvant RT due to its potential to increase toxicity to normal tissue.

### Research Recommendation

The GDG recommended no additional research.

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## Question 10: What is the role of genomic testing in breast cancer?

### Recommendation 10a.

We recommend 21-gene RT-PCR assay among HR-positive, HER-2 negative patients and:

- Premenopausal with tumor size >0.5 cm and pN0 stage:
- Postmenopausal with tumor size >0.5 cm, or pN1Mi or pN1 stage:
- If they are candidate for chemotherapy.

*Strong recommendation, High quality of evidence*

### Consensus Issues

The Consensus Panel adopted the recommendation, and noted that applicability, availability, and affordability are issues for implementation.

### Summary of Evidence

These recommendations were adapted from the NCCN Guideline for Breast Cancer Version 8.2021. The NCCN recommendations were based on several studies described below.

#### HR-positive, HER2-negative, node-negative breast cancer

A report that tested for interaction between chemotherapy benefit and Recurrence Score among women with node-negative, ER-positive breast cancer found that:

1. Patients with high-RS ( $\geq 31$ ) tumors (ie, high risk of recurrence) had a large benefit from chemotherapy (RR, 0.26; 95% CI, 0.13 to 0.53; absolute decrease in 10-year distant recurrence rate: mean, 27.6%; SE, 8.0%).
2. Patients with low-RS ( $< 18$ ) tumors derived minimal, if any, benefit from chemotherapy treatment (RR, 1.31; 95% CI, 0.46 to 3.78; absolute decrease in distant recurrence rate at 10 years: mean, 1.1%; SE, 2.2%).
3. Patients with intermediate-RS tumors did not appear to have a large benefit, but the uncertainty in the estimate cannot exclude a clinically important benefit.

A prospective, randomized trial of endocrine therapy (ET) versus chemoendocrine therapy (CET) in HR-positive, HER2-negative, node-negative breast cancer patients with an intermediate recurrence score of 11-25, showed that ET was non-inferior to CET in terms of invasive disease-free survival (iDFS), distant recurrence-free interval (DRFI), recurrence-free interval (RFI), and overall survival (OS).

## HR-positive, HER2-negative, node-positive breast cancer

The findings of a retrospective analysis of clinical outcomes (distant recurrence, 5-yr breast cancer death rates) in breast cancer patients who were treated according to the RS results support the use of endocrine therapy alone in ER-positive, HER2-negative breast cancer patients with micrometastases or 1-3 positive nodes and a low RS score (< 18). The West German Study Group Phase III PlanB Trial showed that the 3-year disease-free survival in node-positive, HR-positive, HER2-negative breast cancer patients with RS  $\leq$  11 treated with endocrine therapy alone was 98%. These studies suggest that the absolute benefit from chemotherapy is likely to be small in patients with limited nodal disease (1-3 positive lymph nodes) and a low recurrence score.

A retrospective analysis for postmenopausal women with node-positive, ER-positive breast cancer showed that CAF therapy (adjuvant chemotherapy) provides a significant benefit in tumors with a high RS ( $\geq$  31) while it provides no benefit in the low RS (< 18) group.

The benefit of chemotherapy in patients with limited lymph node involvement and a recurrence score of 25 or below remains to be determined.

Other assays available:

1. 70-gene assay (MammaPrint):  
Results from the randomized MINDACT trial demonstrated that the 70-gene assay can identify a subset of patients who have a low likelihood of distant recurrence despite high-risk clinical features (based on tumor size, grade, nodal status).  
It was found that the MammaPrint assay does not have clinical utility in HR-positive, HER2-negative, node-negative breast cancer patients in the low clinical risk category. Definitive data are lacking in the use of MammaPrint assay in patients with HR-positive, HER2-negative, node-positive breast cancer at low clinical risk and in patients with HER2-positive or triple-negative breast cancer (Cardoso et al, 2016).
2. 50-gene assay (PAM50):  
The 50-gene assay (PAM-50) risk of recurrence (ROR) score stratifies patients with HR-positive disease into high, medium, and low risk groups. Several studies have demonstrated the prognostic value of ROR score in estimating risk of disease recurrence.
3. 12-gene assay (EndoPredict):  
This assay appears to be useful in identifying a subgroup of patients with ER-positive, HER2-negative tumors with very low risk of recurrence without adjuvant chemotherapy and helpful in identifying patients at low risk for a late recurrence.
4. Breast Cancer Index:  
The Breast Cancer Index (BCI) is a combination of two profiles, the

HOXB13-to-IL17BR expression ratio (H:I ratio) and the Molecular Grade Index (MGI). Compared with clinical prognostic factors (e.g., age, tumor size, tumor grade, and lymph node status), the H:I ratio has been shown to be prognostic in the setting of adjuvant tamoxifen monotherapy.

The 21-gene assay (Oncotype Dx) is preferred by NCCN for prognosis and prediction of chemotherapy benefit. Other gene expression assays can provide prognostic information but cannot predict chemotherapy benefit (NCCN, 2022).

### Research Recommendation

The GDG recommended to conduct a costing study in setting up breast cancer centers with genomic testing capability.

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## Question 11: What are the recommended fertility preservation and birth control measures among premenopausal breast cancer patients?

### Recommendation 11a.

We recommend that the cancer team discuss to all premenopausal patients the impact of cancer and its treatment such as chemotherapy, endocrine therapy and, radiotherapy on fertility and be asked about their desire for future pregnancies. Patients who may desire future pregnancies should be referred to fertility specialists before starting treatment to discuss options.

*Strong recommendation, Low quality of evidence*

### Recommendation 11b.

We recommend that patients should not become pregnant during or within 1 year of treatment with radiotherapy, chemotherapy, endocrine therapy, or targeted therapy.

*Strong recommendation, High quality of evidence*

### Recommendation 11c.

Fertility preservation options such as oocyte or embryo freezing should be offered to BRCA 1 and 2 mutation carriers due to risk of premature menopause or premature ovarian insufficiency.

*Strong recommendation, Low quality of evidence*

## Consensus Issues

The Panel members selected to adopt these recommendations, and early referral to fertility specialists should be emphasized since this provides more options for fertility preservation. Also, patients and physicians must be informed that a hormone-dependent breast cancer patient may safely undergo ovarian stimulation for fertility preservation by adding letrozole, which minimizes serum levels of estrogen.

## Summary of Evidence

These recommendations were adapted from the NCCN Guideline for Breast Cancer Version 8.2021 and the NICE guideline on fertility problems. The NCCN recommendations were based on several articles outlining the risks of infertility from breast cancer treatment and studies demonstrating the benefit of addressing fertility preservation among patients with breast cancer before commencing therapy.

Considerations for fertility preservation should incorporate patient preference; tumor stage and biology (which determine the urgency, type, and sequence of treatment); age of the patient; risk of premature ovarian failure based on anticipated type and duration of chemotherapy and/or endocrine therapy; as well as the timing and duration allowed for fertility preservation.

Although data are limited, hormone-based birth control is discouraged regardless of the HR status of the patient's cancer. Alternative methods of birth control include intrauterine devices (IUDs), barrier methods, or, for patients with no intent of future pregnancies, tubal ligation, or vasectomy for the partner.

### Research Recommendation

The GDG recommended no additional research.

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## Treatment (Surgical)

Question 12: What is the recommended surgical management for patients with breast cancer?

### Recommendation 12a.

#### **Non-invasive (DCIS)**

We recommend the following options:

- Partial mastectomy with whole breast radiation therapy (breast conserving therapy) OR total mastectomy.
- SLNB may be performed for patients undergoing total mastectomy and selected patients undergoing breast conserving surgery.
- We recommend further surgery (re-excision or mastectomy) after partial mastectomy for positive or less than 2 mm margins.

*Strong recommendation, High quality of evidence*

### Recommendation 12b.

#### **Invasive**

We recommend the following options:

- Partial mastectomy with whole breast radiation therapy (breast conservation therapy) with surgical axillary staging; OR total mastectomy with surgical axillary staging among patients.
- Breast reconstruction should be offered to women undergoing mastectomy; including those who may need radiotherapy.
- We recommend further surgery (re-excision or mastectomy) after partial mastectomy for positive margins (tumor on ink).

*Strong recommendation, High quality of evidence*

### Consensus Issues

These recommendations based on the NCCN Guidelines for Breast Cancer (2021) and the NICE Guideline on the diagnosis and management of early and locally advanced breast cancer (2018), were adopted by the Consensus Panel. The members suggested further surgery (re-excision or mastectomy) among women who have had breast-conserving surgery where invasive cancer and/or DCIS is present within 2mm of, but not at, the radial margins (greater than 0mm and less than 2mm) to minimize the risk of local recurrence.

Re-excision to achieve negative margins is preferred but acceptability and cost may be an issue to the patient. Majority of patients will not be able to afford breast

reconstruction, even those with private insurance. In the future, perhaps the Philippine Health Insurance Corporation (PhilHealth) can consider covering the cost of reconstruction as it is not merely a cosmetic procedure. A panelist also raised that breast reconstruction is not merely a cosmetic procedure and should be discussed with patients who are appropriate candidates.

### Summary of Evidence

For primary treatment of DCIS, the aim is to prevent progression to invasive breast carcinoma. The management strategies include surgery, radiation therapy, and adjuvant endocrine therapy.

Excision of DCIS using either mastectomy or a breast-conserving approach (i.e., lumpectomy with or without WBRT) are the primary treatment options for individuals with DCIS. Breast-conserving therapy (BCT) includes lumpectomy to remove the tumor with negative surgical margins followed by WBRT to eradicate any residual microscopic disease.

According to NCCN, BCT includes lumpectomy to remove the tumor with negative surgical margins succeeded by WBRT for removal of residual microscopic disease. There have been multiple prospective randomized trials of pure DCIS such as: Bijker et al (2006), Emdin et al (2006), Fisher et al (1998), Houghton et al (2003), Julien et al (2000), Cuzick et al (2011), Wapnir et al (2011), McCormick et al (2015), and Holmberg et al (2008) which exhibited that the addition of WBRT after lumpectomy decreases the rate of in-breast disease recurrence, or distant metastasis-free survival.

On the other hand, in the RTOG 9804 trial, at 7 years of follow-up, the local recurrence rate was 0.9% (95% CI, 0.0%–2.2%) in the radiation therapy arm compared to 6.7% (95% CI, 3.2%–9.6%) in the observation arm (HR, 0.11; 95% CI, 0.03–0.47;  $P < 0.001$ ). For a subset of patients with good-risk disease features, the local recurrence rate significantly decreased when radiation therapy was involved. A meta-analysis of multicenter randomized trials also proved that if WBRT was given after lumpectomy for DCIS, there is a statistically and clinically significant reduction in ipsilateral breast events (HR, 0.49; 95% CI; 0.41–0.58,  $P < 0.00001$ ). While in the NSABP B-17 study, with a follow-up of 15 years, radiation therapy resulted in a 52% reduction of ipsilateral invasive recurrence versus excision alone (HR, 0.48; 95% CI, 0.33–0.69,  $P < 0.001$ ). These results were also found in an observational study done by the SEER database (n=108,196 patients).

Patients with DCIS and evidence of widespread disease (i.e., disease involving two or more quadrants) on diagnostic mammography or other imaging, physical examination, or biopsy may require mastectomy.

Radiation therapy was again associated with a 50% reduction in the risk of ipsilateral

recurrence (adjusted HR, 0.47 [95% CI, 0.42–0.53];  $P < 0.001$ ) in a subgroup analysis at 10 years ( $n = 60,000$  women). In a population-based study, WBRT was found to significantly improve survival for patients with higher-risk DCIS (e.g., higher nuclear grade, younger age, and larger tumor size) (Sagara et al, 2016).

Furthermore, the use of RT boost has been denoted to provide a small but statistically significant reduction in IBTR risk (4% at 20 years) in all age groups for invasive breast cancers (Bartelink et al, 2007, 2015; Romestaing et al, 1997; Polgár et al, 2002). In a pooled analysis of pure DCIS patients who were all treated with lumpectomy and WBRT ( $n = 4,131$ ), and either received RT boost with a median dose of 14 Gy ( $n = 2,661$ ) or received no boost ( $n = 1,470$ ), with a median follow-up of 9 years, results show that a decrease in IBTR was found in patients who received boost compared with those who did not at 5 years (97.1% versus 96.3%), 10 years (94.1% versus 92.5%), and 15 years (91.6% versus 88.0%) ( $P = 0.0389$  for all). RT boost was likewise associated with significantly reduced IBTR for the entire cohort of patients (HR, 0.73; 95% CI, 0.57–0.94;  $P = 0.01$ ). For a multivariate analysis that considered factors associated with lower IBTR, including grade, ER-positive status, use of adjuvant tamoxifen, margin status, and age, the use of RT boost still remained to be significantly beneficial (HR, 0.69; 95% CI, 0.53–0.91;  $P < 0.010$ ). In addition, for patients considered very low risk based on negative margins status (defined as no ink on tumor as per National Surgical Adjuvant Breast and Bowel Project definition, or margins  $< 2$  mm as per SSO/ASTRO/ASCO definition), the RT boost was still statistically significant in decreasing the rate of local relapse. However, the magnitude of the absolute benefit of the boost was highest in younger patients. The NCCN panel therefore recommends that an individualized approach based on patient preference and other factors such as longevity be performed when considering RT boost for DCIS.

Several randomized trials document that mastectomy is equivalent to breast-conserving therapy (lumpectomy with whole breast irradiation) with respect to overall survival as primary breast local treatment for the majority of women with stage I and stage II breast cancers (Arriagada et al, 1996; Early Breast Cancer Trialists' Collaborative Group, 2005; Fisher et al, 2002; Veronesi et al, 2002; Darby et al, 2011).

Meanwhile, the NICE recommendations were based on prospective and retrospective cohort studies. There was evidence of decreased local recurrence with a tumor-free tissue margin of  $> 0$  mm in people with DCIS. The committee noted that there was no consistent evidence of benefit for people with invasive disease having a tumor-free tissue margin of  $> 0$  mm. However, based on their experience and knowledge of related evidence, particularly evidence from the Society of Surgical Oncology – American Society for Radiation Oncology (SSO-ASTRO) consensus guideline that tumor on ink is associated with at least a two-fold increase in risk of local recurrence that is not mitigated by additional endocrine therapy or radiotherapy, the committee agreed that a margin of  $> 0$  mm would also be needed in people with invasive disease (Moran 2014). It was therefore agreed that further surgery would be needed for people where

radial margins are involved (i.e., are 0 mm). Despite the low quality of the evidence, the committee made a strong recommendation as they agreed that complete excision of the tumor with clear margins was imperative to providing high-quality care.

There was limited evidence suggesting that a tumor-free tissue margin wider than 2 mm for DCIS might be beneficial in terms of reduced local recurrence, particularly for people who have not had radiotherapy. But the committee noted that no survival benefit had been shown from having wider margins and there was the potential risk of over-diagnosis and over-treatment for people with lower grades of DCIS who may not receive radiotherapy. The committee also noted that for invasive disease there was no evidence of a clear and consistent benefit of having tumor-free tissue margins between >0 mm and 2 mm. Given this uncertainty, no recommendations were made about whether or not further surgery was warranted to achieve margins wider than 0 mm. Instead, it was recommended that the risks and benefits of further surgery be discussed with the person where their radial margins are between >0 mm to 2 mm.

The committee discussed the balance of benefits and harms, noting that optimal surgical treatment should result in less local recurrence and a reduction in the number of second operations needed. In turn, this would likely result in fewer delays in the treatment pathway and would hopefully improve cosmesis. Nevertheless, they also noted that for people with a radial margin of >0 mm to 2 mm, there was uncertainty about the effect on local recurrence and it was possible that this could increase in the group. They balanced this potential harm by recommending more personalized care.

The main benefits of immediate breast reconstruction were also discussed, such as: improved aesthetic satisfaction, better objective cosmetic result, and improved general and functional health-related QOL compared with delayed reconstruction. There was evidence that early reconstruction led to lower rates of surgical complications, major fat necrosis, and surgery required for flap removal or symmetrization. Specifically, immediate reconstruction was associated with a 3% decrease in major fat necrosis (number needed to treat [NNT] 33), a 2% decrease in surgery needed for flap removal (NNT 50), and 31% decrease in somatization procedures (NNT 3) for populations with unspecific reconstruction methods and mixed postmastectomy radiotherapy (PMRT). Offering immediate reconstruction leads to an additional benefit of increased patient choice.

Compared with delayed reconstruction, the harms seen with immediate reconstruction included: higher rates of mastectomy site complications, flap or prosthesis failure, and capsular contracture. Specifically, autologous and implant reconstructions were associated with a 2% increase and a 6% increase in mastectomy site complication, respectively (NNTs 50 and 17). There was also a 2.6% increase in flap/prosthesis failure for populations with unspecific reconstruction methods and mixed PMRT (NNT 39), and 15% increase in capsular contracture following PMRT (NNT 7). There was no clear evidence on the greater detrimental effect of radiotherapy on reconstruction



following immediate compared with delayed reconstructions, or that adjuvant therapy is delayed following immediate reconstructions. It was then recommended that immediate reconstruction, in addition to delayed reconstruction, be offered to all women following mastectomy, including those who might need radiotherapy, with the exception of those where immediate reconstruction is precluded by significant co-morbidity.

Because of the potential adverse effects seen with both immediate and delayed reconstruction, it is important to discuss the risks and benefits of both the method and timing of reconstruction with the patient so he/she can make an informed decision. Although there is uncertainty over the long-term outcomes of radiotherapy, there is some evidence that immediate implant reconstructions may be more affected by radiotherapy than immediate autologous reconstructions, so the patient's decision may involve weighing up what type of reconstruction (implant or autologous) he/she would prefer, and the psychological and health-related QOL impact of delayed reconstruction.

#### Surgical management for cT1-3, cN0 or cN+, M0 Disease

Patients with early-stage operable breast cancer initially undergo upfront definitive surgery (BCS or mastectomy), and adjuvant systemic therapy, if indicated, based on primary tumor characteristics, such as: tumor size, grade, lymph node involvement, ER/PR status, expression of HER2 receptor, and tumor genomics. Some patients with early-stage operable HER2-positive or triple-negative disease may be treated with preoperative systemic therapy first, followed by surgery.

Several randomized trials document that mastectomy is equivalent to BCT, which includes BCS with WBRT with respect to OS as primary treatment for the majority of patients with stage I and stage II breast cancers. The optimal choice of surgery is based on a shared decision made by the patient and clinician after discussing benefits and risks of mastectomy versus BCT in regard to long-term survival, risk of local recurrence, and the impact on cosmetic outcome and overall QOL.

#### Breast Conserving Surgery

BCS allows patients to preserve their breast without sacrificing oncologic outcome. BCS is contraindicated for the following:

- Patients who are pregnant and would require radiation during pregnancy
- Patients who have diffuse suspicious or malignant-appearing microcalcifications on mammography
- Patients who have widespread disease that cannot be incorporated by local excision of a single region or segment of the breast tissue with a satisfactory cosmetic result

- Patients who have diffusely positive pathologic margins
- Patients who have homozygous inactivation for ATM mutation

Relative contraindications to lumpectomy include:

1. Previous RT to the breast or chest wall
2. Active connective tissue disease involving the skin (especially scleroderma and lupus)
3. Persistently positive pathologic margin
4. Known or suspected genetic predisposition to breast cancer who may have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with BCT
5. Those who may be considered for prophylactic bilateral mastectomy for risk reduction
6. Known or suspected Li-Fraumeni syndrome

Several studies of patients with early-stage breast cancer treated with BCS have identified young age as a significant predictor of an increased likelihood of IBTRs after BCT. Risk factors, such as a family history of breast cancer or a genetic predisposition for breast cancer (i.e., BRCA1/2 or other cancer predisposing mutation), are more likely to exist in the population of young patients with breast cancer, thereby confounding the independent contributions of age and treatment to clinical outcome.

With respect to OS outcomes for young patients with breast cancer, BCT or mastectomy are similar. Some studies have shown improved survival and fewer post-surgical complications with BCS.

### Mastectomy

Mastectomy is indicated for patients who are not candidates for BCS or those who choose to undergo this procedure over BCS.

Only limited data are available on the survival impact of risk-reducing contralateral mastectomy in patients with a unilateral breast cancer. Analysis of patients included in the SEER database treated with mastectomy for a unilateral breast cancer from 1998 to 2003 showed that contralateral risk-reducing mastectomy performed at the time of treatment of a unilateral cancer was associated with a reduction in breast cancer-specific mortality only in the population of young patients (18-49 years of age) with stage I/II, ER-negative breast cancer. The 5-year breast cancer survival for this group was only *slightly* improved with contralateral risk-reducing mastectomy versus without. These differences observed in retrospective analysis could be due to selection bias among patients who chose risk-reducing contralateral mastectomy. A statistical simulation of survival outcomes after risk-reducing contralateral mastectomy among patients with stage I or II breast cancer with no *BRCA* mutation found that the absolute 20-year survival benefit from risk-reducing contralateral mastectomy was less than 1%

among all ages, ER status, and cancer stage groups. Data from another meta-analysis found no absolute reduction in risk of distant metastases with risk-reducing mastectomy. Furthermore, among patients with unilateral breast cancer who have an increased familial/genetic risk, a decrease in metastatic contralateral breast cancer incidence was observed in those who received risk-reducing contralateral mastectomy, although no improvement was seen in OS of these patients.

### Margin Assessment

After surgical resection, a careful histologic assessment of resection margins is essential. The NCCN panel notes that benefit of BCS is predicated on achieving pathologically negative margins after resection.

For patients with Stage I or II invasive cancers after BCS, a positive margin is defined as “ink on tumor” (any invasive cancer or DCIS cells on ink). Patients with positive margins generally require further surgery — either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to achieve “no ink on tumor,” this can be done with resection of the involved margin guided by the orientation of the initial resection specimen or re-excision of the entire original excision cavity. There may be select patients with stage III invasive cancers who may be eligible for BCS. For these patients, the margin status would be assessed with similar definitions. If margins remain positive after further surgical re-excision(s), then mastectomy may be required for optimal local disease control.

### Research Recommendation

The GDG recommended no additional research.

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Question 13: What is the recommended axillary staging for patients with invasive breast cancer?

Recommendation 13a.

Clinically node negative

We recommend performing axillary staging using SLNB as the preferred method among patients with early-stage breast cancer.

*Strong recommendation, High quality of evidence*

Recommendation 13b.

Clinically node negative

We recommend performing ALND among patients with early-stage breast cancer when SLNB is not possible.

*Strong recommendation, Moderate quality of evidence*

Recommendation 13c.

Clinically node negative

In elderly patients and with significant competing comorbidities with tumor size of 2cm or less, hormone receptor–positive and human epidermal growth factor receptor 2 (HER2)–negative tumor, for whom axillary staging will not alter the course of treatment, SLNB (or ALND) may be omitted.

*Weak recommendation, Low quality of evidence*

Recommendation 13d.

Clinically node positive

We suggest conducting US-guided needle biopsy of the axillary node among patients with clinically suspicious nodes.

*Weak recommendation, Low quality of evidence*

Recommendation 13e.

Clinically node positive

We recommend performing ALND in patients with positive node biopsy.

*Strong recommendation, Low quality of evidence*

Consensus Issues

The Panel Members adopted the recommendations but stated that not all hospitals are equipped with the machine for performing SLNB. The Panel also did not

recommend the use of axillary US staging among clinically node-negative patients with early-stage breast cancer where the sentinel lymph node is likely to be negative. And if omission of SLNB is considered, a consultation with a medical oncologist can be done before surgery to discuss hormonal therapy.

## Summary of Evidence

### Clinically node-negative

According to the ASCO/Ontario Health (Cancer Care Ontario) Guideline, axillary staging has been a standard aspect of initial surgery when the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 was disclosed by Fisher et al in 2002. However, axillary lymph node dissection (ALND) was associated with substantial morbidity. For patients with clinically negative axillae, sentinel lymph node biopsy (SLNB) is the standard of care for axillary staging in Canada, with results being useful in creating decisions on adjuvant treatment (George et al, 2009).

Several studies showed that the standard of care for patients with a pathologically positive sentinel lymph node was a completion ALND, but current data have suggested that this procedure for certain patients with positive nodes from SLNB did not have an improved survival or regional recurrence benefit (Giuliano et al, 2011; Donker et al, 2014).

For the same effect on the critical outcomes (i.e., OS and DFS), patients given SLNB will experience significant reduction in adverse events, such as: lymphedema and sensory neuropathy. This finding is also applicable for patients who have sonographically abnormal imaging with or without confirmatory biopsy. For other patients, there might be axillary recurrence if ALND is averted. Thus, it was recommended that this option be discussed and evaluated according to individual's circumstances, values, and preferences.

Among low-risk,  $\geq 70$ -year-old women with hormone-positive early-stage cancer, a case-by-case basis must be done because even though avoiding SLNB has no impact on survival, it is associated with an increased risk of recurrence. Patients' preferences should then be weighed against their comorbidities and competing risks for mortality (Choosing Wisely Guideline, 2021).

### Clinically node-positive

For this recommendation on clinically node-positive cases, the ASCO/Ontario Health (Cancer Care Ontario) Guideline reported that the certainty of evidence is low. Moreover, there are no available data on disease control, quality of life, adverse events or complication rate, ability to map, and procedure completion rate. Although the population study by Verheuel et al (2017) described OS, it was considered at critical

risk of bias and deemed not suitable to support the recommendation. Other studies had very heterogenous false negative rates (FNR) (Kramer et al, 2016; Kim et al, 2016; Cools-Lartigue et al, 2013).

### Research Recommendation

The GDG recommended no additional research.

## References

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## Surveillance

Question 14: What is the recommended surveillance for treated patients with breast cancer?

### Recommendation 14a.

We recommend that the follow-up of women with breast cancer includes interval history and physical examination every 3 to 6 months for 5 years and then annually, as well as yearly mammography. In patients treated with breast-conserving therapy, the first follow-up mammogram should be performed 6 to 12 months after the completion of breast-conserving radiation therapy.

*Strong recommendation, Low quality of evidence*

### Recommendation 14b.

We do not recommend screening for metastasis in the absence of clinical signs and symptoms suggestive of metastatic disease.

*Strong recommendation, Low quality of evidence*

### Recommendation 14c.

We do not recommend the routine use of "tumor markers" for surveillance of patients with breast cancer.

*Strong recommendation, Low quality of evidence*

## Consensus Issues

The Consensus Panel adopted these recommendations on surveillance and specified that cost is a major consideration for frequency of testing. In addition, they noted that there is no evidence to support the use of "tumor markers" for breast cancer. Routine bone scans, CT scans, MRI scans, PET scans, or ultrasound examinations in the asymptomatic patient also provide no advantage in survival or ability to palliate recurrent disease and are, therefore, not recommended.

## Summary of Evidence

### Follow up

Patients with breast cancer who have had breast-conserving surgery and radiation therapy should have a mammogram once a year. There is no clear benefit to imaging at shorter intervals. It is also suggested that patients wait 6-12 months after radiation therapy is done before starting annual mammograms. If a physical exam or

surveillance imaging shows something suspicious, the time between mammograms may need to be shorter (Choosing Wisely, 2014; NCCN, 2022).

### Screening for metastasis

If there are no signs and symptoms of relapse, imaging tests to detect metastasis are not necessary (NCCN, 2022). According to the GIVIO Investigators (1994), there was no difference in the overall survival after 71 months of follow up (n=1320), with 20% deaths (n=132) in the intensive group and 18% deaths (n=122) in the control group. Concluding that after the first treatment for breast cancer, a frequent lab tests and x-rays has little effect on survival or health-related quality of life. Similarly, Turco et al (1994) used two follow up protocols to determine whether early detection of metastases in lungs and bone reduces mortality in BCA patients. The clinical follow-up group had a much higher 5-year survival rate without a relapse. For those in the intensive follow-up group, recurrences were noticed earlier, but there was no significant difference between the two follow-up groups in the number of deaths over 5 years (18.6% versus 19.5%) (Turco et al, 1994).

### Tumor Markers

In the 2000 study of ASCO, six cancer tumor markers for colorectal cancer and eight for breast cancer were evaluated. According to them, the use of tumor markers may or may not be suggested (Bast et al, 2001). Tumor markers and routine bone scans, CT scans, MRI scans, PET scans, or ultrasound examinations in asymptomatic patients do not improve survival or help treat relapse, hence is not recommended (NCCN, 2022).

### Research Recommendation

The GDG recommended no additional research.

## References

- Bast Jr, R. C., Ravdin, P., Hayes, D. F., Bates, S., Fritsche Jr, H., Jessup, J. M., ... & Somerfield, M. R. (2001). 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. *Journal of clinical oncology*, 19(6), 1865-1878
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## Breast Specimen Handling and Histopathology Reporting

What are the requirements for handling of breast specimens?

The Consensus Panel recommended to use the CAP Protocol for the handling of breast specimens.

According to the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) estrogen receptor (ER) and progesterone receptor (PgR) testing guideline, time from tissue acquisition to fixation should be as short as possible. Samples for ER and PgR testing should be fixed in 10% neutral buffered formalin (NBF) for 6 to 72 hours, sliced at 5-mm intervals after appropriate gross inspection and margin designation, and placed in a sufficient quantity of NBF for adequate tissue penetration. If tumor comes from remote location, it should be bisected through the tumor on removal and sent to the laboratory immersed in an adequate volume of NBF. Cold ischemia time, fixative type, and time the sample was placed in NBF must be recorded.

In the ASCO/CAP human epidermal growth factor receptor 2 guideline, it is not suggested to utilize unstained slides cut more than 6 weeks before analysis. To be documented on the accession slip or report are the: time the tissue was removed from patient, time the tissue was placed in fixative, duration of fixation, and fixative type.

## Reference

Allison, K. H., Hammond, M. E. H., Dowsett, M., McKernin, S. E., Carey, L. A., Fitzgibbons, P. L., ... & Wolff, A. C. (2020). Estrogen and progesterone receptor testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists guideline update. *Archives of pathology & laboratory medicine*, 144(5), 545-563

## What are the minimum requirements for breast histopathology reporting?

The Consensus Panel recommended to use the CAP Protocols for breast histopathology reporting.

As the NCCN Guidelines stated, pathology reporting is vital in determining the extent of disease and biologic features for treatment. Accuracy of said reporting must be done between the clinician and pathologist relating to relevant patient history, prior breast biopsies, prior irradiation to the chest, pregnancy status, characteristics of the abnormality biopsied (e.g., palpable, mammographically detected microcalcifications), clinical state of lymph nodes, presence of inflammatory change or other skin abnormality, and any prior treatment administered (e.g., chemotherapy, radiation therapy). The specimens should be oriented for the pathologist, and requests for biomarkers should be specified (e.g., ER, PR, and HER2 status).

The College of American Pathologists (CAP) created pathology reporting protocols for the standardized reporting of malignant specimens, wherein there is a protocol for each disease site that includes cancer case summaries (checklists) with background documentation. NCCN emphasized that consistent, unambiguous, and complete pathology reporting is a cornerstone of quality breast cancer care, and its Breast Cancer Panel endorsed the use of the CAP protocols for reporting the pathologic analysis of all breast cancer specimens.

In the CAP Protocol for the Examination of Biopsy Specimens from Patients with Ductal Carcinoma In Situ (DCIS) of the Breast, the case summary covered aspects of: histologic type, architectural pattern, nuclear grade, necrosis, microcalcifications, and additional findings that are vital for the clinical management of patients. Meanwhile, in the CAP Protocol for the Examination of Biopsy Specimens from Patients with Invasive Carcinoma of the Breast, the report contains information on the: histologic type, histologic grade, features of the ductal carcinoma in situ, microcalcifications, and additional pathologic findings such as if several invasive carcinomas vary in histologic type, grade, or the expression of ER, PgR, or HER2. (See Annex E for CAP Protocols).

**Adapted from: Protocol for the Examination of Biopsy Specimens from Patients with Ductal Carcinoma In Situ (DCIS) of the Breast, Version 1.0.1.0 (2021, June).**

**CASE SUMMARY: (DCIS OF THE BREAST: Biopsy)**

*This template is recommended for reporting biopsy specimens but is not required for accreditation purposes.*

**SPECIMEN**

**Procedure**

- Needle biopsy
- Fine needle aspiration
- Other (specify): \_\_\_\_\_
- Not specified

**Specimen Laterality**

- Right
- Left
- Not specified

**TUMOR**

**+Tumor Site (select all that apply)**

- Upper outer quadrant
- Lower outer quadrant
- Upper inner quadrant
- Lower inner quadrant
- Central
- Nipple
- Clock position

**Specify Clock Position (select all that apply)**

- 1 o'clock
- 2 o'clock

3 o'clock

4 o'clock

5 o'clock

6 o'clock

7 o'clock

8 o'clock

9 o'clock

10 o'clock

11 o'clock

12 o'clock

Specify distance from nipple in centimeters (cm): \_\_\_\_\_ cm

Other (specify): \_\_\_\_\_

Not specified

**Histologic Type (Note [A](#))**

Ductal carcinoma in situ (DCIS)

Paget disease

Encapsulated papillary carcinoma without invasive carcinoma

Solid papillary carcinoma without invasive carcinoma

**+Architectural Patterns (Note [B](#)) (select all that apply)**

Comedo

Paget disease (DCIS involving nipple skin)

Cribriform

Micropapillary

Papillary

Solid

Other (specify): \_\_\_\_\_

**Nuclear Grade (Note C)**

- Grade I (low)
- Grade II (intermediate)
- Grade III (high)
- Other (specify): \_\_\_\_\_
- Cannot be determined: \_\_\_\_\_

**Necrosis (Note D)**

- Not identified
- Present, focal (small foci or single cell necrosis)
- Present, central (expansive "comedo" necrosis)
- Other (specify): \_\_\_\_\_
- Cannot be determined: \_\_\_\_\_

**+Microcalcifications (Note E) (select all that apply)**

- Not identified
- Present in DCIS
- Present in non-neoplastic tissue
- Other (specify): \_\_\_\_\_

**ADDITIONAL FINDINGS (Note E)**

**+Additional Findings (specify):** \_\_\_\_\_

**SPECIAL STUDIES**

*For hormone receptor and HER2 reporting, the CAP Breast Biomarker Template should be used. [www.cap.org/cancerprotocols](http://www.cap.org/cancerprotocols).*

**+Breast Biomarker Studies (specify pending studies):** \_\_\_\_\_

**COMMENTS**

**Comment(s):** \_\_\_\_\_

## Explanatory Notes

### A. Histologic Type

This protocol applies only to cases of DCIS. The protocol for invasive carcinoma of the breast applies if invasion or microinvasion (less than or equal to 1 mm) is present. Pleomorphic lobular carcinoma in situ (LCIS) has overlapping features with DCIS and may be treated similarly, but at present there is insufficient evidence to establish definitive recommendations for treatment. Thus, pleomorphic LCIS is not currently included in the pTis classification.

When DCIS involves nipple skin only, without underlying invasive carcinoma or DCIS, the classification is DCIS (i.e., pTis [Paget]). The majority of these cases are strongly positive for HER2.

### B. Architectural Pattern

The architectural pattern has been reported traditionally for DCIS.<sup>1,2</sup> However, nuclear grade and the presence of necrosis are more predictive of clinical outcome.

#### References

- Schwartz GF, Lagios MD, Carter D, et al. Consensus conference on the classification of ductal carcinoma in situ. *Cancer*. 1997;80:1798-1802
- Silverstein MJ, Lagios MD, Recht A, et al. Image-detected breast cancer: state of the art diagnosis and treatment. *J Am Coll Surg*. 2005;201:586-597

### C. Nuclear Grade

The nuclear grade of DCIS is determined using 6 morphologic features (Table 1).<sup>1,2</sup>

**Table 11. Nuclear Grade of Ductal Carcinoma In Situ**

Feature	Grade I (Low)	Grade II (Intermediate)	Grade III (High)
Pleomorphism	Monotonous (monomorphic)	Intermediate	Markedly pleomorphic
Size	1.5 to 2 x the size of a normal RBC or a normal duct epithelial cell nucleus	Intermediate	>2.5 x the size of a normal RBC or a normal duct epithelial cell nucleus
Chromatin	Usually diffuse, finely dispersed chromatin	Intermediate	Usually vesicular with irregular chromatin distribution
Nucleoli	Only occasional		Prominent, often



			multiple
Mitoses	Only occasional	Intermediate	May be frequent
Orientation	Polarized toward luminal spaces	Intermediate	Usually not polarized toward the luminal space

Definition: RBC, red blood cell.

#### References

- Schwartz GF, Lagios MD, Carter D, et al. Consensus conference on the classification of ductal carcinoma in situ. *Cancer*. 1997;80:1798-1802
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#### D. Necrosis

The presence of necrosis<sup>1</sup> is correlated with the finding of mammographic calcifications (ie, most areas of necrosis will calcify). DCIS that presents as mammographic calcifications often recurs as calcifications. Necrosis can be classified as follows:

- **Central (“comedo”)**: The central portion of an involved ductal space is replaced by an area of expansive necrosis that is easily detected at low magnification. Ghost cells and karyorrhectic debris are generally present. Although central necrosis is generally associated with high-grade nuclei (ie, comedo DCIS), it can also occur with DCIS of low or intermediate nuclear grade. This type of necrosis often correlates with a linear and/or branching pattern of calcifications on mammography.
- **Focal (punctate)**: Small foci, indistinct at low magnification, or single cell necrosis.

Necrosis should be distinguished from secretory material, which can also be associated with calcifications, cytoplasmic blebs, and histiocytes, but does not include nuclear debris.

#### References

- Schwartz GF, Lagios MD, Carter D, et al. Consensus conference on the classification of ductal carcinoma in situ. *Cancer*. 1997;80:1798-1802

## E. Microcalcifications

DCIS found in biopsies performed for microcalcifications will almost always be at the site of the calcifications or in close proximity.<sup>1,2,3</sup> The presence of the targeted calcifications in the specimen should be confirmed by specimen radiography. The pathologist must be satisfied that the specimen has been sampled in such a way that the lesion responsible for the calcifications has been examined microscopically. The relationship of the radiologic calcifications to the DCIS should be indicated.

### References

- Owings DV, Hann L, Schnitt SJ, How thoroughly should needle localization breast biopsies be sampled for microscopic examination? A prospective mammographic/pathologic correlative study. *Am J Surg Pathol.* 1990;14:578-583
- Association of Directors of Anatomic and Surgical Pathology. *Recommendations for the Reporting of Breast Carcinoma.* Updated September 2004, Version 1.1. [www.adasp.org/Checklists/Checklists.htm](http://www.adasp.org/Checklists/Checklists.htm). Accessed June 18, 2008
- Silverstein MJ, Lagios MD, Recht A, et al. Image-detected breast cancer: state of the art diagnosis and treatment. *J Am Coll Surg.* 2005;201:586-597

## F. Additional Findings

If the biopsy was performed for a benign lesion and the DCIS is an incidental finding, this should be documented. An example would be the finding of DCIS in an excision for a palpable fibroadenoma. In some cases, other pathologic findings are important for the clinical management of patients.

**Adapted from: Protocol for the Examination of Biopsy Specimens from Patients with Invasive Carcinoma of the Breast, Version 1.1.1.1 (2021, November).**

**CASE SUMMARY: (INVASIVE CARCINOMA OF THE BREAST: Biopsy)**

*This template is recommended for reporting biopsy specimens, but is not required for accreditation purposes.*

**SPECIMEN**

**Procedure**

- Needle biopsy
- Fine needle aspiration
- Other (specify): \_\_\_\_\_
- Not specified

**Specimen Laterality**

- Right
- Left
- Not specified

**TUMOR**

**+Tumor Site (select all that apply)**

- Upper outer quadrant
- Lower outer quadrant
- Upper inner quadrant
- Lower inner quadrant
- Central
- Nipple
- Clock position

**Specify Clock Position (select all that apply)**

1 o'clock

2 o'clock

3 o'clock

4 o'clock

5 o'clock

6 o'clock

7 o'clock

8 o'clock

9 o'clock

10 o'clock

11 o'clock

12 o'clock

Specify distance from nipple in centimeters (cm): \_\_\_\_\_ cm

Other (specify): \_\_\_\_\_

Not specified

**Histologic Type (Note [A](#))**

No residual invasive carcinoma

Invasive carcinoma of no special type (ductal)

Micro-invasive carcinoma

Invasive lobular carcinoma

Invasive carcinoma with mixed ductal and lobular features

Invasive carcinoma with features of (specify): \_\_\_\_\_

Tubular carcinoma

Invasive cribriform carcinoma

Mucinous carcinoma

Invasive micropapillary carcinoma

Apocrine adenocarcinoma

- \_\_\_ Metaplastic carcinoma
- \_\_\_ Encapsulated papillary carcinoma with invasion
- \_\_\_ Solid papillary carcinoma with invasion
- \_\_\_ Intraductal papillary adenocarcinoma with invasion
- \_\_\_ Adenoid cystic carcinoma
- \_\_\_ Neuroendocrine tumor
- \_\_\_ Neuroendocrine carcinoma
- \_\_\_ Invasive carcinoma, type cannot be determined: \_\_\_\_\_
- \_\_\_ Other histologic type not listed (specify): \_\_\_\_\_
- +Histologic Type Comment:** \_\_\_\_\_

**Histologic Grade (Nottingham Histologic Score) (Note [B](#))**

- \_\_\_ Not applicable (no residual carcinoma or microinvasion only)
- \_\_\_ Nottingham Score

**Glandular (Acinar) / Tubular Differentiation**

- \_\_\_ Score 1 (greater than 75% of tumor area forming glandular / tubular structures)
- \_\_\_ Score 2 (10% to 75% of tumor area forming glandular / tubular structures)
- \_\_\_ Score 3 (less than 10% of tumor area forming glandular / tubular structures)
- \_\_\_ Score cannot be determined: \_\_\_\_\_

**Nuclear Pleomorphism**

- \_\_\_ Score 1 (Nuclei small with little increase in size in comparison with normal breast epithelial cells, regular outlines, uniform nuclear chromatin, little variation in size)
- \_\_\_ Score 2 (Cells larger than normal with open vesicular nuclei, visible nucleoli, and moderate variability in both size and shape)
- \_\_\_ Score 3 (Vesicular nuclei, often with prominent nucleoli, exhibiting marked variation in size and shape, occasionally with very large and bizarre forms)
- \_\_\_ Score cannot be determined: \_\_\_\_\_

**Mitotic Rate**

See Table 1 in CAP Protocol.

\_\_\_ Score 1

\_\_\_ Score 2

\_\_\_ Score 3

\_\_\_ Score cannot be determined: \_\_\_\_\_

**Overall Grade**

\_\_\_ Grade 1 (scores of 3, 4 or 5)

\_\_\_ Grade 2 (scores of 6 or 7)

\_\_\_ Grade 3 (scores of 8 or 9)

\_\_\_ Score cannot be determined (explain): \_\_\_\_\_

**+Tumor Size**

\_\_\_ Microinvasion only (less than or equal to 1 mm)

\_\_\_ Greatest dimension of largest invasive focus greater than 1 mm (specify exact measurement in millimeters (mm)): \_\_\_\_\_ mm

**+Additional Dimension in Millimeters (mm): \_\_\_\_\_ x \_\_\_\_\_ mm**

\_\_\_ Tumor size cannot be determined (explain): \_\_\_\_\_

**Ductal Carcinoma In Situ (DCIS) (Note [C](#))**

\_\_\_ Not identified

\_\_\_ Present

**Architectural Patterns (select all that apply)**

\_\_\_ Comedo

\_\_\_ Paget disease (DCIS involving nipple skin)

\_\_\_ Cribriform

\_\_\_ Micropapillary

\_\_\_ Papillary

\_\_\_ Solid

\_\_\_ Other (specify): \_\_\_\_\_

**Nuclear Grade**

\_\_\_ Grade I (low)

\_\_\_ Grade II (intermediate)

\_\_\_ Grade III (high)

\_\_\_ Other (specify): \_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_

**Necrosis**

\_\_\_ Not identified

\_\_\_ Present, focal (small foci or single cell necrosis)

\_\_\_ Present, central (expansive "comedo" necrosis)

\_\_\_ Other (specify): \_\_\_\_\_

\_\_\_ Cannot be determined: \_\_\_\_\_

\_\_\_ Cannot be excluded

**+Lymphovascular Invasion**

\_\_\_ Not identified

\_\_\_ Present

\_\_\_ Cannot be determined: \_\_\_\_\_

**+Microcalcifications (Note [D](#)) (select all that apply)**

\_\_\_ Not identified

\_\_\_ Present in DCIS

\_\_\_ Present in invasive carcinoma

\_\_\_ Present in non-neoplastic tissue

\_\_\_ Other (specify): \_\_\_\_\_

**ADDITIONAL FINDINGS (Note [E](#))**

**+Additional Findings (specify):** \_\_\_\_\_

**SPECIAL STUDIES**

*For hormone receptor and HER2 reporting, the CAP Breast Biomarker Template should be used. [www.cap.org/cancerprotocols](http://www.cap.org/cancerprotocols).*

**+Breast Biomarker Studies (specify pending studies):** \_\_\_\_\_

**COMMENTS**

**Comment(s):** \_\_\_\_\_



## Explanatory Notes

### A. Histologic Type

This protocol applies to all invasive carcinomas of the breast. The World Health Organization (WHO) classification of breast carcinoma is recommended, although the protocol does not preclude the use of other classifications or histologic types. Carcinomas may be classified based on the H&E appearance without the use of immunohistochemical studies.

A modified list is presented in the case summary based on the most frequent types of invasive carcinomas and terminology that is in widespread usage. The modified list is intended to capture the majority of tumors and reduce the frequency of tumors being reported as “other.” Choices are added for tumors with mixed features and those with some but not all features of specific histologic types.

#### WHO Classification of Invasive Carcinoma of the Breast<sup>1</sup>

- No residual invasive carcinoma
- Invasive carcinoma of no special type (ductal)
- Micro-invasive carcinoma
- Invasive lobular carcinoma
- Invasive carcinoma with mixed ductal and lobular features
- Invasive carcinoma with mixed features (specify): \_\_\_\_\_
- Tubular carcinoma
- Invasive cribriform carcinoma
- Mucinous carcinoma
- Invasive micropapillary carcinoma
- Apocrine adenocarcinoma

#### Metaplastic Carcinoma

- Metaplastic carcinoma NOS
- Low grade adenosquamous carcinoma
- Fibromatosis-like metaplastic carcinoma
- Spindle cell carcinoma
- Squamous cell carcinoma

- \_\_\_ Metaplastic carcinoma with mesenchymal differentiation
- \_\_\_ Encapsulated papillary carcinoma with invasion
- \_\_\_ Solid papillary carcinoma with invasion
- \_\_\_ Intraductal papillary adenocarcinoma with invasion
- \_\_\_ Adenoid cystic carcinoma

Neuroendocrine Tumor

- \_\_\_ Neuroendocrine tumor NOS
- \_\_\_ Neuroendocrine tumor, grade 1
- \_\_\_ Neuroendocrine tumor, grade 2

Neuroendocrine Carcinoma

- \_\_\_ Neuroendocrine carcinoma NOS
- \_\_\_ Neuroendocrine carcinoma, small cell
- \_\_\_ Neuroendocrine carcinoma, large cell
- \_\_\_ Invasive carcinoma, type cannot be determined
- \_\_\_ Other histologic type (specify): \_\_\_\_\_
  - \_\_\_ Invasive papillary carcinoma
  - \_\_\_ Oncocytic carcinoma
  - \_\_\_ Lipid-rich carcinoma
  - \_\_\_ Glycogen-rich carcinoma
  - \_\_\_ Sebaceous carcinoma
  - \_\_\_ Mucinous cystadenocarcinoma NOS
  - \_\_\_ Acinar cell carcinoma
  - \_\_\_ Classic adenoid cystic carcinoma
  - \_\_\_ Solid-basaloid adenoid cystic carcinoma
  - \_\_\_ Adenoid cystic carcinoma with high-grade transformation
  - \_\_\_ Secretory carcinoma
  - \_\_\_ Mucoepidermoid carcinoma

- \_\_\_ Polymorphous adenocarcinoma
- \_\_\_ Tall cell carcinoma with reversed polarity
- \_\_\_ Adenomyoepithelioma with carcinoma
- \_\_\_ Epithelial-myoepithelial carcinoma
- \_\_\_ Other type not listed (specify): \_\_\_\_\_

## Reference

- WHO Classification of Tumours Editorial Board. *Breast tumours*. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 2)

## B. Histologic Grade

All invasive breast carcinomas should be graded.<sup>1</sup> The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) should be used for reporting. Within each stage grouping there is a relation between histologic grade and outcome.

The Nottingham combined histologic grade evaluates the amount of tubule formation, the extent of nuclear pleomorphism, and the mitotic count (or mitotic rate). Each variable is given a score of 1, 2, or 3, and the scores are added to produce a grade. The mitotic score is determined by the number of mitotic figures found in 10 consecutive high-power fields (HPF) in the most mitotically active part of the tumor. Only clearly identifiable mitotic figures should be counted; hyperchromatic, karyorrhectic, or apoptotic nuclei are excluded. Because of variations in field size, the HPF size must be determined for each microscope and the appropriate point score determined accordingly. It is recommended that the size be measured by using a micrometer. However, the diameter of an HPF can also be calculated by using the method below.

### Measuring the Size of a High-Power Field (HPF) With a Ruler

Use a clear ruler to measure the diameter of a low-power field. This number can be used to calculate a constant based on the following formula:

$$\text{Eyepiece Magnification} \times \text{Objective Magnification} \times \text{Microscopic Field Diameter} = \text{Constant}$$

When the value of the constant is known, the diameter of an HPF can be calculated for other objectives by using the following formula:

Unknown Field Diameter = Constant/(Eyepiece Magnification x Objective Magnification)

Half of the field diameter is the radius of the field ( $r$ ), which can then be used to calculate the area of the HPF:

$3.1415 \times r^2 = \text{Area of Microscopic Field}$

If the microscopic field diameter or the area of the field is known, Table 1 can be used to determine the number of mitoses corresponding to different scores.

**Table 12. Score Categories According to Field Diameter and Mitotic Count**

<b>Scoring Categories of Mitotic Counts</b>				
Field diameter (mm)	Area (mm <sup>2</sup> )	Number of mitoses per 10 fields corresponding to:		
		Score 1	Score 2	Score 3
0.40	0.125	≤4	5 to 9	≥10
0.41	0.132	≤4	5 to 9	≥10
0.42	0.139	≤5	6 to 10	≥11
0.43	0.145	≤5	6 to 10	≥11
0.44	0.152	≤5	6 to 11	≥12
0.45	0.159	≤5	6 to 11	≥12
0.46	0.166	≤6	7 to 12	≥13
0.47	0.173	≤6	7 to 12	≥13
0.48	0.181	≤6	7 to 13	≥14
0.49	0.189	≤6	7 to 13	≥14
0.50	0.196	≤7	8 to 14	≥15
0.51	0.204	≤7	8 to 14	≥15
0.52	0.212	≤7	8 to 15	≥16
0.53	0.221	≤8	9 to 16	≥17
0.54	0.229	≤8	9 to 16	≥17
0.55	0.238	≤8	9 to 17	≥18
0.56	0.246	≤8	9 to 17	≥18
0.57	0.255	≤9	10 to 18	≥19
0.58	0.264	≤9	10 to 19	≥20
0.59	0.273	≤9	10 to 19	≥20

0.60	0.283	≤10	11 to 20	≥21
0.61	0.292	≤10	11 to 21	≥22
0.62	0.302	≤11	12 to 22	≥23
0.63	0.312	≤11	12 to 22	≥23
0.64	0.322	≤11	12 to 23	≥24
0.65	0.332	≤12	13 to 24	≥25
0.66	0.342	≤12	13 to 24	≥25
0.67	0.353	≤12	13 to 25	≥26
0.68	0.363	≤13	14 to 26	≥27
0.69	0.374	≤13	14 to 27	≥ 28

From Pathology Reporting of Breast Disease.<sup>2</sup> Copyright 2005 National Health Service Cancer Screening Programme and The Royal College of Pathologists. Adapted with permission.

#### References

- Ellis IO, Elston CW. Histologic grade. In: O'Malley FP, Pinder SE, eds. *Breast Pathology*. Philadelphia, PA: Elsevier; 2006:225-233
- *Pathology Reporting of Breast Disease*. A Joint Document Incorporating the Third Edition of the NHS Breast Screening Programme's *Guidelines for Pathology Reporting in Breast Cancer Screening* and the Second Edition of The Royal College of Pathologists' *Minimum Dataset for Breast Cancer Histopathology* Published by the NHS Cancer Screening Programmes jointly with The Royal College of Pathologists. NHSBSP Publication No 58. January 2005. <http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp58.html>. Accessed April 8, 2009

### C. Ductal Carcinoma In Situ

#### Nuclear Grade of DCIS

The nuclear grade of DCIS is determined using 6 morphologic features (Table 1).<sup>1</sup>

**Table 13. Nuclear Grade of Ductal Carcinoma in Situ**

Feature	Grade I (Low)	Grade II (Intermediate)	Grade III (High)
<b>Pleomorphism</b>	Monotonous (monomorphic)	Intermediate	Markedly pleomorphic
<b>Size</b>	1.5 to 2 x the size of a normal red blood cell	Intermediate	>2.5 x the size of a normal red blood cell

	or a normal duct epithelial cell nucleus		or a normal duct epithelial cell nucleus
<b>Chromatin</b>	Usually diffuse, finely dispersed chromatin	Intermediate	Usually vesicular with irregular chromatin distribution
<b>Nucleoli</b>	Only occasional	Intermediate	Prominent, often multiple
<b>Mitoses</b>	Only occasional	Intermediate	May be frequent
<b>Orientation</b>	Polarized toward luminal spaces	Intermediate	Usually not polarized toward the luminal space

### Necrosis

The presence of necrosis is correlated with the finding of mammographic calcifications (ie, most areas of necrosis will calcify). Ductal carcinoma in situ that presents as mammographic calcifications often recurs as calcifications. Necrosis can be classified as follows:

Central (“comedo”): The central portion of an involved ductal space is replaced by an area of expansive necrosis that is easily detected at low magnification. Ghost cells and karyorrhectic debris are generally present. Although central necrosis is generally associated with high-grade nuclei (ie, comedo DCIS), it can also occur with DCIS of low or intermediate nuclear grade.

Focal: Small foci, indistinct at low magnification, or single cell necrosis.

Necrosis should be distinguished from secretory material, which can also be associated with calcifications, but does not include nuclear debris.

### References

- Schwartz GF, Lagios MD, Carter D, et al. Consensus conference on the classification of ductal carcinoma in situ. *Cancer*. 1997;80:1798-1802

### **D. Microcalcifications**

Cancer found in biopsies performed for microcalcifications will almost always be at the site of the calcifications or in close proximity. The presence of the targeted calcifications in the specimen should be confirmed by specimen radiography. The pathologist must be satisfied that the specimen has been sampled in such a way that the lesion responsible for the calcifications has been examined microscopically. The

relationship of the radiologic calcifications to the invasive carcinoma and the DCIS should be indicated.

If calcifications can be seen in the specimen radiograph but not in the initial histologic sections, deeper levels should be examined. If needed, radiographs of the paraffin block(s) may be obtained to detect calcifications remaining in the block(s). If microcalcifications cannot be confirmed by routine microscopic evaluation, polarized light may be helpful, since calcium oxalate crystals are refractile and polarizable but usually clear or tinged yellow in H&E sections. On rare occasions, calcifications do not survive tissue processing or prolonged fixation in formalin. Foreign material can sometimes simulate calcifications (eg, metallic fragments after surgery or trauma).

### **E. Additional Findings**

In some cases, additional pathologic findings are important for the clinical management of patients. If multiple invasive carcinomas are present and differ in histologic type, grade, or the expression of ER, PgR, or HER2, this information should be included as text in this section.

## References

- Allison, K. H., Hammond, M. E. H., Dowsett, M., McKernin, S. E., Carey, L. A., Fitzgibbons, P. L., ... & Wolff, A. C. (2020). Estrogen and progesterone receptor testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists guideline update. *Archives of pathology & laboratory medicine*, 144(5), 545-563
- Fitzgibbons, P, and Connolly, J. With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees. (2021). *Protocol for the Examination of Biopsy Specimens from Patients with Ductal Carcinoma In Situ (DCIS) of the Breast Version 1.0.1.0*. College of American Pathologists (CAP)
- Fitzgibbons, P, and Connolly, J. With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees. (2021). *Protocol for the Examination of Biopsy Specimens from Patients with Invasive Carcinoma of the Breast Version 1.1.1.1*. College of American Pathologists (CAP)
- National Comprehensive Cancer Network. (2022). Breast Cancer. *NCCN Clinical Practice Guidelines in Oncology Version 3.2022*



## Annexes

### Annex A. GDG COI Declaration and Management

#### Annex A.1. Technical Advisory Group COI Declaration and Management

Name	Affiliation	Conflict of Interest		
		Intellectual	Monetary	Management
Dr. Nilo C. de los Santos	East Avenue Medical Center	None	None	May participate in the guideline development
Dr. Clarito U. Cairo, Jr.	Department of Health	None	None	May participate in the guideline development
Ms. Alma B. Abainza-Sanchez	Philippine Health Insurance Corporation	None	None	May participate in the guideline development
Dr. Samuel S. Duran	East Avenue Medical Center	None	None	May participate in the guideline development
Dr. Allan Troy D. Baquir	East Avenue Medical Center	None	None	May participate in the guideline development

## Annex A.2. Steering Committee COI Declaration and Management

Name	Affiliation	Conflict of Interest		
		Intellectual	Monetary	Management
Dr. Felicidad R. Claudia-Ordoñez	East Avenue Medical Center	None	None	May participate in the guideline development
Ms. Maria Dolores Manalastas	Department of Health	None	None	May participate in the guideline development
Dr. Marc Anthony Cepeda	Philippine Health Insurance Corporation	None	None	May participate in the guideline development
Dr. Jose Montoya	Philippine Society of Medical Oncology	None	None	May participate in the guideline development
Dr. Kathleen Baldivia	Philippine Radiation Oncology Society	None	None	May participate in the guideline development
Dr. Joan Uy-Valdez	Philippine College of Radiology	None	None	May participate in the guideline development
Dr. Shalimar Cortez	Philippine Society of General Surgeons	None	None	May participate in the guideline development
Dr. Eileen Borje	Philippine Society of General Surgeons	None	None	May participate in the guideline development
Dr. Lorlyn Agatep	Pain Society of the Philippines	None	None	May participate in the guideline development

### Annex A.3. Consensus Panel COI Declaration and Management

Name	Affiliation	Conflict of Interest		
		Intellectual	Monetary	Management
Dr. Glomar C. Malana	East Avenue Medical Center	None	None	May participate in the guideline development
Dr. Katherine Hernandez	Philippine Society of Medical Oncology	None	None	May participate in the guideline development
Dr. Amabelle Gerona	Philippine Society of Medical Oncology	None	None	May participate in the guideline development
Dr. Ma. Cecilia Pagdanganan	Philippine Society of Breast Surgeons	None	None	May participate in the guideline development
Dr. Frances Marion Dela Serna	Philippine Society of Breast Surgeons	None	None	May participate in the guideline development
Dr. Ida T. Lim	Philippine College of Surgeons Cancer Commission	None	None	May participate in the guideline development
Dr. Ruth Anne Manansala-Kong	Philippine Academy of Family Physicians	None	None	May participate in the guideline development
Dr. Paulo Mendoza	Philippine Society of Pathologists	None	None	May participate in the guideline development
Dr. Edna May Go	Philippine Society of Pathologists	None	None	May participate in the guideline development
Dr. Virgilio Novero Jr.	Philippine Society for Fertility Preservation	None	None	May participate in the guideline development
Dr. Eileen Manalo	Philippine Society for Fertility Preservation	Non-declaration	Non-declaration	Excluded in the participation in the guideline development

Dr. Jonas Santiago	Philippine Society of Nuclear Medicine	None	None	May participate in the guideline development
Dr. Jamilla Gomez	Philippine Society of Nuclear Medicine	None	None	May participate in the guideline development
Ms. Giselle Arroyo	ICanServe	None	None	May participate in the guideline development
Dr. Jason Gaddi	Philippine College of Radiology	None	None	May participate in the guideline development
Dr. Catherine SC Teh	Philippine College of Surgeons Cancer Commission	None	None	May participate in the guideline development
Dr. Cynthia Pusag	Philippine Radiation Oncology Society	None	None	May participate in the guideline development
Dr. Jose Rhoel De Leon	Surgical Oncology Society of the Philippines	None	None	May participate in the guideline development
Dr. Gemma Leonora Uy	Surgical Oncology Society of the Philippines	None	None	May participate in the guideline development
Dr. June Michael Razon	Philippine Society of Hospice and Palliative Medicine	With COI	With COI	Excluded in the participation in the guideline development

## Annex B. Summary of ADAPTE Evidence

### Annex B.1. NCPG PIPOH Framework

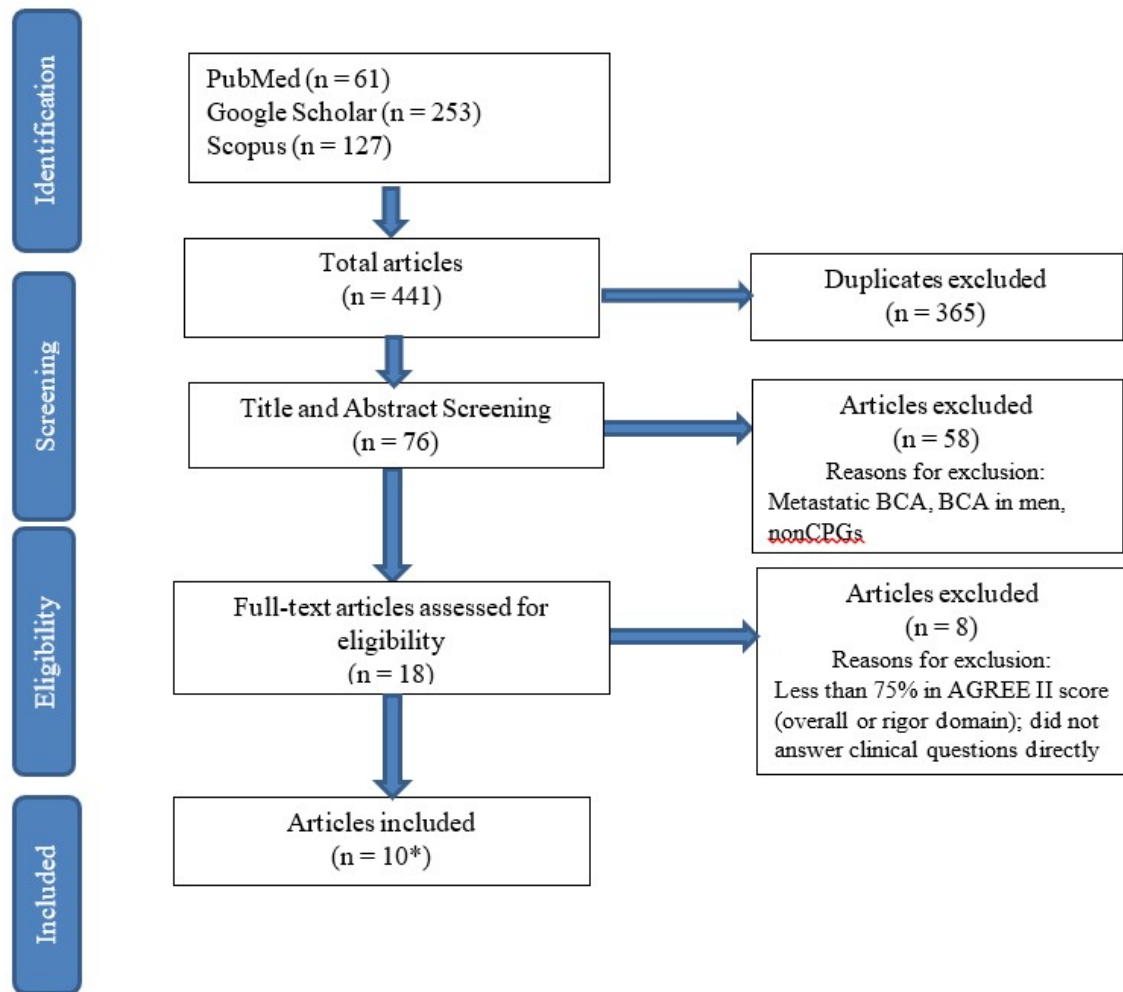
Population	Adult breast cancer stages 0-3; all types
Intervention	Diagnosis and Clinical and Surgical Management
Professionals	Physicians/medical doctors, allied health professionals, and health policy makers
Outcomes	Overall survival rate, disease-free survival, recurrence, remission, diagnostic accuracy
Health Care Setting	Secondary and Tertiary Level of Care

### Annex B.2. Search Strategy

Utilizing the PICO for key search terms of each clinical question, search strategy was conducted with the following study type filters used, database and filter for dates of publication.

<b>Database</b>	<b>Year of Publication</b>	<b>Search string</b>
PubMed	2011 – 2021	“Breast Cancer” AND “Clinical Practice Guidelines”
Scopus	2011 – 2021	“Breast Cancer” AND “Clinical Practice Guidelines”
Google Scholar	2011 – 2021	“Breast Cancer”

### Annex B.3. PRISMA Flow



\* 3 CPGs with <75% overall AGREE II score

#### Annex B.4. AGREE II Guideline Evaluation

Source Guideline	Scope and Purpose	Stakeholder Involvement	Rigor of Development	Clarity of Presentation	Applicability	Editorial Independence	Overall Assessment
Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline	91.7	80.6	77.1	91.7	50.0	66.7	75.0
Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	52.8	50.0	60.4	91.7	10.4	83.3	50.0
Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with early breast cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS	88.9	55.6	44.8	100.0	29.2	83.3	66.7
Management of Breast	100.0	94.4	99.0	100.0	77.1	91.7	91.7

Cancer (MaHTAS 2019)							
Radiation Therapy for the Whole Breast: An American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline	75.0	69.4	76.0	91.7	20.8	50.0	66.7
Fertility problems: assessment and treatment (NICE 2017)	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Early and locally advanced breast cancer: diagnosis and management (NICE 2018)	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Breast Cancer Version 8.2021 (NCCN)	88.9	55.6	86.5	100.0	35.4	100.0	83.3
Breast Cancer Version 3.2022 (NCCN)	88.9	55.6	86.5	100.0	35.4	100.0	83.3
Breast Cancer Screening and Diagnosis Version 1.2021	88.9	55.6	86.5	100.0	35.4	100.0	83.3



## Annex B.5. Source Guidelines Characteristics

<b>Title</b>	<b>Code</b>	<b>Publisher</b>	<b>Country, language</b>	<b>Publication date</b>	<b>Search Duration</b>	<b>Recommendation Standards</b>	<b>AGREE II Score (Rigor)</b>
Breast Cancer Screening and Diagnosis, Version 1.2021	Bca-NCCN2021S CR	NCCN	USA, English	2021	07/21 to 05/22	NCCN Categories of Evidence and Consensus	86.5
Early and locally advanced breast cancer: diagnosis and management	Bca-NICE2018	NICE	UK, English	2018	07/21 to 05/22	n/a	100
Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Bca-ESMO2019	Oxford University Press	Europe, English	2019	07/21 to 05/22	IDSA Levels of evidence and grades of recommendation	60.4
Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with early breast cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS	Bca-ESMO2020	Elsevier Ltd.	Europe, English	2020	07/21 to 05/22	IDSA Levels of evidence and grades of recommendation	44.8

Management of Breast Cancer	Bca-MaHTAS2019	Malaysian Health Technology Assessment Section (MaHTAS)	Malaysia, English	2019	07/21 to 05/22	GRADE	99
Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline	Bca-ASCO2021A	ASCO	USA, English	2021	07/21 to 05/22	GRADE	77.1
Fertility problems: assessment and treatment	Bca-NICE2017	NICE	UK, English	Updated 2017	07/21 to 05/22	n/a	100
Breast Cancer, Version 8.2021	Bca-NCCN2021	NCCN	USA, English	2021	07/21 to 05/22	NCCN Categories of Evidence and Consensus	86.5
Breast Cancer, Version 3.2022	Bca-NCCN2022	NCCN	USA, English	2022	07/21 to 05/22	NCCN Categories of Evidence and Consensus	86.5
Radiation Therapy for the Whole Breast: An American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline	Bca-ASTRO2018	ASTRO	USA, English	2018	07/21 to 05/22	GRADE	66.7

## Annex C. CPG Questions in PICO Framework

### Annex C.1. Diagnosis

1. What is the recommended imaging work-up for patients with suspicious breast symptoms/complaints?

Population	Intervention	Comparator	Outcome
<b>Patients with any breast abnormality</b>	1. Breast ultrasound 2. Mammography	Breast ultrasound and/or mammography (gold standard) * <40 breast ultrasound only	Diagnostic accuracy (Positive predictive value, etc.), all-cause mortality, breast cancer related mortality, morbidity, false positive, false negative, adverse events, QOL

2. What is the recommended biopsy technique to establish diagnosis of suspicious breast lesions?

Population	Intervention	Comparator	Outcome
<b>Patients with any breast abnormality</b>		Core needle biopsy	Diagnostic accuracy, all-cause mortality, breast cancer related mortality, morbidity, false positive, false negative, adverse events, QOL

3. What is the recommended work-up for patients with confirmed breast cancer?

Population	Intervention	Comparator	Outcome
<b>Patients with confirmed breast cancer</b>	1. Chest imaging 1.1 X-ray 1.2 CT scan 2. Bone Scan 3. Serologic Exam (in general) 4.1 Liver Function Test only 4.2 Liver Function Test + Serum Calcium 5. Abdominal Imaging *liver ultrasound only versus whole abdomen ultrasound	Histopathology (gold standard)	Diagnostic accuracy, all-cause mortality, breast cancer related mortality, morbidity, false positive, false negative, adverse events, QOL

## Annex C.2. Treatment (Chemotherapy and Radiotherapy)

4. What are the indications for neoadjuvant chemotherapy for patients with early breast and locally advanced cancer?

Population	Intervention	Comparator	Outcome
<b>Patients with early and locally advanced breast cancer</b>	Chemotherapy alone 1. Neoadjuvant chemotherapy 1.1 All regimens in adjuvant setting can be used in the neoadjuvant	1. Neoadjuvant chemotherapy 1.1. All regimens in adjuvant setting	Response rates, complete pathologic response, OS

5. What are the indications for adjuvant chemotherapy for patients with early and locally advanced breast cancer?

Population	Intervention	Comparator	Outcome
<b>Patients with early and locally advanced breast cancer</b>	Chemotherapy alone 1. Adjuvant chemotherapy 1.1 Doxorubicin-cyclophosphamide (AC Protocol) 1.2 Fluorouracil-doxorubicin-cyclophosphamide (FAC Protocol) 1.3 AC + Paclitaxel 1.4 Docetaxel-doxorubicin-cyclophosphamide (TAC) 1.5 Docetaxel-cyclophosphamide (TC)	No 1. Adjuvant chemotherapy, to be done after adequate surgery; if Her2 positive will need trastuzumab; if hormone positive will need hormone therapy on top of the standard chemotherapy 1.1 CMF versus AC 1.2 FAC versus CMF 1.3 AC alone 1.4 TAC versus FAC 1.5 TC versus AC 1.6 AC + weekly paclitaxel	1.1 Recurrence free survival, overall survival, QOL 1.2 Overall survival, QOL 1.3 Disease free survival, OS, QOL 1.4 DFS, OS, QOL 1.5 DFS, OS, QOL 1.6 DFS, OS, QOL, toxicities 1.7 DFS, OS, QOL, adverse events

1.6 AC + weekly paclitaxel	versus AC + 3 weekly paclitaxel
1.7 Dose dense AC + 2 weekly paclitaxel	versus AC weekly docetaxel
	versus AC 3 weekly docetaxel
	1.7 Sequential A + C + T,
	versus AC every 3 weeks +
	paclitaxel every 3 weeks versus
	dose dense protocol

6. What are the indications and recommended regimen for HER2-targeted treatment for patients with breast cancer?

Population	Intervention	Comparator	Outcome
<b>Patients with confirmed breast cancer Estrogen and/ or Progesterone Receptor Positive</b>	Hormone treatments alone	No hormonal therapy	QOL, overall survival, disease-free survival, mortality-free survival, all-cause mortality, breast cancer related mortality, morbidity, adverse events  1.1 Recurrence free survival, Overall survival 1.2 Recurrence, OS, adverse events, QOL 1.3 Recurrence, OS, adverse events, QOL 1.4 Recurrence, OS, adverse events, QOL 1.5 Recurrence, OS, adverse events, QOL
	1. Adjuvant therapy		
	1.1 Tamoxifen	1.1 versus Observation	
	1.2 Anastrozole	1.2 versus tamoxifen	
	1.3 Letrozole	1.3 versus tamoxifen	
	1.4 Exemestane	1.4 versus tamoxifen	
	1.5 Triptorelin +tamoxifen, triptorelin + exemestane (ovarian suppression)	1.5 versus tamoxifen	
	1.6 Fulvestrant	If with surgery, and/or with chemotherapy, and/or with bisphosphonate, and/or with radiotherapy	
	2. Neoadjuvant therapy		
	2.1 All hormonal agents can be used in the neoadjuvant setting		
	3. Combination of adjuvant or neoadjuvant hormonal treatments		

7. What is the indication of adjuvant hormonal therapy for patients with breast cancer?

Population	Intervention	Comparator	Outcome
<b>Patients with confirmed breast cancer</b>			QOL, overall survival, disease-free survival, mortality-free survival, all-cause mortality, breast cancer related mortality, morbidity, adverse events
<b>1.1 Her2 positive breast cancer in the adjuvant</b>	1.1 Adjuvant trastuzumab (subcutaneous, intravenous)		Cost effectiveness

8. What are the indications for bone-modifying agents for patients with breast cancer?

Population	Intervention	Comparator	Outcome
<b>Patients with confirmed breast cancer with bone metastases</b>	Bisphosphonates alone 1. Zoledronic acid 2. Denusomab	No bisphosphonate 1. versus Placebo (Kohno JCO 2005) 2. versus Placebo 3. versus Zoledronic acid (Stopeck JCO 2010)  If with surgery, and/or with chemotherapy, and/or with hormonal therapy, and/or with radiotherapy	Skeletal related events (QOL)

9. What are the indications for radiation therapy for patients with breast cancer?

Population	Intervention	Comparator	Outcome
<p><b>Patients with confirmed breast cancer (Stage 0-III)</b></p>	<p>1. External beam radiation therapy (Conventional Fractionation)            A) Whole Breast Irradiation +/- Regional Node RT +/- Boost</p> <p>2. External beam radiation therapy (Hypofractionated Radiation)            A) Whole Breast Irradiation +/- Regional Node RT +/- Boost</p> <p>3. Accelerated partial breast radiation therapy            A) Interstitial Multicatheter PBI</p>	<p>No radiotherapy</p> <p>Conventional Fractionated RT            a) If with surgery (following BCS or following MRM), and/or b) with chemotherapy (following adjuvant chemo or following neoadjuvant chemo), and/or c) with hormonal therapy, and/or d) with bisphosphonates</p> <p>Hypofractionated RT a) If with surgery (following BCS or following MRM), and/or b) with chemotherapy (following adjuvant chemo or following neoadjuvant chemo), and/or c) with hormonal therapy, and/or d) with bisphosphonates</p> <p>No boost            No full RNI (Axilla/SCV/IMN)</p>	<p>QOL, overall survival, disease-free survival, mortality-free survival, all-cause mortality, breast cancer related mortality, morbidity, adverse events</p>



10. What is the role of genomic testing in breast cancer?

<b>Population</b>	<b>Intervention</b>	<b>Comparator</b>	<b>Outcome</b>
<b>Patients with breast cancer</b>	Genomic testing	No genomic testing	QOL, overall survival, disease-free survival, mortality-free survival, all-cause mortality, breast cancer related mortality, morbidity, adverse events

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11. What are the recommended fertility preservation and birth control measures among premenopausal breast cancer patients?

<b>Population</b>	<b>Intervention</b>	<b>Comparator</b>	<b>Outcome</b>
<b>Patients with breast cancer</b>	Fertility preservation	No fertility preservation	QOL, overall survival, disease-free survival, mortality-free survival, all-cause mortality, breast cancer related mortality, morbidity, adverse events

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### Annex C.3. Treatment (Surgical)

12. What is the recommended surgical management for patients with breast cancer?

Population	Intervention	Comparator	Outcome
<b>Patients with confirmed breast cancer</b>	Surgery 1. Breast-conserving surgery a. Lumpectomy b. Quadrantectomy c. Partial mastectomy d. Segmental mastectomy 2. Mastectomy (total)	No surgery  If with chemotherapy, and/or with hormonal therapy, and/or with bisphosphonate, and/or with radiotherapy	Overall survival, disease-free survival, mortality-free survival, all-cause mortality, breast cancer related mortality, morbidity, adverse events, QOL

13. What is the recommended axillary staging for patients with invasive breast cancer?

Population	Intervention	Comparator	Outcome
<b>Patients with invasive breast cancer</b>	1. Axillary clearance alone (Axillary lymph node dissection - ALND) - clinically positive LN  2. Axillary sentinel node biopsy alone - clinically negative LN	No axillary staging	Overall survival, recurrence rate, adverse events, disease-free survival, mortality-free survival, all-cause mortality, breast cancer related mortality, morbidity, QOL

## Annex C.4. Surveillance

14. What is the recommended surveillance for treated patients with breast cancer?

<b>Population</b>	<b>Intervention</b>	<b>Comparator</b>	<b>Outcome</b>
<b>Treated patients with breast cancer</b>	Surveillance	No surveillance	Diagnostic accuracy, cancer-related mortality, relapse

## Annex C.5. Source Guideline Content Comparison

A check (✓) indicates inclusion of the relevant discussion in the guideline										
	Bca-NCCN 2021 SCR	Bca-NCCN 2021	Bca-NCCN 2022	Bca-NICE 2017	Bca-NICE 2018	Bca-ESMO 2019	Bca-ESMO 2020	Bca-MaHTA S2019	Bca-ASCO 2021A	Bca-ASTR O2018
<b>DIAGNOSIS</b>										
What is the recommended imaging work-up for patients with suspicious breast symptoms/complaints?	✓		✓						✓	
What is the recommended biopsy technique to establish diagnosis of suspicious breast lesions?	✓							✓		
What is the recommended workup for patients with confirmed breast cancer?		✓	✓		✓	✓	✓	✓		
<b>CLINICAL MANAGEMENT</b>										
What are the indications for neoadjuvant chemotherapy for patients with early breast and locally advanced cancer?			✓			✓				
What are the indications for adjuvant chemotherapy for patients with early and locally advanced breast cancer?			✓							
What are the indications and recommended regimen for HER2-targeted treatment for patients with breast cancer?			✓							

What is the indication of adjuvant hormonal therapy for patients with breast cancer?			✓					✓		
What are the indications for bone-modifying agents for patients with breast cancer?			✓							
What are the indications and fractionation for radiation therapy for patients with breast cancer?		✓	✓							✓
What is the role of genomic testing in breast cancer?		✓	✓			✓				
What are the recommended fertility preservation and birth control measures among premenopausal breast cancer patients?		✓		✓		✓				
<b>SURGICAL MANAGEMENT</b>										
What is the recommended surgical management for patients with breast cancer?		✓			✓					
What is the recommended axillary staging for patients with invasive breast cancer?	✓								✓	
<b>SURVEILLANCE</b>										
What is the recommended post-treatment surveillance for breast cancer?	✓		✓							

## Annex D. AGREE II Reporting Checklist (Self-Evaluation)

TITLE OF CPG: \_\_\_\_\_

EVALUATOR: \_\_\_\_\_ DATE: \_\_\_\_\_

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE														
<b>DOMAIN 1. SCOPE AND PURPOSE</b>																	
<b>1. THE OVERALL OBJECTIVE(S) OF THE GUIDELINES IS (ARE) SPECIFICALLY DESCRIBED.</b>	<input type="checkbox"/> Health intent <input type="checkbox"/> Expected benefit or outcome <input type="checkbox"/> Target		<table border="1" style="width: 100%; text-align: center;"> <tr> <td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td> </tr> <tr> <td>Strongly Disagree</td><td></td><td></td><td></td><td></td><td></td><td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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<input type="checkbox"/> Target population <input type="checkbox"/> Intervention or exposure <input type="checkbox"/> Comparisons <input type="checkbox"/> Outcomes <input type="checkbox"/> Health care setting or context		<table border="1" style="width: 100%; text-align: center;"> <tr> <td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td> </tr> <tr> <td>Strongly Disagree</td><td></td><td></td><td></td><td></td><td></td><td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree	
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Strongly Disagree						Strongly Agree											
<b>2. THE HEALTH QUESTION(S) COVERED BY THE GUIDELINE IS (ARE) SPECIFICALLY DESCRIBED)</b>	<input type="checkbox"/> Target population <input type="checkbox"/> Clinical condition <input type="checkbox"/> Severity/stage <input type="checkbox"/> Comorbidities <input type="checkbox"/> Excluded populations		<table border="1" style="width: 100%; text-align: center;"> <tr> <td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td> </tr> <tr> <td>Strongly Disagree</td><td></td><td></td><td></td><td></td><td></td><td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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Strongly Disagree						Strongly Agree											
<b>DOMAIN 2. STAKEHOLDER INVOLVEMENT</b>																	
<b>4. THE GUIDELINE DEVELOPMENT GROUP INCLUDES INDIVIDUALS FROM ALL RELEVANT PROFESSIONAL GROUPS.</b>	<input type="checkbox"/> Name of participant <input type="checkbox"/> Discipline/content expertise <input type="checkbox"/> Institution <input type="checkbox"/> Geographical location <input type="checkbox"/> A description of the member's role in the guideline development		<table border="1" style="width: 100%; text-align: center;"> <tr> <td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td> </tr> <tr> <td>Strongly Disagree</td><td></td><td></td><td></td><td></td><td></td><td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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Strongly Disagree						Strongly Agree											
<b>5. THE VIEWS AND PREFERENCES OF THE TARGET POPULATION (PATIENTS, PUBLIC, ETC.) HAVE BEEN SOUGHT.</b>	<input type="checkbox"/> Statement of type of strategy used to capture patient/public views and preferences <input type="checkbox"/> Methods by which preferences and views were sought		<table border="1" style="width: 100%; text-align: center;"> <tr> <td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td> </tr> <tr> <td>Strongly Disagree</td><td></td><td></td><td></td><td></td><td></td><td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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Strongly Disagree						Strongly Agree											

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE														
<p><b>6. THE TARGET USERS OF THE GUIDELINE ARE CLEARLY DEFINED.</b></p> <p><b>DOMAIN 3. RIGOUR OF DEVELOPMENT</b></p>	<input type="checkbox"/> Outcomes/ information gathered on patient/public information <input type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations <input type="checkbox"/> The intended guideline audience <input type="checkbox"/> How the guideline may be used by its target audience		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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Strongly Disagree						Strongly Agree											
<p><b>7. SYSTEMATIC METHODS WERE USED TO SEARCH FOR EVIDENCE.</b></p>	<input type="checkbox"/> Named electronic databases or evidence source where the search was performed <input type="checkbox"/> Time periods searched <input type="checkbox"/> Search terms used <input type="checkbox"/> Full search strategy included		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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Strongly Disagree						Strongly Agree											
<p><b>8. THE CRITERIA FOR SELECTING THE EVIDENCE ARE CLEARLY DESCRIBED.</b></p>	<input type="checkbox"/> Target population <input type="checkbox"/> Study design <input type="checkbox"/> Comparisons <input type="checkbox"/> Outcomes <input type="checkbox"/> Language <input type="checkbox"/> Context		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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<p><b>9. THE STRENGTHS AND LIMITATIONS OF THE BODY OF EVIDENCE ARE CLEARLY DESCRIBED. TOOLS EXIST THAT CAN FACILITATE THE REPORTING OF THIS CONCEPT.</b></p>	<input type="checkbox"/> Study design included in body of evidence <input type="checkbox"/> Study methodology limitations <input type="checkbox"/> Appropriateness/ relevance of primary and secondary outcomes considered <input type="checkbox"/> Consistency of results across studies		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE														
<p><b>10. THE METHODS FOR FORMULATING THE RECOMMENDATIONS ARE CLEARLY DESCRIBED. SPECIFY AREAS OF DISAGREEMENTS AND METHODS USED TO RESOLVE THEM.</b></p> <p><b>11. THE HEALTH BENEFITS, SIDE EFFECTS, AND RISKS HAVE BEEN CONSIDERED IN FORMULATING THE RECOMMENDATIONS.</b></p>	<input type="checkbox"/> Direction of results across studies <input type="checkbox"/> Magnitude of benefit vs magnitude of harm <input type="checkbox"/> Applicability to practice context. <input type="checkbox"/> Recommendation development process <input type="checkbox"/> Outcomes of the recommendation development process <input type="checkbox"/> How the process influenced the recommendations		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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	Strongly Disagree						Strongly Agree										
<input type="checkbox"/> Supporting data and report of benefits <input type="checkbox"/> Supporting data and report of harms/side effects/ risks <input type="checkbox"/> Reporting of the balance/trade-off between benefits and harms/side effects/risks <input type="checkbox"/> Recommendations reflect considerations of both benefits and harms/side effects/risks		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree	
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<p><b>12. THERE IS AN EXPLICIT LINK BETWEEN THE RECOMMENDATIONS AND THE SUPPORTING EVIDENCE.</b></p>	<input type="checkbox"/> How the guideline development group linked and used the evidence to inform recommendations. <input type="checkbox"/> Link between each recommendation and key evidence <input type="checkbox"/> Link between recommendations and evidence summaries/or evidence tables in the results section of the guideline		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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<p><b>13. THE GUIDELINE HAS BEEN EXTERNALLY REVIEWED BY EXPERTS PRIOR TO ITS PUBLICATION.</b></p>	<input type="checkbox"/> Purpose and intent of the external review <input type="checkbox"/> Methods taken to undertake the external review		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE														
<p><b>14. A PROCEDURE FOR UPDATING THE GUIDELINE IS PROVIDED.</b></p> <p><b>DOMAIN 4. CLARITY OF PRESENTATION</b></p>	<p><input type="checkbox"/> Description of the external reviewers</p> <p><input type="checkbox"/> Outcomes/information gathered from the external review</p> <p><input type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations.</p> <p><input type="checkbox"/> A statement that the guideline will be updated</p> <p><input type="checkbox"/> Explicit time interval or explicit criteria to guide decisions about when an update will occur</p> <p><input type="checkbox"/> Methodology for the updating procedure</p>	<p>Comments:</p>	<table border="1" data-bbox="869 593 1197 683"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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Strongly Disagree						Strongly Agree											
<p><b>15. THE RECOMMENDATIONS ARE SPECIFIC AND UNAMBIGUOUS.</b></p>	<p><input type="checkbox"/> A statement of the recommended action</p> <p><input type="checkbox"/> Intent or purpose of the recommended action</p> <p><input type="checkbox"/> Relevant population</p> <p><input type="checkbox"/> Caveats or qualifying statements, if relevant</p> <p><input type="checkbox"/> If there is uncertainty about the best care option, the uncertainty should be stated in the guideline</p>	<p>Comments:</p>	<table border="1" data-bbox="869 974 1197 1064"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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Strongly Disagree						Strongly Agree											
<p><b>16. THE DIFFERENT OPTIONS FOR MANAGEMENT OF THE CONDITION OR HEALTH ISSUE ARE CLEARLY PRESENTED.</b></p>	<p><input type="checkbox"/> Description of management options</p> <p><input type="checkbox"/> Population or clinical situation most appropriate to each option</p>	<p>Comments:</p>	<table border="1" data-bbox="869 1332 1197 1422"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE														
<b>17. KEY RECOMMENDATIONS ARE EASILY IDENTIFIABLE.</b>  <b>DOMAIN 5. APPLICABILITY</b>	<input type="checkbox"/> Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms <input type="checkbox"/> Specific recommendations grouped together in one section		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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<b>18. THE GUIDELINE DESCRIBES FACILITATORS AND BARRIERS TO ITS APPLICATION.</b>	<input type="checkbox"/> Types of facilitators and barriers that were considered <input type="checkbox"/> Method by which information regarding the facilitators and barriers to implementing recommendations were sought. <input type="checkbox"/> Information/ description of the types of facilitators and barriers that emerged from the injury <input type="checkbox"/> How the information influenced the guideline development process and/or formation of the recommendations <input type="checkbox"/> Additional materials to support the implementation		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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Strongly Disagree						Strongly Agree											
<b>19. THE GUIDELINE PROVIDES ADVICE AND/OR TOOLS ON HOW THE RECOMMENDATIONS CAN BE PUT INTO PRACTICE.</b>	<input type="checkbox"/> Types of cost information that were considered <input type="checkbox"/> Methods by which the cost information was sought		<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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Strongly Disagree						Strongly Agree											
<b>20. THE POTENTIAL SOURCE IMPLICATIONS OF APPLYING THE RECOMMENDATIONS HAVE BEEN CONSIDERED.</b>			<table border="1"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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Strongly Disagree						Strongly Agree											

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE														
<p><b>21. THE GUIDELINE PRESENTS MONITORING AND/OR AUDITING CRITERIA.</b></p> <p><b>DOMAIN 6. EDITORIAL INDEPENDENCE</b></p>	<p><input type="checkbox"/> Information/description of the cost information that emerged from the inquiry</p> <p><input type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations.</p> <p><input type="checkbox"/> Criteria to assess guideline implementation or adherence to recommendations</p> <p><input type="checkbox"/> Criteria for assessing impact of implementing the recommendations</p> <p><input type="checkbox"/> Advice on the frequency and interval of measurement</p> <p><input type="checkbox"/> Operational definitions of how the criteria should be measured.</p>		<table border="1" data-bbox="861 560 1189 649"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
1	2	3	4	5	6	7											
Strongly Disagree						Strongly Agree											
<p><b>22. THE VIEWS OF THE FUNDING BODY HAVE NOT INFLUENCED THE CONTENT OF THE GUIDELINE.</b></p>	<p><input type="checkbox"/> The name of the funding body or source of funding</p> <p><input type="checkbox"/> A statement that the funding body did not influence the content of the guideline</p>		<table border="1" data-bbox="861 1075 1189 1164"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
1	2	3	4	5	6	7											
Strongly Disagree						Strongly Agree											
<p><b>23. COMPETING INTERESTS OF GUIDELINE DEVELOPMENT GROUP MEMBERS HAVE BEEN RECORDED AND ADDRESSED.</b></p>	<p><input type="checkbox"/> Types of competing interests considered</p> <p><input type="checkbox"/> Methods by which potential competing interests were sought</p> <p><input type="checkbox"/> a description of the competing interests</p> <p><input type="checkbox"/> How the competing interests influenced the guideline process and</p>		<table border="1" data-bbox="861 1254 1189 1344"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
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<p><b>OVERALL GUIDELINE ASSESSMENT</b></p> <p><b>1. RATE THE OVERALL QUALITY OF THIS GUIDELINE</b></p> <p><b>2. I WOULD RECOMMEND THIS GUIDELINE FOR USE.</b></p>	<p>development of recommendations</p>		<table border="1" data-bbox="879 524 1192 607"> <tr> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> </tr> <tr> <td>Strongly Disagree</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>Strongly Agree</td> </tr> </table> <p>Comments:</p> <p>YES</p> <p>YES WITH MODIFICATTION</p> <p>NO</p>	1	2	3	4	5	6	7	Strongly Disagree						Strongly Agree
1	2	3	4	5	6	7											
Strongly Disagree						Strongly Agree											