Guideline Resource Unit
guru@ahs.ca

Staging Investigations for Patients with Newly Diagnosed Breast Cancer

Without Signs and/or Symptoms of Metastases

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Cancer Care Alberta

Clinical Practice Guideline BR-012 – Version 3
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Background

In Canada, breast cancer accounts for one-quarter (25.6%) of all new cancer cases in females and less than 1% (0.2%) in males.[1] Imaging plays an important role in the work-up of patients newly diagnosed with breast cancer because accurate staging determines optimal treatment. However, unnecessary investigations can lead to the misuse of limited resources and potential harm to patients. This harm may include delays in treatment, invasive procedures, over-treatment, radiation exposure, and misdiagnosis. Therefore, careful consideration and appropriate use of imaging are essential to mitigate these risks.

Staging investigations in breast cancer patients gained significant attention with the release of the American Society for Clinical Oncology's (ASCO's) Choosing Wisely recommendations in 2012.[2] The campaign aimed to promote conversations between clinicians and patients about avoiding unnecessary medical tests, treatments, and procedures. At the time, it recommended against performing positron emission tomography (PET), computed tomography (CT), and bone scans in the work up of early-stage breast cancer patients (ductal carcinoma in situ [DCIS], or clinical stage I or II disease) at low risk for metastasis due to a lack of evidence demonstrating clinical benefit. However, in the time since these recommendations were released, clinical practice has shifted significantly, with the increasing use of neoadjuvant chemotherapy in more early-stage breast cancer treatment, necessitating a re-evaluation of staging practices.

The purpose of this guideline is to provide consensus-based recommendations about staging investigations for patients newly diagnosed with biopsy proven breast cancer and without signs and/or symptoms of distant metastases.

Guideline Questions

1. What staging investigations should be used for patients newly diagnosed with breast cancer and without signs and/or symptoms of metastatic disease?

Search Strategy

A systematic review of clinical practice guidelines for breast cancer staging, available in English, online, and published within the past 5 years (i.e., between May 2018 and May 2024) was conducted. Several strategies were employed to identify relevant guidelines, including manual searches of the websites of established oncology-focused health organizations, as well as utilizing the PubMed, Trip Pro, and ECRI Guidelines Trust databases. When multiple guidelines referencing breast cancer staging were issued by the same organization within a 5-year period, we exclusively referenced the latest iteration. Guidelines from lesser-known organizations were excluded to prioritize recommendations from widely recognized and established entities in the field. In total, five guidelines from four organizations were considered in developing our recommendations for staging investigations: the American College of Radiology (ACR), Cancer Care Ontario (CCO), European Society for Medical Oncology (ESMO) covering both early- and advanced-stage cancers, and the

National Comprehensive Cancer Network (NCCN). Additionally, two guidelines from Cancer Care Ontario and the National Institute for Health and Care Excellence (NICE) were considered to clarify the role of magnetic resonance imaging (MRI) in staging.

Target Population

The following recommendations apply to adult patients (i.e., ≥18 years of age) newly diagnosed with breast cancer and without signs and/or symptoms of distant metastases. Additional targeted diagnostic imaging investigations may be indicated for patients presenting with signs and/or symptoms of metastatic disease and/or clinical suspicion of metastases.

Recommendations

The AJCC Cancer Staging Manual 8th Edition distinguishes between three stage group tables: the Anatomic Stage Group table, the Clinical Prognostic Stage Group table, and the Pathological Prognostic Stage Group table.[3] For the purposes of our guidelines on staging patients newly diagnosed with breast cancer, we will refer to Anatomic Stage Grouping. See Appendix A for the full table.

All patients with suspected breast cancer should undergo a bilateral diagnostic mammogram and breast and axillary ultrasound as part of their initial imaging workup. Beyond this initial imaging, further staging investigations in patients without signs and/or symptoms of distant metastases are based on the clinical stage of the disease, as outlined below:

1. **Stage 0 (DCIS)**: Staging investigations are not recommended.
2. **Stage I**: Staging investigations are not recommended.
3. **Stage II**:
    a. **Stage IIA (T0/1N1, T2N0)**: Staging investigations are not recommended routinely, post-operatively or prior to neoadjuvant chemotherapy, irrespective of tumour biology.
    b. **Stage IIB (T2N1, T3N0)**: Staging investigations with CT scan of the chest and abdomen (with or without pelvis) with contrast if no contraindications, and bone scan are recommended.
4. **Stage III:** Staging investigations with CT scan of the chest and abdomen (with or without pelvis) with contrast if no contraindications, and bone scan are recommended.
5. **PET/CT** is not recommended routinely but may be considered for further evaluation of equivocal findings on conventional imaging.
6. **MRI** Breast may be considered pre-operatively for select cases if required for surgical planning to assess cancer extent, multifocal or multicentric disease, poorly defined invasive lobular carcinoma (ILC), or to detect occult primary disease in patients with axillary nodal metastases.

Discussion

The above recommendations are primarily adapted from national and international breast cancer guidelines. These recommendations were thoroughly discussed by the Provincial Breast Tumour

Team Executive during a guidelines meeting held in Calgary, Alberta, on May 10, 2024. A first draft of the guideline was sent to the Working Group in July, and it was presented on October 3, 2024, at the Provincial Breast Tumour Team Meeting. Following this, the guideline was shared across the province for further feedback.

Stage 0 breast cancer (DCIS). NCCN is the only guideline that specifically addresses staging investigations for stage 0 (DCIS) breast cancer.[4] It emphasizes selective use of breast MRI when indicated and does not include any other imaging recommendations. Further details on the use of breast MRI are provided in a subsequent section.

Stage I breast cancer. The ACR, CCO, ESMO, and NCCN guidelines all address appropriate investigations for stage I breast cancer. CCO advises against the routine use of conventional anatomic imaging (i.e., chest X-ray, liver ultrasound [US], and chest-abdomen-pelvis CT scans) and/or metabolic imaging modalities (i.e., PET/CT, PET/MR, bone scans), irrespective of biomarker status.[5] ESMO and NCCN guidelines support this approach by not recommending any staging investigations, with all three guidelines stating that breast MRI is useful in certain circumstances.[4,6]

NCCN notes that for patients with cT1c, cN0 human epidermal growth factor receptor (HER2)-positive disease and triple-negative breast cancer (TNBC) who are candidates for preoperative systemic therapy, additional tests to consider include chest CT with or without contrast, abdominal CT with or without contrast or MRI with contrast, and a bone scan or PET/CT as clinically indicated.[4] The ACR states that there is no evidence to support the use of whole-body bone scans in stage I breast cancer, and lists CT chest, abdomen, and pelvis as "Usually Not Appropriate." ACR does make reference of NCCN's note for CT chest, abdomen, and pelvis with IV contrast in patients with clinical stage I breast cancer if the tumour is greater than 1 cm and is triple negative or HER2-positive.[7]

Stage II breast cancer. Staging investigations for patients with stage II breast cancer generated significant discussion within the guideline working group. The ACR distinguishes between stage IIA and stage IIB breast cancer, aligning staging recommendations for stage IIA with those for stage I (see above section), whereas stage IIB recommendations are grouped with stage III (see below section).[7] CCO maintains consistent advice across stages I and II, advising against routine staging tests using conventional anatomic and/or metabolic imaging for patients without symptoms of distant metastasis, irrespective of biomarker status or planned neoadjuvant therapy.[5] However, their most recent guidelines incorporating PET/CT allow for Stage IIB disease but only T3N0 and not T2N1 disease. Recommendations against routine staging is supported by a small retrospective study conducted in Ontario with asymptomatic pathological stage T1-2, N0-1 breast cancer that aimed to assess local practice and outcomes of staging investigations.[8] Results showed that 57% of patients underwent baseline staging investigations, totaling 332 tests, yet only five patients were diagnosed with overt metastatic disease. Among the patients who received initial staging imaging, 42% underwent an additional 138 follow-up tests, none of which identified metastases.

ESMO suggests considering a CT scan of the chest, abdominal imaging (US, CT, or MRI) and bone scan for patients with clinically positive axillary nodes or large tumours (e.g., 5 cm), but also non-specifically for “aggressive biology” (undefined). Supplementary material emphasizes that

assessment of distant metastases (bone, liver and lung) is recommended only for patients with stage IIB and higher disease, especially with extended lymph node involvement, for patients with a high risk of recurrence at first diagnosis and/or in symptomatic patients.[6] FDG-PET-CT may serve as an alternative to CT and bone scans. Additionally, brain imaging should not be performed routinely in asymptomatic patients.

NCCN specifies that routine systemic staging is not warranted for localized breast cancer (i.e., invasive, non-inflammatory, non-metastatic [M0]).[4] However, additional tests may be considered for patients who are ≥cT2 or cN+ and M0 before starting neoadjuvant therapy. These additional tests, to be considered based on clinically judgement, include chest CT with or without contrast, abdominal with or without pelvis CT with contrast or MRI with contrast, and bone scan or PET/CT.

Stage III. The ACR, CCO, ESMO, and NCCN guidelines all provide recommendations for these investigations. The ACR states that for patients newly diagnosed with stage IIB-III breast cancer, staging investigations that are considered appropriate include CT of the chest-abdomen-pelvis with IV contrast, bone scan, and FDG-PET/CT from the skull base to mid-thigh.[7] In 2024, CCO updated part of its 2019 guideline based on new level 1 evidence regarding the utility of PET/CT.[5] For patients with newly diagnosed locally advanced breast cancer, where CCO previously recommended using either anatomic and/or metabolic imaging modalities, it now recommends PET/CT as the preferred modality for baseline staging tests. This recommendation applies regardless of whether the patient is symptomatic for distant metastasis and regardless of biomarkers profile.[5] The study that prompted this change was a prospective, randomized trial comparing PET/CT to conventional anatomic imaging in clinical stage III or IIb (T3N0, but not T2N1) patients planning to undergo neoadjuvant therapy sponsored by the Ontario Clinical Oncology Group (OCOG).[9] The results showed that 23% of patients who had PET-CT imaging were upstaged to stage IV, compared to 11% of those who underwent convention staging. The working group's interpretation of this study and the utility of PET/CT is discussed in a subsequent section. Note that in centers without access to PET scanners, CCO states that either anatomic and/or metabolic imaging modalities may be used for baseline staging tests.

In ESMO's guideline for advanced breast cancer, it is highly recommended that the minimal staging work-up should include imaging of chest and abdomen (preferably with a CT scan), and bone imaging before the initiation of systemic therapy.[10] PET-CT, if available, may be used instead of, but not in addition to CT scans and a bone scan. Brain imaging is not routinely recommended for asymptomatic patients with advanced breast cancer, including those with HER2-positive and/or TNBC. The NCCN states that breast MRI is optional, once again for mammographically occult tumours.[4] Additional imaging studies are recommended only if there are signs and symptoms of metastatic disease. These additional imaging studies have been noted previously.

PET. The OCOG PET ABC study was a prospective, randomized trial comparing PET/CT to conventional anatomic imaging in clinical TNM stage III or IIb (T3N0, but not T2N1) patients with histological evidence of invasive ductal (not lobular) carcinoma of the breast planning to undergo

neoadjuvant therapy previously mentioned, is the first and only randomized controlled trial on this subject.[9] OCOG demonstrated that PET-CT detected more distant metastases than conventional staging, and fewer PET-CT patients received combined modality therapy. However, it should be noted that the study did not include Stage IIA and T2N1 disease of Stage IIB disease and found no difference in detection rates for inflammatory breast cancer. Limitations included a small sample size without power for survival analysis, limited long-term follow-up, and a lack of confirmatory biopsies in most upstaged patients, potentially leading to false positives. According to NCCN guidelines, "FDG-PET/CT is most beneficial and accurate for advanced disease (stage III) and invasive ductal (compared to lobular) histology but may be useful in selected circumstances of earlier stage disease (stage IIA, T1N1, T2N0 disease) such as: equivocal CT+ bone scan results; suspicion of undetected nodal and/or distant disease; and treatment response assessment."[4] Following the guidelines working group meeting in May, the Joint European Association of Nuclear Medicine (EANM)-Society of Nuclear Medicine and Molecular Imaging (SNMMI) guideline on the role of PET/CT in patients with no special type breast cancer was published and subsequently endorsed by several key international oncology and radiology organizations.[11] The experts concluded that for baseline staging, PET/CT can be recommended for stage IIB (preferably before surgery) and stage III (including inflammatory breast cancer), and may be useful in patients with clinical stage IIA (T1N1 or T2N0), though there is insufficient data to recommend its routine use. PET/CT can be performed instead of, and not in combination with, conventional imaging modalities for staging.

MRI. MRI is one of the most sensitive imaging techniques for detecting breast cancer, with the potential to be highly specific. However, as CCO notes, its performance depends on the quality of the equipment, the MRI techniques used, and the expertise of the personnel conducting the analysis.[12] CCO recommends that preoperative breast MRI should be considered on a case-by-case basis for various purposes, including surgical planning of breast-conserving surgery (BCS) in patients with suspected or known multicentric or multifocal disease. It is also recommended to identify additional lesions in patients with dense breasts, and to assess the presence of pectoralis major muscle or chest wall invasion in patients with posteriorly located tumours or suspected invasion. Additionally, breast MRI is advised for planning skin/nipple-sparing mastectomies, autologous reconstruction, oncoplastic surgery, and BCS with suspected nipple/areolar involvement. Finally, CCO suggests considering breast MRI for patients with familial/hereditary breast cancer who have not had a recent breast MRI as part of screening or diagnosis.

The NCCN also delineates specific indications and applications where breast MRI may be beneficial.[4] These include its use for staging evaluation to determine the extent of cancer or the presence of multifocal or multicentric cancer in the ipsilateral breast, and for screening the contralateral breast at the time of initial diagnosis. Additionally, breast MRI is recommended for evaluating breast cancer both before and after preoperative systemic therapy to assess disease extent, treatment response, and the potential for breast-conservation therapy. Finally, the NCCN states that breast MRI may aid in identifying clinically occult disease in patients with axillary nodal metastases (cT0, cN+), Paget disease, or ILC poorly defined on mammography, US, or physical examination.

NICE advises against routine provision of breast MRI in the preoperative evaluation of patients with biopsy-proven invasive breast cancer or DCIS.[13] However, breast MRI may be considered for patients with invasive breast cancer in cases where there is discrepancy in the assessment of disease extent from clinical examination, mammography and US, affecting treatment planning. It is also recommended when breast density limits accurate mammographic assessment or when assessing tumour size for potential BCS in ILC.

Conclusions

Overall, the reviewed guidelines recommend against routine systemic staging for early-stage breast cancer, with comprehensive staging reserved for higher stages, high-risk patients, or when clinical signs of metastasis are present. Advanced imaging modalities such as PET/CT are primarily recommended for more advanced stages or when conventional imaging results are inconclusive. Generally, MRI use is recommended only in select circumstances. This approach emphasizes the careful use of imaging to balance the benefits of thorough assessment against the risks and potential harms of over-imaging. However, it is noteworthy that most of these guidelines lack references to peer-reviewed studies, primarily due to the absence of high-level evidence.

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Appendix A: AJCC 8th Edition Tumour (T), Node (N), Metastasis (M) Anatomic Stage Group*

Stage	Tumour	Regional Lymph Node	Distant Metastasis
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
IB	T1	N1mi	M0
IIA	T0	N1	M0
IIA	T1	N1	M0
IIA	T2	N0	M0
IIB	T2	N1	M0
IIB	T3	N0	M0
IIIA	T0	N2	M0
IIIA	T1	N2	M0
IIIA	T2	N2	M0
IIIA	T3	N1	M0
IIIA	T3	N2	M0
IIIB	T4	N0	M0
IIIB	T4	N1	M0
IIIB	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

*Table adapted from Hortobagyi GN, Connolly JL, D'Orsi CJ, Edge SB, Mittendorf EA, et al: Breast. In: Amin MB, Edge S, Greene F, et al, eds; American Joint Committee on Cancer. AJCC cancer staging manual. 8th ed. New York, NY: Springer. 2017.[3]

Notes:

- T1 includes T1mi.
- T0 and T1 tumours with nodal micrometastases (N1mi) staged as Stage IB.
- T2, T3, and T4 tumours with nodal micrometastases (N1mi) staged using N1 category.
- M0 includes M0(i+).
- Designation pM0 not valid; any M0 is clinical.
- If patient presents with M1 disease prior to neoadjuvant systemic therapy, stage is Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal presence of distant metastases, provided studies performed within 4 months of diagnosis in absence of disease progression, and provided patient has not received neoadjuvant therapy.
- Staging following neoadjuvant therapy denoted with 'yc' or 'yp' prefix to T and N classification. No anatomic stage group assigned if complete pathological response to neoadjuvant therapy (e.g., ypT0ypN0cM0).

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Breast Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a guideline working group comprised of members from the Alberta Provincial Breast Tumour Team and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in April 2011 and revised in July 2012 and November 2024.

Maintenance

A formal review of the guideline will be conducted in 2027. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

ACR, American College of Radiology; ASCO, American Society of Clinical Oncology; BCS, breast conserving surgery; CCO, Cancer Care Ontario; CT, computed tomography; DCIS, ductal carcinoma in situ; EANM, European Association of Nuclear Medicine; ER, estrogen receptor; ESMO, European Society of Medical Oncology; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; PET, positron emission tomography; SNMMI, Society of Nuclear Medicine and Molecular Imaging; TNBC, triple-negative breast cancer; US, ultrasound.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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