Guideline 1-14 Version 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Baseline Staging Imaging for Distant Metastasis in Women with Stage I, II, and III Breast Cancer

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Report Date: October 7, 2019

An assessment conducted in November 2025 deferred the review of Guideline 1-14 Version 3. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document
(PEBC Assessment & Review Protocol)

Guideline 1-14 Version 3 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1096

[1] A full list of participants is provided in Appendix 1.

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Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To provide recommendations for the use of imaging tests to detect distant metastases in women with newly diagnosed breast cancer.

TARGET POPULATION

Women with newly diagnosed primary breast cancer (originated in the breast) who have no symptoms of distant metastasis.

INTENDED USERS

This guideline is intended for health care professionals, policy makers, program planners, and institutions involved in the management of women with clinical and pathologically confirmed primary breast cancer.

RECOMMENDATIONS

Recommendation 1

Staging tests using conventional anatomic (chest X-ray, liver ultrasound, chest-abdomen-pelvis computed tomography [CT] scan) and/or metabolic imaging modalities (positron emission tomography [PET]/CT, PET/magnetic resonance [MR], bone scintigraphy) should not be ordered routinely for women newly diagnosed with clinical stage I or stage II breast cancer, and with no symptoms of distant metastasis, regardless of biomarker status.

Qualifying Statements for Recommendation 1

- Baseline conventional anatomic imaging modalities (chest X-ray, liver ultrasound, bone scan, chest-abdomen-pelvis CT scan) should not be ordered routinely in women with newly diagnosed stage I or II breast cancer because this population exhibits an extremely low prevalence of asymptomatic distant metastasis.
- Although PET/CT may improve the detection rate, the prevalence of distant metastasis in women with early stage I or II breast cancer is very low, and PET/CT may add unnecessary anxiety and resource use. Therefore, the use of PET/CT, as part of the baseline staging in women clinically diagnosed with early-stage breast cancer (I, II) and with no symptoms for distant metastasis is not recommended at this time.
- Although women with triple negative and human epidermal growth factor receptor 2-positive breast cancer have an increased risk of disease recurrence, the association of distant metastasis and biomarker profile in early-stage breast cancer has not been adequately studied in prospective studies of staging investigation. The benefit and risks of the routine use of biomarker profiles to assess for distant metastasis is still unclear and, thus, its use to guide decisions on imaging staging for clinical early-stage breast cancer is not recommended regardless of whether the patient is going for neoadjuvant therapy.

Recommendation 2

March 2024: In women newly diagnosed with stage III breast cancer, baseline staging tests, using PET/CT is the preferred modality and should be considered regardless of whether the patient is symptomatic for distant metastasis or not, and regardless of biomarker profile.

Qualifying Statements for Recommendation 2

- Staging tests should be considered at initial diagnosis, so that appropriate treatment recommendations can be made.

Added in November 2024:

- The following indications are funded for PET scanning in Ontario based on these eligibility criteria (https://www.ccohealth.ca/en/what-we-do/general-health/pet-scans-ontario/oncology-indications):
    - PET for the staging of patients with histologically confirmed clinical stage 2b or stage 3 breast cancer being considered for curative intent combined modality treatment; and/or repeat PET on completion of neoadjuvant therapy, prior to surgery (when there is clinical suspicion of progression)
    - PET for re-staging of patients with locoregional recurrence, after primary treatment, being considered for ablative or salvage therapy.
- March 2024: A prospective, randomized trial (registration # NCT02751710) of PET/CT versus conventional anatomic imaging in clinical stage III patients who will receive neoadjuvant therapy has shown that whole-body PET-CT resulted in upstaging 43 (23%) patients to stage IV compared with 21 (11%) conventional staged patients (absolute difference, 12.3% [95% CI, 3.9 to 19.9];P = .002). As a result the treatment was changed in 35 (81.3%) of 43 upstaged PET-CT patients and 20 (95.2%) of the 21 upstaged conventional patients.
- March 2024: In centres without access to PET scanners, baseline staging tests, using either anatomic (chest X-ray, liver ultrasound, chest-abdomen-pelvis CT scan) and/or metabolic imaging modalities (CT, MR, bone scintigraphy), may be used.

Baseline Staging Imaging for Distant Metastasis in Women with Stage I, II, and III Breast Cancer

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To provide recommendations for the use of imaging tests to detect distant metastases in women with newly diagnosed breast cancer.

TARGET POPULATION

Women with newly diagnosed primary breast cancer (originated in the breast) who have no symptoms of distant metastasis.

INTENDED USERS

This guideline is intended for health care professionals, policy makers, program planners and institutions involved in the management of women with clinical and pathologically confirmed primary breast cancer.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1
Staging tests using conventional anatomic (chest X-ray, liver ultrasound, chest-abdomen-pelvis computed tomography [CT] scan) and/or metabolic imaging modalities (positron emission tomography [PET]/CT, PET/magnetic resonance [MR], bone scintigraphy) should not be ordered routinely for women newly diagnosed with clinical stage I or stage II breast cancer, and with no symptoms of distant metastasis, regardless of biomarker status.
Qualifying Statements for Recommendation 1
• Baseline conventional anatomic imaging modalities (chest X-ray, liver ultrasound, bone scan, chest-abdomen-pelvis CT scan) should not be ordered routinely in women with newly diagnosed stage I or II breast cancer because this population exhibits an extremely low prevalence of asymptomatic distant metastasis. • Although PET/CT may improve the detection rate, the prevalence of distant metastasis in women with early stage I or II breast cancer is very low, and PET/CT may add unnecessary anxiety and resource use. Therefore, the use of PET/CT, as part of the baseline staging in women clinically diagnosed with early-stage breast cancer (I, II) and with no symptoms for distant metastasis is not recommended at this time. • Although women with triple negative and human epidermal growth factor receptor 2-positive (HER2+) breast cancer have an increased risk of disease recurrence, the association of distant metastasis and biomarker profile in early-stage breast cancer has not been adequately studied in prospective studies of staging investigation. The benefit and risks of the routine use of biomarker profiles to assess for distant metastasis is still unclear and, thus, its use to guide decisions on imaging staging for clinical early-stage breast cancer is not recommended.
Key Evidence for Recommendation 1
This recommendation was based on studies using the clinical and/or pathological Staging System for Breast cancer from the 7th Edition of the American Joint Committee on Cancer (AJCC) [1].

- The 2012 Australian guideline [2] reported a median prevalence of distant metastasis detected by conventional anatomic imaging of 0.2% and 1.2% for stage I and stage II breast cancer (seven studies each stage), respectively. The prevalence of distant metastasis detected by PET/CT imaging for stage II breast cancer was reported to be 3.3% (one study).
- Eight prospective [3-10], and 14 retrospective [11-24] studies reported the prevalence of distant metastasis overall, by stage, and by site. According to these studies conventional imaging modalities detected very low median prevalence of asymptomatic distant metastasis in women clinically diagnosed with early-stage breast cancer: 1.0% and 1.9% for stage I and II, respectively. PET/CT detected an overall median prevalence of distant metastasis of 3.0% for stage I and 10% for stage II.

Interpretation of Evidence for Recommendation 1

There is insufficient good-quality evidence to support or refute the use of functional imaging modalities such as PET/CT at baseline for staging of patients with stage II breast cancer. For stage II breast cancer patients who are otherwise asymptomatic, the relation between detection of metastasis by PET/CT imaging and survival has not been evaluated in a prospective randomized controlled trial (RCT) published to date.

Recommendation 2

March 2024: In women newly diagnosed with stage III breast cancer, baseline staging tests, using PET/CT is the preferred modality and should be considered regardless of whether the patient is symptomatic for distant metastasis or not, and regardless of biomarker profile.

Qualifying Statements for Recommendation 2

- Staging tests should be considered at initial diagnosis, so that appropriate treatment recommendations can be made.

Added in November 2024:

- The following indications are funded for PET scanning in Ontario based on these eligibility criteria (https://www.ccohealth.ca/en/what-we-do/general-health/pet-scans-ontario/oncology-indications):
    - PET for the staging of patients with histologically confirmed clinical stage 2b or stage 3 breast cancer being considered for curative intent combined modality treatment; and/or repeat PET on completion of neoadjuvant therapy, prior to surgery (when there is clinical suspicion of progression)
    - PET for re-staging of patients with locoregional recurrence, after primary treatment, being considered for ablative or salvage therapy.
- March 2024: In centres without access to PET scanners, baseline staging tests, using either anatomic (chest X-ray, liver ultrasound, chest-abdomen-pelvis CT scan) and/or metabolic imaging modalities (CT, MR, bone scintigraphy), may be used.

Key Evidence for Recommendation 2

The data informing this recommendation are derived from the 2012 Australian guideline [2], 10 retrospective [12-14,16,19-24] studies, and 11 prospective studies [3,4,6-10,25-28, 60].

- The 2012 Australian guideline [2] forms the evidentiary basis of this recommendation. This guideline reported a median prevalence detection of distant metastasis for stage

III breast cancer of 8% and 26% by conventional anatomic and functional imaging (PET/CT), respectively.

- Eleven prospective [3,4,6-10,25-28] and 10 retrospective [12-14,16,19-24] studies demonstrated that a significant proportion of women initially diagnosed with stage III breast cancer exhibited distant metastasis, with a median prevalence detected by conventional anatomic and functional PET/CT imaging of 21% and 26%, respectively.
- March 2024: A prospective, randomized trial [60](registration # NCT02751710) of PET/CT versus conventional anatomic imaging in clinical stage III patients who will receive neoadjuvant therapy has shown that whole-body PET-CT resulted in upstaging 43 (23%) patients to stage IV compared with 21 (11%) conventional staged patients (absolute difference, 12.3% [95% CI, 3.9 to 19.9];P = .002). As a result the treatment was changed in 35 (81.3%) of 43 upstaged PET-CT patients and 20 (95.2%) of the 21 upstaged conventional patients.

Interpretation of Evidence for Recommendation 2

Women with newly diagnosed stage III breast cancer have been clearly shown to be at an increased risk of distant metastasis. Baseline staging with PET/CT is preferred, however, either conventional anatomic or metabolic imaging is a reasonable practice when PET is not avaliable as these modalities could provide additional diagnostic and prognostic information, and would likely change treatment.

IMPLEMENTATION CONSIDERATIONS

Patient-specific material needs to be developed to educate patients on the choices made by their healthcare providers on the use of imaging tests to detect distant metastases based on staging. The necessary benefit/risk information including prevalence of distant metastases given staging and/or presence of biomarker profile should be provided.

Patient anxiety needs to be managed through clear and transparent qualitative and quantitative information as to the value/risk associated with choice of imaging test based on staging.

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Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

BACKGROUND FOR GUIDELINE

In Ontario, there is no clearly defined standard of care for staging for distant metastasis in women with newly diagnosed and biopsy-confirmed breast cancer, whose clinical presentation is suggestive of early-stage breast cancer. Recent literature and data within Ontario have demonstrated significant overuse of diagnostic imaging tests for the purposes of staging in patients with early-stage breast cancer. Health care policy initiatives such as the Choosing Wisely Campaign and the increasing focus of value-based healthcare by CCO, including the Quality-Based Procedures (QBP) program are intended to reduce low value care and limit overuse of non-evidence-based potentially harmful practices. As such, this prompted a request from the Breast Cancer Disease Site Group (DSG) to update the existing 2011 PEBC evidence and indications surrounding the use of imaging for baseline staging tests in primary breast cancer. The Cancer Quality Council of Ontario has advocated efforts to enhance awareness among physicians and patients and to use knowledge translation to increase adherence to recommendations.

This guideline addresses baseline imaging investigations for women with newly diagnosed primary breast cancer who are otherwise asymptomatic for distant metastasis. It does not addresses imaging investigations that may be indicated in surveillance/follow-up care or patients treated for recurrence.

GUIDELINE DEVELOPERS

This guideline was developed by the Staging in Early Stage Breast Cancer GDG (Appendix <1>), which was convened at the request of the Breast Cancer Advisory Group.

The project was led by a small Working Group of the Staging in Early Stage Breast Cancer GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations and responding to comments received during the document review process. The Working Group had expertise in medical oncology, surgical oncology, diagnostic imaging, radiation oncology, and health research methodology. Other members of the Staging in Early

Stage Breast Cancer GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based guidance documents using the methods of the Practice Guidelines Development Cycle [29,30]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [31] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

To be considered for endorsement or adaptation, guidelines must have reported a clear systematic review and evidence synthesis methodology, including a search for clinical practice guidelines, systematic reviews, meta-analyses, and/or clinical studies; and be issued within the past three years (2015-2018).

Three recently published guidelines were located in the targeted search of known guideline developers and professional organizations: two focused on the management of breast cancer [32,33] and one on the initial work-up of women with stage I breast cancer [34]. However, a clear systematic review methodology was not presented, and therefore none of the guidelines were considered for endorsement or adaptation.

One additional guideline from Alberta Health Sciences, Cancer Care [35], which significantly overlapped in scope with the objectives and research questions of the present document was also identified, but not considered for endorsement or adaptation due to its issue date (2012).

PATIENT AND CAREGIVER-SPECIFIC CONSULTATION GROUP

One patient participated as an active member of the baseline staging in primary breast cancer Working Group. The patient representative attended and participated in Working Group meetings and teleconferences. She provided feedback on draft guideline documents throughout the entire practice guideline development process, communicating the perspective of patients and members of the public.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document [1]. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

The Baseline Staging Imaging for Distant Metastasis in Women with Stage I, II, and III Breast Cancer GDG would like to thank the following individuals for their assistance in developing this report:

- Fulvia Baldassarre, Melissa Brouwers, Judy Brown, Glenn Fletcher, Leta Forber, Sheila McNair, Derek Muradali, Francisco Perera, Brian Pinchuk, Jonathan Sussman, Maureen Trudeau, Rebecca Wong, and Xiaomei Yao for providing feedback on draft versions.
- Ananya Nair and Megan Smyth for conducting a data audit.
- Sara Miller for copy editing.

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Section 4: Systematic Review

INTRODUCTION

Over 7000 women will develop breast cancer each year in the province of Ontario [36]. Appropriate staging investigations in patients with newly diagnosed breast cancer can aid in expediting care at tertiary care and associated cancer centres. Accurate disease staging is important in decision-making for patients with primary breast cancer, both in treatment planning (locoregional versus systemic therapy) and in establishing prognosis. Determining the presence of metastasis both at presentation and after treatment is a key factor in optimal diagnosis and determining ongoing treatment [37,38]. Due to widespread screening and public awareness, most women are now diagnosed with early-stage (stage I and II), localized disease. The incidence of distant metastatic disease even in the most common metastatic sites such as lung, liver, and bone, are exceedingly rare (<1% in all patients with early-stage breast cancer), questioning the need for universal baseline intensive staging [39-42]. Indeed, a recent population-based study of early-stage breast cancer patients in Ontario has demonstrated significant overuse of diagnostic imaging tests for the purposes of staging, with approximately 80% of patients receiving these tests [43]. Not only did it lead to additional confirmatory investigations in approximately one-quarter of these patients, some of these tests lead to invasive biopsies to negate the false positive findings and misdiagnoses that range from 10-66%. [44,45]. In addition, additional imaging tests expose patients to potentially harmful radiation, psychological distress, heightened anxiety, and possible delays to treatment.

Health care policy initiatives such as the Choosing Wisely Campaign and the increasing focus on value-based care through programs such as CCO's QBP [46,47] are aimed to limit overuse of practices that have little evidence of efficacy and are potentially harmful. As such, this prompted a request from the Breast Cancer DSG to update the existing 2011 PEBC guidelines and indications surrounding the use of imaging for baseline staging tests in primary breast cancer. The purpose of this guideline is to provide recommendations that outline which tests should be included in the staging investigation of patients with primary, biopsy-confirmed early-stage breast cancer, in an effort to standardize clinical practice across the province and to expedite the subsequent assessment and treatment of patients in the cancer centres.

The Working Group of the Staging in Early-Stage Breast Cancer developed this guideline to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research question outlined below.

RESEARCH QUESTION

Should women with newly diagnosed primary breast cancer receive imaging staging tests to rule out distant metastases? If so, when should they be performed and what are the optimal staging imaging modalities?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in more detail below.

1. Search and evaluation of existing systematic reviews: If existing systematic reviews were identified that addressed the research questions and were of reasonable quality, then they were included as part of the evidence base.
2. Original systematic review of the primary literature: This review focused on areas or dates not covered by existing and accepted reviews.

During project planning it was anticipated that the primary evidence base for the role of FDG-PET/CT in the staging of early breast cancer would be the PET recommendation reports produced by the CCO's PEBC in conjunction with the Ontario PET Steering Committee. These reports are designed for the Ontario Steering Committee as a guide in their deliberations regarding indications for the use of PET imaging https://www.cancercare.on.ca/toolbox/qualityguidelines/specialized_services/pet_recommendation_reports/. Due to the comprehensive review of the literature and regular updates of these reports, they served as the evidentiary base for these technologies. However, the initial review of the PET recommendation reports revealed that data on detection of distant metastasis were not consistently reported by initial stage and, therefore, it was considered necessary to conduct a full literature search to identify the studies reporting on this outcome by initial stage.

Search for Systematic Reviews

A systematic review of the literature was conducted with the goal of capturing relevant literature (existing systematic reviews and primary studies) on conventional anatomic and metabolic imaging modalities used to stage breast cancer. The website of the Cochrane Database of Systematic Reviews (CDSR) (www.cochrane.org/evidence), along with the electronic databases MEDLINE (OVID), and EMBASE (OVID) were searched. The search included terms for breast cancer, imaging staging, and publication type. Details of the literature search strategy are presented in Appendix 2. Systematic reviews were searched from January 2000 to May 10, 2017, and updated in April 2019. If a suitable guideline or systematic review was found, the search of the primary literature would be conducted from the end of the reported search to update the evidence from the identified or systemic review(s).

Systematic reviews were included if they met the following criteria:

1. They addressed the use of baseline imaging investigations in women with newly diagnosed primary breast cancer who are otherwise asymptomatic;
2. They associated the results of the imaging investigation with any patient outcome such as unsuspected distant metastasis and/or upstaging by initial stage, change in management, and where available data on progression-free survival (PFS) or overall survival (OS);
3. The literature search strategy was available and reproducible (i.e., reported sources, dates and keywords used); and
4. Presented a summary table with a clear description from individual studies.

Any identified systematic review that addressed the research question would be evaluated based on their clinical content and relevance, using A Measurement Tool to Assess Systematic Reviews (AMSTAR) [48]. The results of the AMSTAR assessment would be used to determine whether any existing review could be incorporated as part of the evidentiary base.

A systematic review of the primary literature was planned if no suitable systematic reviews were identified. If a suitable systematic review was found, a systematic review of the primary literature would be conducted from the end of the reported search to update the identified systematic review. Primary literature identified in this systematic review was eligible for inclusion if it met all the criteria described below.

Inclusion Criteria

1. Fully published RCTs on women with early-stage (no clinically metastatic disease) breast cancer who received baseline imaging investigation for distant metastases that reported on unsuspected distant metastasis, upstaging by initial stage, and/or change in management;
2. Fully published non-randomized studies on women with early-stage breast cancer who received baseline imaging investigation for distant metastases that reported on unsuspected distant metastasis, upstaging by initial stage, and/or change in management. Prospective and retrospective studies should have a minimum sample size of 30 and 50 participants, respectively; and
3. The following anatomic and metabolic imaging tests were considered for inclusion:
    - Chest X-ray
    - Liver ultrasound
    - Chest-abdomen-pelvis CT scan
    - Head CT scan
    - MR imaging: everything but breast, or as problem solving from other imaging
    - PET
    - FDG-PET/CT
    - Bone scintigraphy/scan.

Exclusion Criteria

Studies were excluded if they were:

1. Letter, case reports, comments, books, notes, or editorial publication types;
2. Studies that reported on patients undergoing imaging staging because of suspicious of distant metastases; and
3. Articles published in a language other than English.

A review of the titles and abstracts that resulted from the search was conducted by two reviewers (NV, GF) independently. For items that warranted full-text review, one author (NV) reviewed each item independently and consulted members of the Working Group whenever there was uncertainty.

Data Extraction and Assessment of Quality and Potential for Bias

Data from included studies were extracted by one Working Group member (NV). If more than one publication for the same study was identified, only the most updated version of the data was used. Data audit was conducted by another individual (AN) to verify the accuracy of all the extracted data.

For primary studies, key characteristics including author, publication year, time frame, study design, sample size, mean or median age, initial stage determination, imaging modality, stage distribution, verification of metastases as well as the outcomes of interest (unsuspected distant metastases, prevalence of metastases reported by site and by stage, change in management, OS, PFS) stated in each trial design were summarized. There is a lack of evidence regarding the impact that imaging investigation for distant metastasis in early-stage breast

cancer has on OS. The members of the Working Group believe that the anticipated benefits associated with baseline imaging investigation for distant metastasis are small and outweighed by the risk of anxiety, radiation exposure, cost, and false positive patients who would receive unnecessary and more aggressive treatment (i.e., systemic therapy rather than conserving surgery). Therefore, a 10% detection rate for distant metastasis was considered a reasonable threshold for considering baseline imaging investigation for distant metastasis. The members of the Working Group considered that this 10% threshold was determined as the best estimate of the infliction point where the risks-benefits ratio of testing patients with asymptomatic early-stage breast cancer changes from being harmful to being beneficial.

Ratios, including hazard ratios, were expressed with a ratio <1.0 indicating that the intervention/experimental procedure had a better outcome than the comparison group.

Assessment of Study Quality and Potential for Bias

The quality of the systematic review identified in the literature search was appraised by two reviewers (NV, FB) using the AMSTAR tool [48].

The quality of the diagnostic studies included in this review was assessed by one author (NV) using a modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [49].

A random-effect model was used for statistical pooling of the data; pooled data were presented with 95% confidence intervals (95% CI) and displayed using forest plot. A I-square statistic was used to test for heterogeneity between studies. Statistical analyses were performed using StataCorp. 2011 [50].

RESULTS

Existing Systematic Reviews

The Screening and Diagnostic Test Evaluation Program (STEP) established within the Sydney School of Public Health, and funded by the National Health and Medical Research Council in Australia, released a systematic review in 2012 to evaluate the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer [2]. The systematic review not only significantly overlapped in scope with the objectives of this evidentiary base, but it also provided a comprehensive summary of the best available evidence up to June 2011. It was assumed by the members of the Working Group that any relevant document published entirely within its search dates (1995-June 2011) would have been identified by this review. Therefore, the STEP systematic review was determined to be the main evidence source for the accompanying guideline, to be supplemented by additional data from relevant studies identified in the primary literature search.

Primary Literature

The primary literature search was used to update the evidence from the systematic review produced by the Australian STEP [2] and, therefore, only primary literature published from 2011 was considered because it corresponds to the end date of the search in the 2012 STEP systematic review (June 2011).

Literature Search Results

The initial literature search, after removal of duplicates, resulted in 5689 citations from which 129 were verified to be eligible for full-text review. From these, 31 full-report publications from June 2011 (end date of search in the 2012 systematic review included as part of this evidentiary base) were found to be relevant and therefore included in this review to inform recommendations surrounding the use of imaging for staging of early-stage breast cancer. The remaining 99 publications were excluded because they failed to pass the pre-defined inclusion criteria.

Fourteen studies enrolled patients prospectively [3-10,25-28,51,52], and 17 evaluated patients retrospectively [11-24,53-55]. A flow diagram of the literature search is shown in Figure 4-1, and the studies that meet the inclusion criteria are cited in Table 4-1.

Figure 4-1. Literature Search Flow Diagram of Included Studies Assessing the Evidence of Staging Imaging for Distant Metastases in Newly Diagnosed Breast Cancer

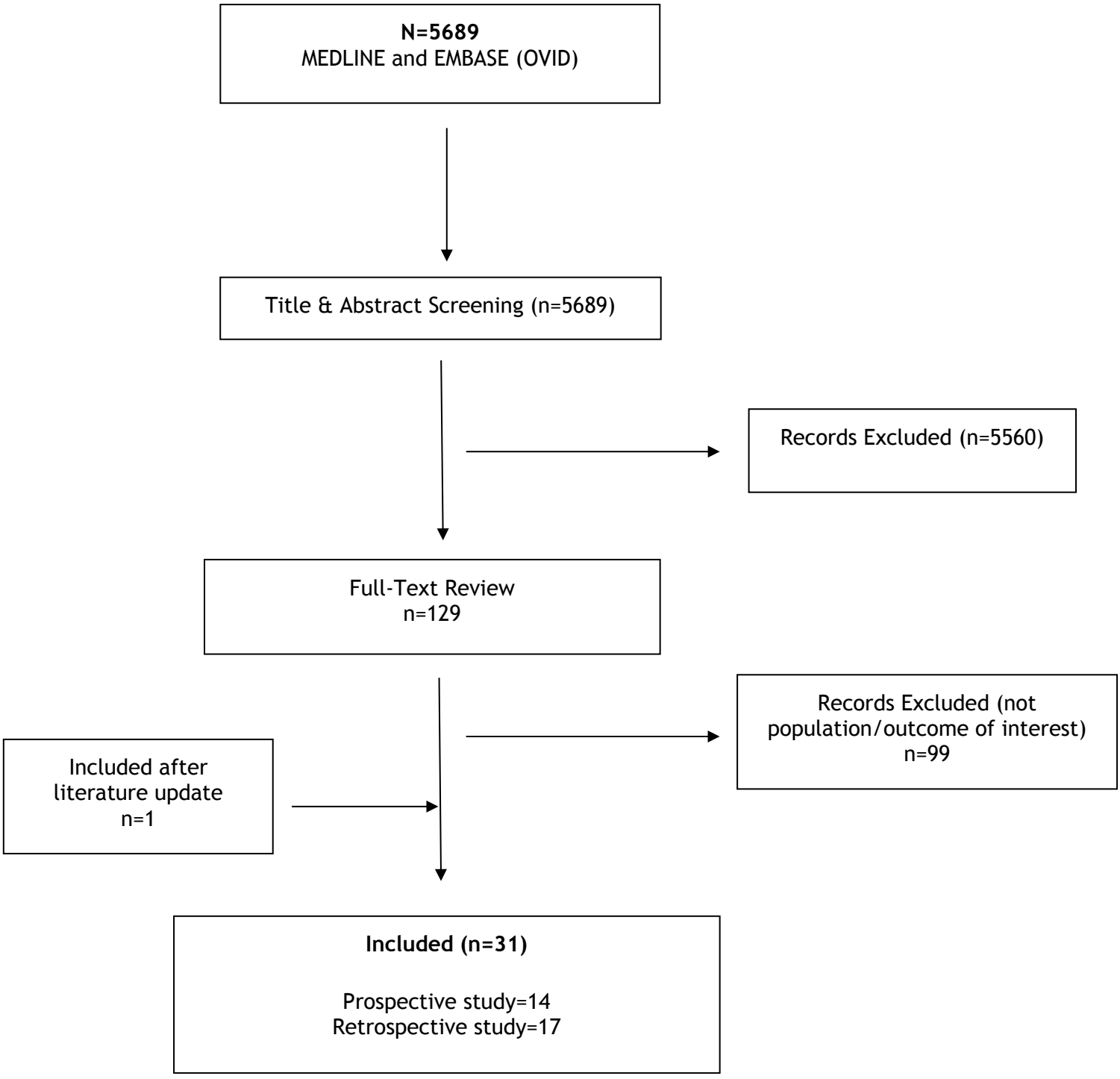


Table 4-1. Studies Selected for Inclusion

Question	Number of Included Studies (ref)
Should women with newly diagnosed primary breast cancer receive imaging staging tests to rule out distant metastases? If so, when should they be performed (pre- versus post-treatment) and what are the optimal staging imaging modalities?	1 Systematic Review [2] 14 Prospective Studies [3-10,25-28,51,52] 17 Retrospective Studies [11-24,53-55]

Study and Patients Characteristics

This systematic review identified studies assessing imaging modalities that include anatomic (chest X-ray, liver ultrasound, chest-abdomen-pelvis CT scan) and/or metabolic imaging modalities (PET/CT, PET/MR, bone scintigraphy) for staging in women with newly diagnosed breast cancer, and reporting the outcomes of interest. One systematic review [2], 14 prospective cohort studies [3-10,25-28,51,52], and 17 retrospective studies [11-24,53-55] met the inclusion criteria. The study population comprised women with all presentations of breast cancer including locally advanced breast cancer [9,10,25-28], inflammatory breast cancer [26], and invasive lobular and ductal carcinoma [14], and a mixed population of newly diagnosed breast cancer. All studies reported data on the overall prevalence of asymptomatic distant metastases and on the prevalence of metastases by site and by stage of disease at the time of initial diagnosis. Four studies reported detection of distant metastasis by biomarker profile (estrogen receptor [ER]/progesterone receptor [PR]/human epidermal growth factor receptor 2 [HER2]): one conventional imaging [21] and three PET/CT studies [10,22,23].

A summary of the systematic review is presented below and the characteristics of the newly identified observational studies are depicted in Table 4-2.

Evaluation of the Evidence on Staging Imaging for Detection of Asymptomatic Distant Metastases in Newly Diagnosed Breast Cancer: STEP, School of Public Health, Sidney Medical School, University of Sydney, Australia, 2012 [2].

The 2012 STEP study systematically reviewed the literature published between 1995 and 2011 with the aim to assess the evidence surrounding staging imaging for detection of asymptomatic distant metastases in women with newly diagnosed breast cancer. The systematic review included 22 studies; nine reporting on conventional imaging only (one prospective and eight retrospective studies), eight reporting on FDG-PET and/or FDG-PET integrated with CT (FDG-PET/CT) (five prospective, two retrospective, and one with study design not reported), and five reporting on both conventional imaging and FDG-PET or FDG-PET/CT.

The study population included women with all presentations of breast cancer: locally advanced breast cancer (3 study), inflammatory breast cancer (2 studies), large (>30 mm in diameter) tumours (1 study), and a mixed population of stages and presentations (18 studies). Characteristics of the studies such as author, publication year, time frame, study design, mean or median age, and stage distribution, as well as the outcomes of interest were summarized and presented in evidence tables. All studies reported data on the overall prevalence of asymptomatic distant metastases, and on the prevalence of metastases by site and stage of disease.

Table 4-2. Characteristics of Included Observational Studies Assessing Imaging Investigation for Distant Metastases

Author Publication year (Time frame)	Study Design	Population (n)	Age in years, mean or median (range)	Initial Stage Determination	Imaging Modality	Stage distribution n (%)	Verification of Metastases	Outcomes	Notes
Positron Emission Tomography-Computed Tomography (PET/CT)									
Gajjala et al., 2018 [28]	PROSP	61 LABC (stage III)	51 (27-78)	According to the AJCC: Clinical examination, mammography, breast MRI, ultrasonography	FDG-PET/CT	14 (23): IIIA 42 (68): IIIB 5 (9): IIIC	Biopsy or by fine needle aspiration cytology (FNAC), or MRI of the spine	Unsuspected distant metastases	
Yararbas et al., 2018 [24]	RET	234 Pre-op: 114 Post-op: 120	(23-87)	histopathological results: 125 According to the AJCC: Physical examination, breast and axillary US, and MRI in a few cases: 109	FDG-PET/CT	3 (1): I 43 (18): IIA 66 (28): IIB 82 (35): IIIA 16 (7): IIIB 24 (10): IIIC	Judgement of two experienced nuclear medicine physicians, histopathology, MRI, US	Distant metastasis (unclear if symptomatic)	
Lebon et al., 2017 [16] 2006-2015	RET	214 107 <40 y old 107 ≥40 y old HR+/HER2- (34%) HER2+ (33%) TNBC (33%)	<40: 34.5±4 ≥40: 56±10.7	According to the AJCC: Clinical examination, mammography, breast MRI, ultrasonography	FDG-PET/CT	<u><40 y old</u> 12 (11): I 32 (30): IIA 30 (28): IIB 33 (31): III <u>≥40 y old</u> 12 (11): I 32 (30): IIA 30 (28): IIB 33 (31): III	All PET/CT scans were reinterpreted by an interpreter who was unaware of the original PET/CT report or any other imaging, follow-up imaging, and pathology for small number of patients	Unsuspected distant metastases	Suspicious metastases on PET/CT was not confirmed by histology because the main goal of this study was to compare DM rates in women >40 and <40 years old
Ulaner et al., 2017 [23] 2011-2014	RET Single institution (MSKCC-HIS)	483 ER+/HER2-: 238 HER2+: 245	ER+/HER2- 55 (27-89) HER2+ 50 (24-87)	According to the AJCC: Physical exam, mammography, breast ultrasound, breast MRI, and/or surgical findings	FDG-PET/CT	ER+/HER2- 238 15 (6) I 71 (30) IIA 95 (40) IIB 23 (10) IIIA 26 (11) IIIB	Histopathology (imaging follow-up was used in two patients because histology was not available)	Unsuspected distant metastases, Upstaging	

Author Publication year (Time frame)	Study Design	Population (n)	Age in years, mean or median (range)	Initial Stage Determination	Imaging Modality	Stage distribution n (%)	Verification of Metastases	Outcomes	Notes
						8 (3) IIIC HER2+: 245 21 (9) I 72 (29) IIA 93 (38) IIB 32 (13) IIIA 21 (6) IIIB 6 (3) IIIC			
Evangelista et al., 2017 [4] 2011-2015	PROSP	275 TNBC or HER2+ Pre-op: 149 Post-op: 126	53 (27-89)	According to the AJCC: Physical examination, mammography, breast ultrasound, breast MRI, and/or surgical findings	FDG-PET/CT	Pre-op 149 8 (5) I 68 (46) II 72 (48) III Post-op 126 26 (21) I 44 (35) II 56 (44) III	Histopathology if available. Otherwise follow-up imaging	Unsuspected distant metastasis	15% of the patients in the post-operative setting had symptoms suspicious of metastases. The mean interval between surgery and PET/CT was 45±22 days
Ulaner et al., 2016 [22] 2007-2013	RET Single institution (MSKCC-HIS)	232 TNBC	51 (25- 93)	According to the AJCC: Physical exam, mammography, breast ultrasound, breast MRI, and/or surgical findings	FDG-PET/CT	n: 232 23 (10) I 82 (35) IIA 87 (38) IIB 23 (10) IIIA 14 (6) IIIB 3 (1) IIIC	Histopathology if not available, follow-up imaging was used	Unsuspected distant metastases, upstaging, survival	
Garg et al., 2016 [25] 2014-2015	PROSP	79 LABC (stage III)	50 (18- 80)	According to AJCC	FDG-PET/CT	79 LABC III	Histopathology in patients with solitary or doubtful metastasis. Other image-detected metastatic lesions were considered positive if they were multiple with	Unsuspected distant metastasis, upstaging, change in management	

Author Publication year (Time frame)	Study Design	Population (n)	Age in years, mean or median (range)	Initial Stage Determination	Imaging Modality	Stage distribution n (%)	Verification of Metastases	Outcomes	Notes
							typical appearance of metastases*. MRI was undertaken in suspicious skeletal lesions		
Nursal et al., 2016 [18] 2012- 2014	RET	419	51±10.	Physical exam, mammography, breast MRI and ultrasonography	FDG-PET/CT	104 (25) I 315 (75) II	MRI, biopsy	Distant metastases	
Hogan et al., 2015 [14] 2006-2013	RET Single institution (MSKCC-HIS)	235 ILC: 146 IDC: 89	ILC 57 (34-92) IDC 59 (33-90)	Physical examination, mammography, breast ultrasound, breast MRI imaging or surgical findings	FDG-PET/CT	<u>ILC 146</u> 8 (5) I 50 (35) II 88 (60) III <u>IDC: 89</u> 0 (0) I 0 (0) II 89 (100) III	Histopathology	Unsuspected distant metastasis	
Hulikal et al., 2015 [27] 2013-2014	PROSP	38 LABC (stage III)	27-73	According to AJCC	FDG-PET/CT	<u>LABC: 38</u> 10 (26) IIIA 25 (65) IIIB 3 (9) IIIC	Histopathology	Unsuspected distant metastases, change in management	
Krammer et al., 2015 [51] 2010-2013	PROSP	101 Preoperative†: 91 Postoperative‡: 10 67 ER+ 37 ER- 56 PR+ 48 PR-	54±10	Clinical examination, mammography, breast and local lymph nodes US	FDG-PET/CT	As detected by CI <u>Preoperative</u> 47 (52) IIA 23 (25) IIB 6 (7) IIIA 5 (6) IIIB 10 (11) IV	Histopathology. follow-up imaging	Unsuspected distant metastases, change in management	<u>Preoperative</u> Patients with clinical tumour stage ≥T2 or positive lymph nodes <u>Postoperative</u> Patients with clinical node

* Multiple lung nodules or lytic/marrow lesions in the skeleton

† Patients with clinical tumour stage ≥ T2 or positive lymph nodes were included preoperatively

‡ Clinical node negative patients with stage T1 tumours were included postoperatively if following sentinel lymph node biopsy, they were positive for malignant cells

Author Publication year (Time frame)	Study Design	Population (n)	Age in years, mean or median (range)	Initial Stage Determination	Imaging Modality	Stage distribution n (%)	Verification of Metastases	Outcomes	Notes
		56 HER2+ 48 HER2-				Postoperative 5 (50) IIA 3 (30) IIIA 1 (10) IIIC 1 (10) IV			negative with stage T1 tumours, if positive for malignant cells after sentinel lymph node biopsy (SLNB)
Groheux et al., 2015 [6] 2006-2012	PROSP	85 TNBC	> 18	According to AJCC: Physical exam, mammography, breast ultrasound and MRI	FDG-PET/CT	32 (38) II 53 (62) III	Histopathology or imaging follow-up	Unsuspected distant metastases	
Ng et al., 2015 [10] 2004-2014	PROSP	154 LABC	49 (26-70)	Physical examination, breast mammography, ultrasound, tumor core biopsy, chest, abdomen and pelvis CT scan, whole-body bone scan	FDG-PET/CT	20 (13) IIA 81 (53) IIB 43 (28) IIIA 7 (5) IIIB 3 (2) IIIC 99 ER+ 55 ER- 86 PR+ 68 PR- 52 HER2+ 102 HER2-	PET/CT results were compared with initial CI results. In selected patients, follow-up imaging and/or biopsy were performed to confirm metastatic disease CI: chest, abdominal, and pelvis CT, whole-body bone scintigraphy	Unsuspected distant metastases	
Riedl et al., 2014 [19] 2003-2012	RET	134 75 ER+HER2- 26 HER2+ 28 TNBC 5 Unspecified	36 (22-40)	According to AJCC: Physical exam, mammography, breast ultrasound and MRI	FDG-PET/CT	20 (15) I 44 (33) IIA 47 (35) IIB 13 (10) IIIA 8 (6) IIIB 2 (1) IIIC	Histopathology	Unsuspected distant metastases	Include ER+/HER2- (75), HER2+ (26), Triple-negative (28)
Jeong et al., 2014 [15] 2010-2013	RET	178 Clinical negative axillary nodal involvement	55 (33-82)	Clinical examination, mammography, breast and abdominal US, chest x-ray, MRI	FDG-PET/CT	178 (100) I	Histopathology, follow-up imaging	Unsuspected distant metastases	Patients with no sign of axillary lymph node metastasis by conventional diagnostic

Author Publication year (Time frame)	Study Design	Population (n)	Age in years, mean or median (range)	Initial Stage Determination	Imaging Modality	Stage distribution n (%)	Verification of Metastases	Outcomes	Notes
									modalities (breast US or MRI)
Cochet et al., 2014 [3] 2006-2010	PROSP	142	51 (25-85)	Physical examination, mammogram and/or breast and liver ultrasound, chest X-ray, bone scintigraphy, CT	FDG-PET/CT	22 (15) IIA 57 (40) IIB 12 (9) IIIA 19 (13) IIIB 15 (11) IIIC 17 (12) IV	Imaging and clinical follow-up and/or pathology	Distant metastases, change in management	Four patients were downstaged by PET/CT from stage IV to stage II or III
Manohar et al., 2013 [9]	PROSP	43 LABC 40 IDC 1 AMC 1 PC 1 ASC	49 (28-80)	Physical examination, chest X-ray, abdominal ultrasound, whole body bone scintigraphy	FDG PET/CT	3 (7) IIB 15 (35) IIIA 24 (56) IIIB 1 (2) IIIC	Histopathology, clinical or imaging at a mean follow-up of 8-months	Unsuspected distant metastases	Distant metastases missed by conventional imaging
Groheux et al., 2013 [26]	PROSP	117 LABC (stage III) 35 IBC 82 NIBC		Physical examination, mammography, breast and axilla sonography, breast MRI	FDG-PET/CT	IBC 29 (83) IIIB 6 (5) IIIC	Histopathology, further work-up or patient follow-up, and MRI imaging for bone foci	Distant metastases, change in management	
Sen et al., 2013 [20] 2009-2012	RET	77 Postoperative Patients with histologically proven breast cancer who underwent surgery with no previous CT or RT	52 (26-87)	Abdominal US, CT (chest, abdmomen), bone scan. Only 47 patients were assessed for metastatic disease through conventional imaging	FDG-PET/CT performed in the early postoperative period (7-57 days after mastectomy or breast-conserving surgery) and before systemic therapy	19 (25) I 38 (49) II 18 (23) III	Histopathology, clinical and follow-up data, imaging follow-up including FDG-PET/CT	Postoperative distant metastases that were previously undetected	
Gunalp et al., 2012 [13]	RET	336 Preoperative: 141	Pre-op 47 (28-78) Post-op	Physical examination, mammography, breast and axilla	FDG-PET/CT	Pre-op 19 (14) I 51 (36) IIA 49 (35) IIB	Histopathology or patient follow-up. For bone foci, MRI	Unsuspected distant metastases	

Author Publication year (Time frame)	Study Design	Population (n)	Age in years, mean or median (range)	Initial Stage Determination	Imaging Modality	Stage distribution n (%)	Verification of Metastases	Outcomes	Notes
		Postoperative:195	48 (25-75)	ultrasound, breast MRI. Clinical stage III underwent conventional imaging: bone scan, abdominal and pelvic CT (or US or MRI), chest imaging		12 (9) IIIA 2 (2) IIIB 8 (6) IV	was performed instead of biopsy		
Bernsdorf et al., 2012 [52] 2008-2010	PROSP	103	55 (24-81)	Physical examination, mammography, US (chest wall and axilla), chest X-ray, blood parameters	FDG-PET/CT	11 (11) I 54 (52) II 37 (34) III 1 missing	Histology or follow-up imaging (PET/CT or others)	Unsuspected distant metastases	
Groheux et al., 2012 [8] 2006-2011	PROSP	254	NR	Physical examination, mammography, breast MRI, breast and locoregional US	FDG-PET/CT	44 (17) IIA 56 (22) IIB 63 (25) IIIA 74 (29) IIIB 17 (7) IIIC	Histopathology, imaging follow-up	Unsuspected distant metastases, change in management, disease-specific survival	
Garami et al., 2012 [5] 2008-2010	PROSP	115	56	Physical examination, mammography, breast and abdominal ultrasound, chest X-ray, bone scintigraphy	FDG-PET/CT	63 (55) I 49 (43) II	Direct sampling (pulmonary resection, liver biopsy), follow-up imaging (CT, MRI)	Unsuspected distant metastases and change in management	
Groheux et al., 2011 [7] 2006-2010	PROSP	131	48 (26-81)	Physical examination, mammography, breast and axilla ultrasound, breast MRI	FDG-PET/CT	36 (27) IIA 48 (37) IIB 47 (36) IIIA	Surgery, histology, patient follow-up, and MRI for bone foci.	Unsuspected distant metastases	

Author Publication year (Time frame)	Study Design	Population (n)	Age in years, mean or median (range)	Initial Stage Determination	Imaging Modality	Stage distribution n (%)	Verification of Metastases	Outcomes	Notes
Conventional Anatomic Imaging (chest X-ray, liver ultrasound, chest-abdomen-pelvis computed tomography [CT] scan)									
Gajjala et al., 2018 [28]	PROSP	61 LABC (stage III)	51 (27-78)	According to the AJCC: Clinical examination, mammography, breast MRI, ultrasonography	Bone scan, abdominal and pelvis US	14 (23): IIIA 42 (68): IIIB 5 (9): IIIC	Biopsy or by fine needle aspiration cytology (FNAC), or MRI of the spine	Unsuspected distant metastases	
Bychkovsky et al., 2016 [11] 2006-2007	RET Multicenter study (two academic centers in Boston, Massachusetts)	237 135 ER+/PR+ 54 HER2+ 48 TNBC	52 (23-90)	According to AJCC	Body CT	130 (55) IIA 107 (45) IIB	Histology (12 pts), follow-up imaging	Unsuspected distant metastases	
Garg et al., 2016 [25] 2014-2015	PROSP	79 LABC (stage III)	50 (18 – 80)	According to AJCC	Chest X-ray, abdominal US, bone scintigraphy	79 LABC III	Histopathology in patients with solitary or doubtful metastasis. Other image-detected metastatic lesions were considered positive if they were multiple with typical appearance of metastases[§]. MRI was undertaken in suspicious skeletal lesions	Unsuspected distant metastasis, upstaging, change in management	

[§] Multiple lung nodules or lytic/marrow lesions in the skeleton

Author Publication year (Time frame)	Study Design	Population (n)	Age in years, mean or median (range)	Initial Stage Determination	Imaging Modality	Stage distribution n (%)	Verification of Metastases	Outcomes	Notes
Krammer et al., 2015 2010-2013 [51]	PROSP	101 Preoperative**: 91 Postoperative††: 10 67 ER+ 37 ER- 56 PR+ 48 PR- 56 HER2+ 48 HER2-	54±10	Clinical examination, mammography, breast and local lymph nodes US	Abdominal US, chest X-ray, bone scan	As detected by CI <u>Preoperative</u> 47 (52) IIA 23 (25) IIB 6 (7) IIIA 5 (6) IIIB 10 (11) IV <u>Postoperative</u> 5 (50) IIA 3 (30) IIIA 1 (10) IIIC 1 (10) IV	Histopathology. follow-up imaging	Unsuspected distant metastases, change in management	<u>Preoperative</u> Patients with clinical tumour stage ≥T2 or positive lymph nodes <u>Postoperative</u> Patients with clinical node negative with stage T1 tumours, if positive for malignant cells after sentinel lymph node biopsy (SLNB)
Hulikal et al., 2015 [27] 2013 2014	PROSP	38 LABC (stage III)	27-73	According to AJCC	Chest and abdominal CECT, bone scan	<u>LABC: 38</u> 10 (26) IIIA 25 (65) IIIB 3 (9) IIIC	Histopathology	Unsuspected distant metastases, change in management	
Chen et al., 2014 [12] 2000-2010	RET	3411 2094 ER+ 1317 ER- 2280 PR+ 1131 PR- 771 HER2+ 2640 HER2-	60 (18-75)	According to AJCC: Physical exam, mammography, breast ultrasound and MRI	Bone Scan, liver US, chest x-ray	411 (12) I 2561 (75) II 439 (13) III 2094:ER+ 1317 ER- 2280 PR+ 1131 PR- 771 HER2+ 2640 HER2-	Bone metastases indicated by BS were confirmed by CT or MRI; liver metastases indicated by LUS were confirmed by liver dual phase scan CT; lung metastases indicated by chest X-ray were confirmed by chest CT or MRI	Unsuspected distant metastases by site	

** Patients with clinical tumour stage ≥ T2 or positive lymph nodes were included preoperatively

†† Clinical node negative patients with stage T1 tumours were included postoperatively if following sentinel lymph node biopsy, they were positive for malignant cells

Author Publication year (Time frame)	Study Design	Population (n)	Age in years, mean or median (range)	Initial Stage Determination	Imaging Modality	Stage distribution n (%)	Verification of Metastases	Outcomes	Notes
Groheux et al., 2013 [26]	PROSP	117 LABC (stage III) 35 IBC 82 NIBC		Physical examination, mammography, breast and axilla sonography, breast MRI	Bone scanning chest X-ray or CT, abdomino-pelvic ultrasound and/or CT, bone scintigraphy	IBC 29 (83) IIIB 6 (5) IIIC	Histopathology, further work-up or patient follow-up, and MRI imaging for bone foci	Distant metastases, change in management	
Tanaka et al., 2012 [21] 2006-2011	RET	483	<50: 108 ≥50: 375	Physical examination	Contrast-enhanced computed tomography (CECT)	155 (32) I 261 (54) II 67 (14) III 381 ER+ 100 ER- 314 PR+ 167 PR- 65 HER2+ 393 HER2-	Follow-up CT scan (plain or CECT) within 3-4 months or further imaging follow-up (PET, MRI)	Unsuspected distant metastases	
Combined Conventional Anatomic and/or Metabolic Imaging Modalities									
Piatek et al., 2016 [53] 2000-2010	RET Multicenter study (university of California Norris Comprehensive Cancer Center, Los Angeles County-University of Southern California Medical Center	362 Stage III	NR	History, physical exam, chest X-ray	CT, bone scan, PET	175 (42) IIIA 105 (25) IIIB 140 (33) IIIC only 362 had routine staging imaging studies	Judgement of radiologist/physician or subsequent imaging or histology	Unsuspected distant metastasis, change in management, relapse-free survival.	Imaging abnormalities were not routinely biopsied.

Author Publication year (Time frame)	Study Design	Population (n)	Age in years, mean or median (range)	Initial Stage Determination	Imaging Modality	Stage distribution n (%)	Verification of Metastases	Outcomes	Notes
Linkugel et al., 2015 [17] 1998-2012	RET	882	55.0	Clinical examination	PET, chest and abdominal and/or pelvis CT, bone scintigraphy	312 (35) I 570 (65) II	Histopathology, Follow-up imaging (x-ray, CT, bone scan, sonogram, MRI, or PET)	Unsuspected distant metastases	
Chu et al., 2012 [55] 1998-2010	RET	256 158 N2 98 N3	N2 59 (27-86) N3 57 (31-84)	According to AJCC	Bone scan (n=62) CT scan (n=78) PET (n=39)	256 Stage III 158 N2 98 N3	Judgement of multidisciplinary tumour board and histopathology in most of the cases	Distant metastases at time of diagnosis or within 1 month after definitive surgery	
Botsikas et al., 2016 [54] 2010-2014	RET	58	47.4±11.2	Clinical examination and conventional imaging	FDG-PET/MR	13 (22) I 30 (52) II 12 (21) III 1 (2) IV	Follow-up imaging, biopsy	Unsuspected distant metastases	

Abbreviations: AJCC, American Joint Committee on Cancer; AMC, atypical medullary carcinoma; ASC, adenosquamous carcinoma; CECT, contrast enhanced computed tomography; CI; conventional imaging; CT, chemotherapy; CT, computed tomography; ER, estrogen receptor; FDG, fluorodeoxyglucose; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LABC, locally advanced breast cancer; MRI, magnetic resonance imaging; NIBC, noninflammatory breast cancer; PA, posteroanterior; PC, papillary carcinoma; PET, positron emission tomography; pre-op, preoperative; post-op, postoperative; PROSP, prospective; RET, retrospective; RT, radiotherapy; TNBC, triple-negative breast cancer; US, ultrasound

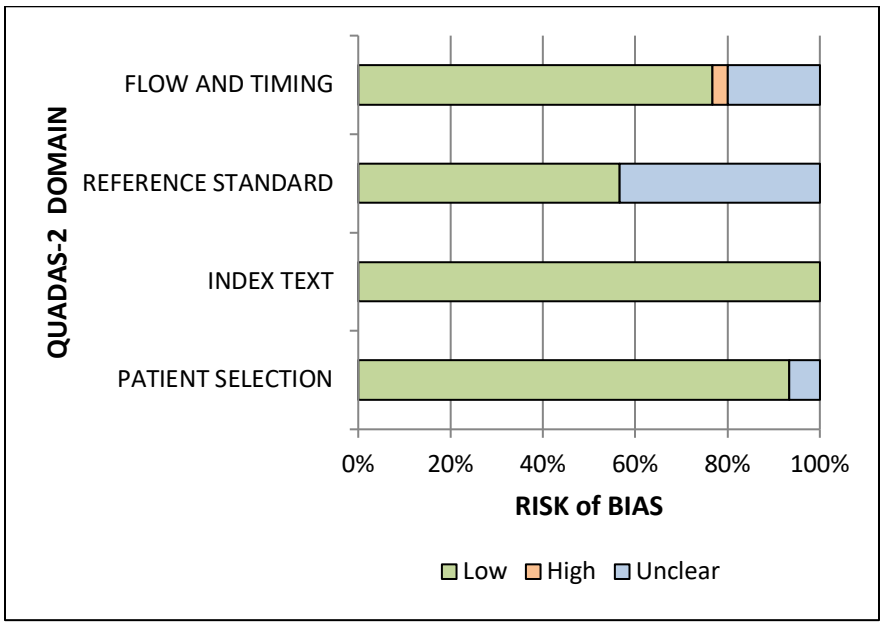
Study Design and Quality

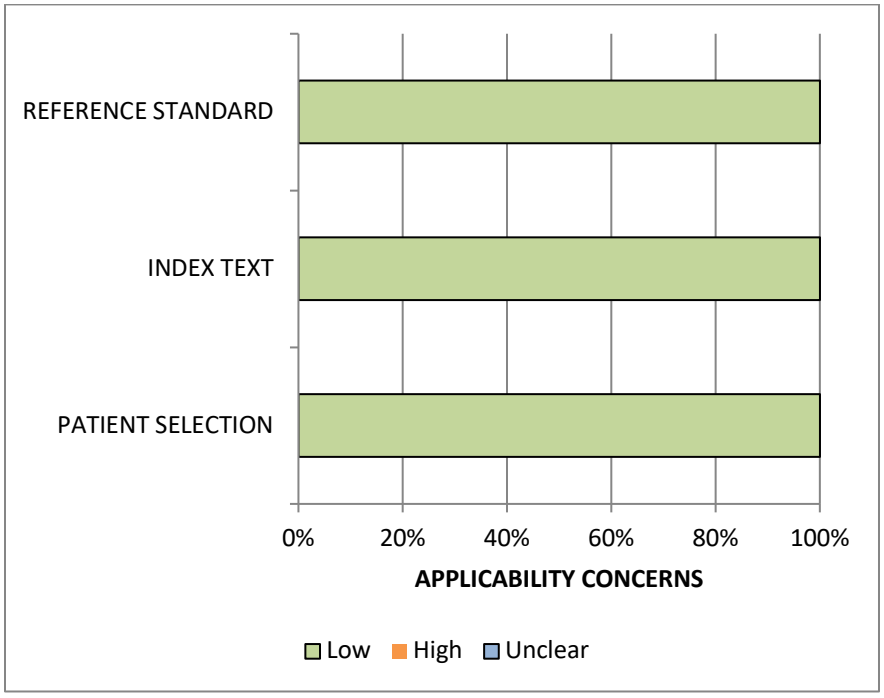
The identified 2012 STEP systematic review from Australia was assessed for quality using the AMSTAR criteria described at www.amstar.ca. The systematic review scored well. The results of the AMSTAR assessment are presented in Appendix 3.

The study quality for primary literature was assessed using the QUADAS-2 tool (Figure 4-2, Appendix 4). All the studies were judged to have low concerns regarding applicability.

For the domains relating to bias, three studies were unclear as to whether they avoided the inclusion of patients with symptoms for distant metastasis and therefore there is an unknown risk of bias for patient selection [15,24,55]. The reference standard was considered on the basis of clinical and short-term follow-up imaging of the metastatic lesions, and/or on the judgment of a multidisciplinary tumour board when biopsy/histopathology was not feasible, as there is no gold standard for the detection of real metastases. Fifteen studies did not provide enough information to determine whether the results of the reference standard test were blinded to the results of the index test [3,5,9-13,17,18,20,21,24,27,28,53], and the risk for bias is related to the potential influence of previous knowledge on its interpretation [49]. Seven studies were identified to have concerns regarding flow and timing. One study was judged to have high risk of bias because only a proportion of suspicious findings received confirmation of the diagnosis by the test used as the reference standard, which may lead to verification bias [11]. The other six studies did not provide sufficient information to determine whether suspicious findings were confirmed by the reference standard and/or whether all the patients with suspected metastasis receive the same reference standard [7,18,21,26,53,55]. The overall evidence quality was considered to be from low to moderate because it is mainly derived from retrospective studies with bias concerns.

Figure 4-2. Graphical Display for QUADAS-2 Assessment of Study Quality of Included Studies Assessing the Evidence of Staging Imaging for Distant Metastases in Newly Diagnosed Breast Cancer





Outcomes: Imaging Staging Tests in Women with Newly Diagnosed Primary Breast Cancer

1. Detection of Asymptomatic Distant Metastases Overall

Systematic Reviews

The 2012 Australian systematic review by Brennan et al. (2012) identified 22 eligible studies (8 prospective, 13 retrospective, and 1 with study design not reported) published between 1995 and 2011 and including 14,824 patients with newly diagnosed breast cancer undergoing imaging tests to detect asymptomatic distant metastases. All studies reported data on prevalence of asymptomatic distant metastases with a median prevalence of 7% (range, 1.2-48.8%). Conventional anatomic imaging studies were shown to have lower median distant metastases prevalence than studies of metabolic PET (PET/CT). The median prevalence detected by anatomic imaging alone; metabolic PET with or without CT; and both anatomic imaging and metabolic PET with or without CT was reported to be 2.1%, 10.3%, and 31.8%, respectively. The most common distant metastases sites were bone, lung, and liver with a median of 5.8% (range, 0-31.8%), 2.6% (range, 0-12.2%) and 1.5% (range, 0-14.6%), respectively.

Primary Literature (Table 4-3 to Table 4-6)

Thirty-one studies including 10,264 patients with a median age across studies of approximately 51 years (range, 15–93 years) were included in this systematic review.

The median prevalence of metastatic disease among included studies was 14%, ranging from 0% in patients staged with PET/CT for whom the conventional diagnostic modalities showed no sign of axillary node metastasis [15] to 37% after PET/CT in patients initially staged with inflammatory carcinoma stage IIIC [26]. Similar estimates were reported by conventional imaging (12%, 8 studies), and estimates for underlying prevalence detected by studies that included PET/CT was estimated to be 15% (24 studies). According to four studies comparing the performance of PET/CT with that of conventional imaging in women with newly diagnosed breast cancer, PET/CT outperformed conventional imaging for the detection of distant metastases not detected by conventional imaging; a median prevalence of 33% and 21% was reported for PET/CT and conventional imaging, respectively [25-28,51]. One study evaluating the clinical utility of FDG-PET/MRI for preoperative breast cancer staging reported that bone metastases detected by PET were confirmed by whole body MRI (2/58, 3%). The most common sites of metastatic tumour were bone (median 8%, range 0.5-28%), lung (median 4%, range 0.4-18%), and liver (median 4%, range 0.2-16%).

Five studies, three on PET/CT and two on conventional imaging reported detection of unsuspected distant metastases by biomarker. In one study, the overall prevalence detected by PET/CT in patients with ER+/HER2- and HER2+ breast cancer was 13% (11% bone, 2% liver, 2% lung) and 12% (8% bone, 4% liver, 2% lung), respectively. Distant metastasis by stage distribution and biomarker was demonstrated in approximately 7% stage I, 10% stage II, and 26% stage III patients with ER+/HER2- breast cancer, and in 0% stage I, 10% stage II, and 22% stage III patients with HER2+ [23]. In another study of patients with triple-negative breast cancer (TNBC), PET/CT detected an overall prevalence of distant metastases of 13% (5% bone, 3% liver, 3% lung); 0% initial stage I, 10% stage II, and 32% stage III [22]. The third study on PET/CT reported distant metastases in 10% and 4% of initial stage II patients with TNBC and ER+PR+HER2-, respectively. Likewise, the biomarker distribution among patients with initial stage III breast cancer was 6% TNBC, 7% ER+PR+HER2-, 1% ER+PR-HER2+, 4% ER+PR+HER2+, and 4% ER-PR-HER2+ [10].

For conventional imaging, one study demonstrated distant metastases detected by body scan in 2% for each initial stage II ER+/PR+, HER2+, and TNBC [11]. Another study reported the biomarker distribution among distant metastases detected by CT to be 5% each for ER+, ER-,

PR+, HER2+, and HER2-, and 6% for PR- breast cancer, but the prevalence of distant metastasis by biomarker was not stratified by initial clinical stage. [21].

2. Detection of Distant Metastases by Initial Staging of Breast Cancer (at diagnosis), and by Site of Metastasis

Systematic Reviews (All Stages)

The systematic review by Brennan et al. (2012) reported a low median prevalence of distant metastases in women initially diagnosed with stage I and II breast cancer, with much higher prevalence in those initially diagnosed with stage III. For stage I, a median prevalence from seven studies, all on conventional imaging alone, was 0.2% (range, 0-5%). For stage II, the overall median prevalence was reported to be 1.2% (range, 0-34%); 1.1% on conventional imaging alone (7 studies), 3.3% on PET/CT (1 study), and 34.3% on both (1 study).

For women initially diagnosed with stage III breast cancer, the median prevalence was reported to be 8% (6 studies) on conventional imaging, 26% (4r studies) on PET or PET/CT, and 34% (1 study) on both. Two studies including only cases of inflammatory breast cancer reported a prevalence of 30.5% and 48.8%, respectively.

Primary Literature (Table 4-3 to 4-6)

Stage I

Detection of distant metastases in stage I from in 12 PET/CT studies [4,5,13-16,18-20,22-24], two conventional imaging studies [12,21], and one study reporting on both (conventional imaging and PET/CT) [17] was 3.0% (range, 0-8.8%), 1.0% (range, 0-1.9%), and 0.3%, respectively (Tables 4-3 to 4-5).

For conventional imaging, the median from two studies that reported detection of metastasis by site was 2.5%, 1.0%, and 0.5%, for bone, Liver, and lung, respectively [12,21]. Only one PET/CT study with 19 women initially detected with stage I breast cancer reported 5%, 0%, and 0% for bone, liver, and lung metastases, respectively [13] (Table 4-6).

The detection of distant metastasis by imaging modality in women initially diagnosed with stage I breast cancer, including studies from the systematic review by Brennan et al. (2012), is depicted in Figure 4-3.

In two PET/CT studies reporting by biomarker status of the primary breast cancer, unsuspected distant metastasis was detected in 7%, 0%, and 0% of patients with ER+/HER2-, HER2+, and TNBC, respectively [22,23] (Figure 4-6).

As expected, significantly shorter survival and/or disease-free survival was reported for patients with distant metastasis when compared to those without distant metastasis [8,22,26].

Stage II

For stage II breast cancer, the median prevalence from 17 PET/CT studies [3-10,13,14,16,18-20,22-24], three conventional studies [11,12,21], and one study reporting on both PET/CT and conventional imaging[17] was 10% (range, 0-33%), 1.9% (range, 1.9-2.1%), and 1.8%, respectively (Tables 4-3 to 4-5).

The median prevalence of metastasis in bone, liver, and lung by three PET/CT studies was 1.0% (range, 0-21%), 1.0% (range, 0-4.0%), and 0% (range, 0-2%), respectively [9,10,13]. In two studies on conventional imaging the median prevalence was 1.4%, 0.4%, and 0.5% for bone, liver, and lung, respectively [12,21] (Table 4-6).

The detection of distant metastasis by imaging modality in women initially diagnosed with stage II breast cancer, including studies from the systematic review by Brennan et al. (2012), is depicted in Figure 4-4.

In two PET/CT studies reporting by biomarker, unsuspected distant metastasis was detected in 10% of each of these three groups: patients with ER+/HER2-, HER2+, and TNBC, [22,23] (Figure 4-6).

Stage III

For stage III breast cancer, the prevalence of distant metastases was reported by 19 PET/CT studies [3,4,6-10,13,14,16,19,20,22-28], four conventional imaging studies [12,21,25,27], and one study reporting on both imaging modalities [55].

The median prevalence of distant metastases detected by PET/CT studies was 26%, ranging from 13% to 64%. Studies reporting on detection of distant metastasis by conventional imaging and by both modalities reported median detection rates of 21% (range, 3-31%) by conventional imaging and 16% when both conventional and PET/CT imaging were used (Tables 4-3 to 4-5).

The median prevalence of metastasis in bone, liver, and lung from three PET/CT studies was 11% (range, 7.5-43%), 5% (range, 1.9-14%), and 10% (range, 3.8-14%), respectively [9,10,13]. The median prevalence of metastasis in bone, liver, and lung from two conventional studies was 7.6%, 7.7%, and 12.1%, respectively [12,21] (Table 4-6).

The detection of distant metastasis by imaging modality in women initially diagnosed with stage III breast cancer, including studies from the systematic review by Brennan et al. (2012), is depicted in Figure 4-5.

In two PET/CT studies reporting by biomarker, unsuspected distant metastasis was detected in 26% ER+/HER2-, 22% HER2+, and 32% TNBC [22,23] (Figure 4-6).

3. Timing of Baseline Staging: Pre- versus Post-Treatment

Two studies addressed the issue of timing of staging investigations in the evaluation of newly diagnosed breast cancer patients [4,13]. In the non-randomized study by Evangelista et al. [4], 275 patients with stage I-III triple negative or HER2+ breast cancer were staged either before neoadjuvant systemic therapy and surgery (54%) or post-surgery (45%). Almost one-quarter of stage III patients receiving pre-treatment staging were upstaged to stage IV. All the patients who were upstaged pre-treatment had a worse outcome than those that were not upstaged. Change in treatment was reported in 15 patients; one patient received a more aggressive surgical approach, 12 patients had systemic treatment only, and two received a combination of systemic and local treatment. For those who had staging imaging after completing surgery, the upstage rate was lower (10%) and there was no observed difference in prognosis in those who were upstaged versus not. The retrospective study by Gunalp et al. [13] retrospectively examined 341 patients who were referred for PET/CT staging after a diagnosis of breast cancer. Patients had clinical stages I-IV breast cancer. PET/CT scans were performed pre- or postoperatively. The paper did not indicate whether any of the patients received neoadjuvant systemic therapy, and the specific clinical stage distribution of the preoperative versus postoperative groups was not reported.

Given the design limitations for these two studies, no conclusions can be drawn about the value of pre- versus post-treatment staging. Since many patients in Ontario with clinical stage III disease will receive neoadjuvant systemic therapy with curative intent [56], it makes sense to perform staging investigations in this group prior to the initiation of treatment.

4. PET/CT Considerations in Stage III Disease

As identified in this review, the prevalence of distant metastases in patients with clinical stage III breast cancer who undergo PET/CT scanning is high, and greater than seen with

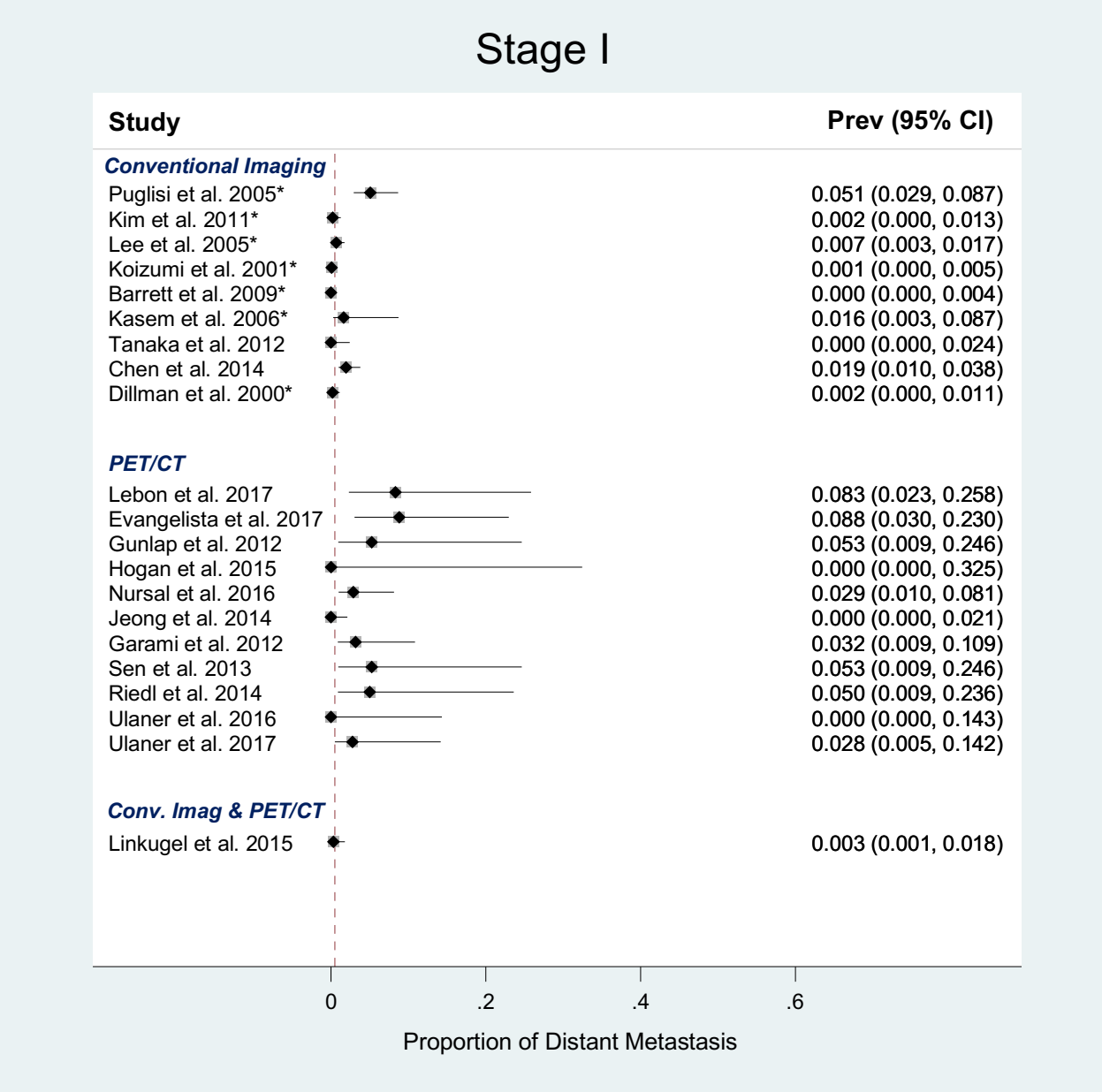
conventional imaging. Since upstaging patients to stage IV would likely alter their treatment intent, it is important to accurately identify the presence of distant metastases. In Ontario, PET/CT scanning is not currently funded for the staging of patients with breast cancer on the basis that the existing evidence is comprised largely of observational, retrospective, single institution studies. To generate better quality evidence, the Ontario Clinical Oncology Group has initiated a randomized trial of PET/ CT versus conventional imaging in patients who present with clinical stage III invasive ductal cancer. In the same study, a cohort of similarly staged patients with invasive lobular cancer will be staged with both modalities.

The primary outcome of this study will be the proportion of patients who are upstaged to stage IV disease. Secondary endpoints include final treatment intent, the rates of additional testing generated by the staging tests, survival, prediction of response to treatment, and economic analysis.

The Guideline Working Group members believe that although the existing data are suggestive of the benefit of staging with PET/CT in clinical stage III disease, high-quality evidence related to PET/CT will be generated by the randomized trial, and it would be prudent to wait for the results before adopting PET/CT scanning as the standard of practice.

March 2023 Update. The results of this trial are now complete [60]. This trial included patients that had histological evidence of invasive ductal carcinoma of the breast and TNM stage III or IIb (T3N0, but not T2N1). Patients (N=184) in the experimental arm recived whole-body 18 F-FDG PET-CT only for staging. Patients (N=185) in the control arm recived conventional staging consisting of a bone scan and CT with contrast of the chest/abdomen and pelvis to include visualization of the lungs, liver, adrenal glands, and pelvis. This trial showed that whole-body PET-CT resulted in upstaging 43 (23%) patients to stage IV compared with 21 (11%) of conventionally staged patients (absolute difference, 12.3% [95% CI, 3.9 to 19.9];P = .002). As a results the treatment was changed in 35 (81.3%) of 43 upstaged PET-CT patients and 20 (95.2%) of the 21 upstaged conventional patients [60].

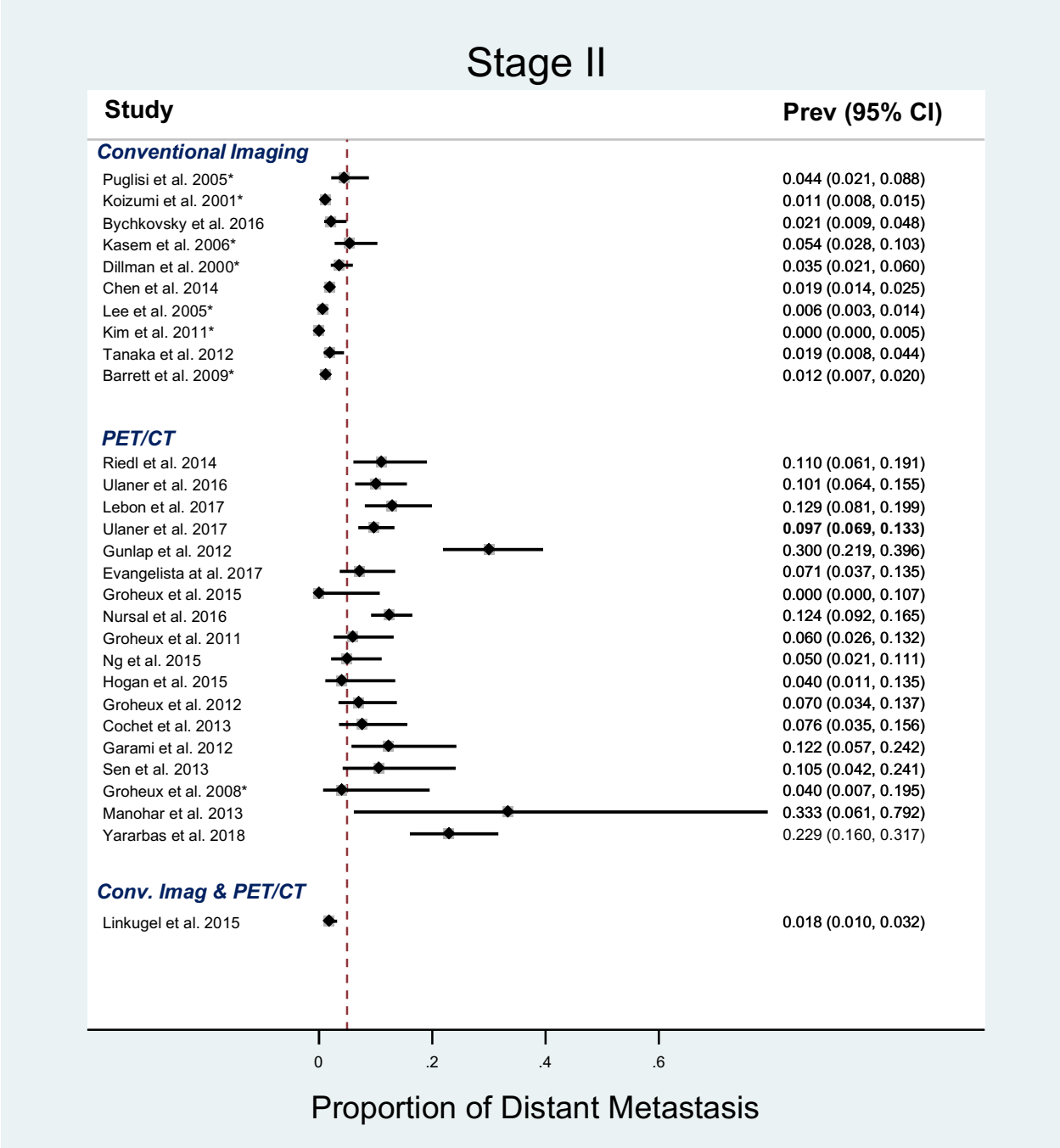
Figure 4-3. Plot of Individual Studies and Pooled Prevalence of Distant Metastasis Detected by Imaging Modality in Women Initially Diagnosed with Stage I Breast Cancer, Including 95% Confidence Intervals (95% CI)



* From the systematic review by M.E. Brennan and N. Houssami, 2012.

Prevalence of distant metastasis detected by conventional and PET/CT imaging, including studies from the 2012 Australian systematic review by Brennan et al., ranged from 0% to 5% and from 0% to 8.8%, respectively. Conventional imaging and PET/CT combined (one study) detected a prevalence of 0.3% (95% CI 0.1 to 1.8%). The overall prevalence of distant metastasis ranged from 0% to 8.8%. Moderate to high levels of heterogeneity were observed among studies (I-square: 52% for PET/CT and >75% for conventional imaging, respectively).

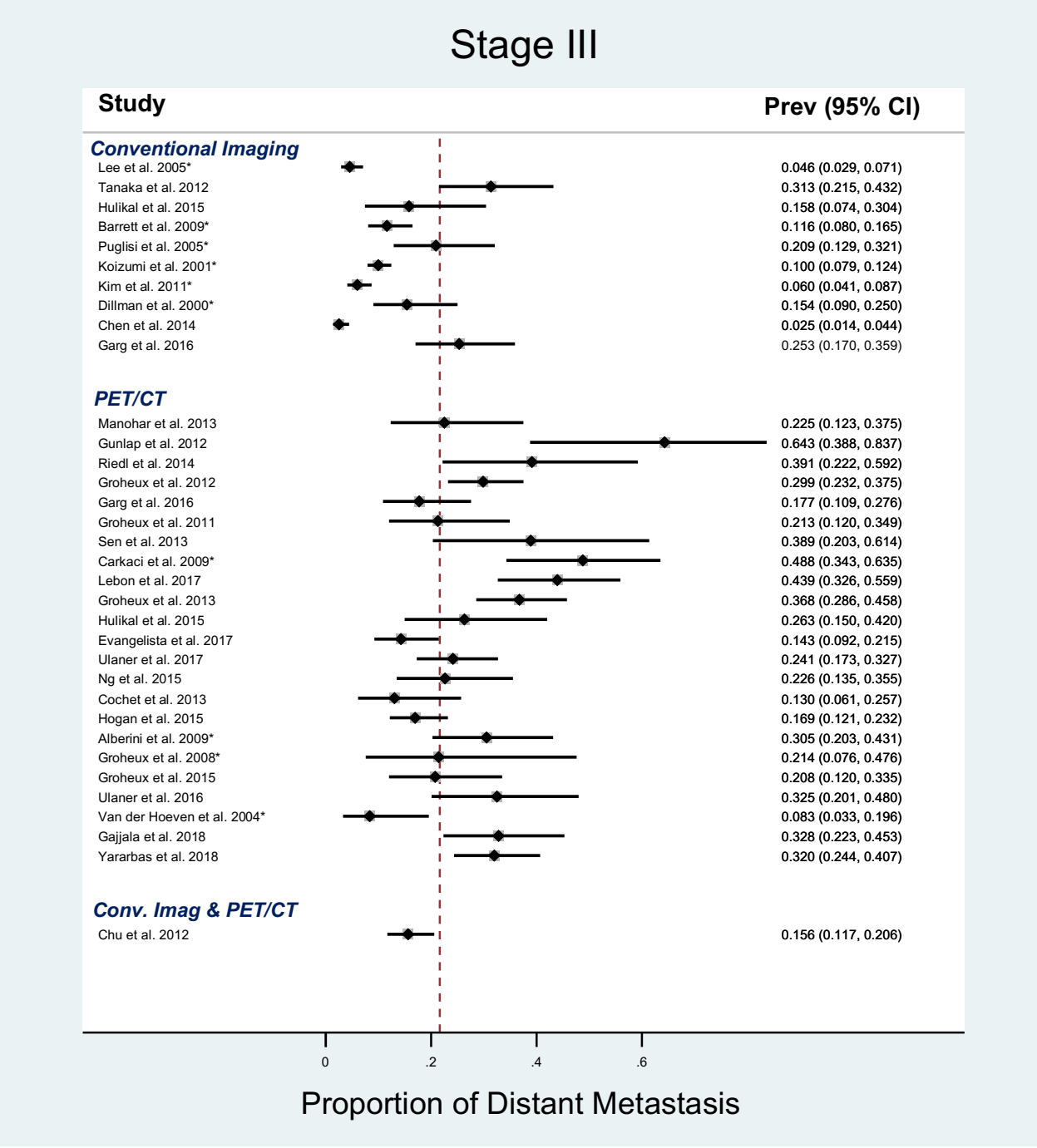
Figure 4-4. Plot of Individual Studies and Pooled Prevalence of Distant Metastasis Detected by Imaging Modality in Women Initially Diagnosed with Stage II Breast Cancer



* From the systematic review by M.E. Brennan and N. Houssami, 2012.

In women newly diagnosed with stage II breast cancer, the prevalence of distant metastasis detected by conventional imaging and PET/CT ranged from 0% to 5.4% and from 0% to 33%, respectively. Conventional imaging and PET/CT combined (one study) detected a prevalence of 1.8% (95% CI 1 to 3.2%). The overall prevalence of distant metastasis ranged from 0% to 33%. The included studies were statistically heterogeneous (I-square: 67% for PET/CT and >75% for conventional imaging).

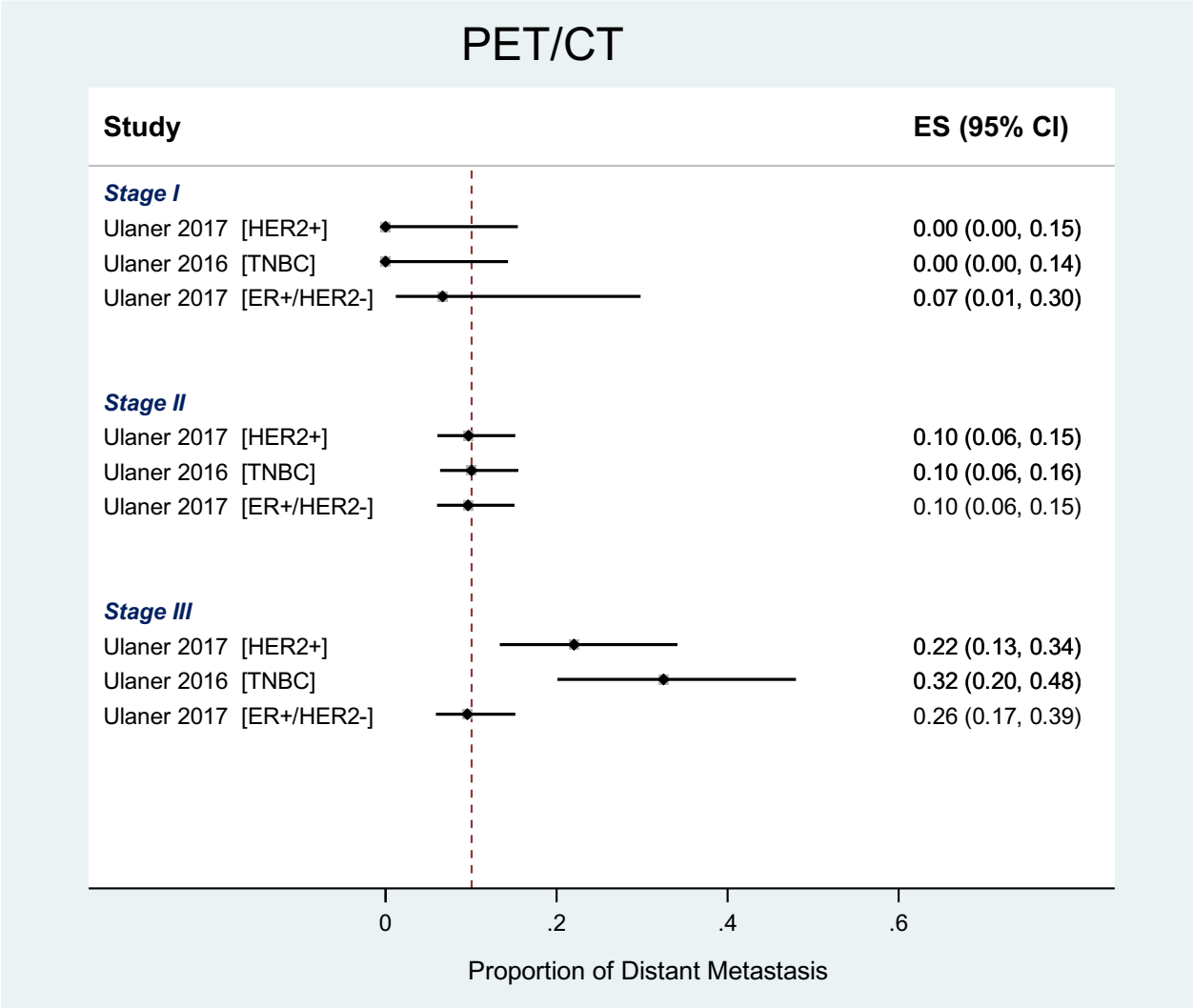
Figure 4-5. Forest Plot of Individual Studies and Pooled Prevalence of Distant Metastasis Detected by Imaging Modality in Women Initially Diagnosed with Stage III Breast Cancer



* From the systematic review by M.E. Brennan and N. Houssami, 2012.

In women newly diagnosed with stage III breast cancer, the prevalence of distant metastasis detected by conventional imaging and PET/CT ranged from 2.5% to 31.3% and from 8.3% to 64%, respectively. Conventional imaging and PET/CT combined (one study) detected a prevalence of 15.6% (95%CI 11.7 to 20.6%). The overall prevalence of distant metastasis ranged from 2.5% to 64.3%. The included studies were statistically heterogeneous (I-square: 74.4% for PET/CT and >75% for conventional imaging).

Figure 4-6. Plot of Individual Studies and Pooled Prevalence of Distant Metastasis by Biomarker Profile Detected by PET/CT in Women Initially Diagnosed with Early-Stage Breast Cancer



In women with HER2+, TNBC, or ER+/HER2- early-stage breast cancer, the PET/CT prevalence of distant metastasis reported by single studies is 0%, 10%, and 22% for stage I; 0%, 10%, and 32% for stage II, and 7%, 10%, and 26% for stage III, respectively.

Table 4-3. Unsuspected Distant Metastasis Detected by FDG-PET/CT in Women with Newly Diagnosed Primary Breast Cancer

		Prevalence of metastases by site				Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
Author	Unsuspected metastases (%)	Bone (%)	Liver (%)	Lung (%)	Other (%)	Stage I (%)	Stage II (%)	Stage III (%)		
Gajjala et al., 2018 [28]	20/61 (33)	11 (18)	6 (10)	7 (11)	DN 11 (18) Brain 1 (2)	N/A	N/A	20/61 (33)	20/61 (33)	NR
Yararbas et al., 2018 [24]	64/234 (27)	43 (18)	9 (4)	16 (7)	DN 37 (16) Pleura 3 (1) Surrenal 4 (2)	0	25/109 (23)	39/122 (32)	64/234 (27)	NR
Lebon et al., 2017 [16]						2/24 (8)	16/124 (13)	29/66 (44)	NR	NR
	<40 y old 23/107 (21)	<40 y old 11 (10)	<40 y old NR	<40 y old 2 (2)	<40 y old DN 6 (6)	<40 y old 1/12 (8)	<40 y old 3/32 (9): A 5/30 (17): B	<40 y old 14/33 (42)		
	≥40 y old 24/107 (22)	≥40 y old 7 (7)	≥40 y old 3 (3)	≥40 y old 1 (0.9)	≥40 y old DN 6 (6)	≥40 y old 1/12 (8)	≥40 y old 4/32 (13): A 4/30 (13): B	≥40 y old 15/33 (45)		
Ulaner et al., 2017[23]	61/483 (13)	46 (10)	13 (3)	8 (2)	DN 7 (2)	1/36 (3)	32/331 (10) 6/143 (4) A 26/188 (14) B	28/116 (24) 7/55 (13) A 18/47 (38) B 3/14 (21) C	NR	NR
	ER+/HER2- 32/238 (13)	ER+/HER2- 27 (11)	ER+/HER2- 4 (2)	ER+/HER2- 4 (2)	ER+/HER2- Pleura 1 (0.4) DN 3 (1) >1 site 6 (3)	ER+/HER2- 1/15 (7)	ER+/HER2- 3/71 (4): A 13/95 (14): B	ER+/HER2- 2/23 (9): A 12/26 (46): B 1/8 (13): C		
	HER2+ 29/245 (12)	HER2+ 19 (8)	HER2+ 9 (4)	HER2+ 4 (2)	HER2+ DN 4 (2) >1 site 7 (3)	HER2+ 0/21 (0)	HER2+ 3/72 (4): A 13/93 (14): B	HER2+ 5/32 (16) 6/21 (29) 2/6 (33)		
Evangelista et al., 2017 [4]	Pre-op 22/149 (15)	14 (9)	6 (4)	5 (3)	DN 40 (27%)	3/34 (9) 1/8 (13) TNBC	8/112 (7) 4/68 (6)	18/126 (14) 17/70 (24)	Pre-op 15/149 (10%) 1-enlarged surgical	Pre-op 3.6-year Kaplan-Meier Estimate

		Prevalence of metastases by site				Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
Author	Unsuspected metastases (%)	Bone (%)	Liver (%)	Lung (%)	Other (%)	Stage I (%)	Stage II (%)	Stage III (%)		
	Post-op 7/126 (5)	5 (4)	--	3 (2)	--	2/26	4/44	1/56 (2)	approach, 12-systemic treatments, 2-systemic + local treatment Post-op 18/126 (14%) 3-further surgery, 8-additional external bean radiotherapy, 7-more aggressive systemic treatment or a combination of local and systemic therapies	positive PET/CT finding including axillary lymph nodes vs negative PET/CT finding OS: 76% vs 92% p=0.063 DFS: 65% vs 100% p<0.001 post-op No differences were found between patients with positive and negative PET/CT findings (OS and DFS, both p>0.05)
Ulaner et al., 2016 [22]	30/232 (13) TNBC	11 (5)	8 (3)	7 (3)	Pleura 1 (0.4) DN 8 (3) >1 site 5 (2)	0/23 (0)	17/169 (10) 4/82 (5): A 13/87 (15): B	13/40 (33) 4/23 (17): A 8/14 (57): B 1/3 (33): C	NR	3-year Kaplan-Meier Estimate Initial stage IIB patients: upstaged to IV (13/87) vs not upstaged 0.33 [95%CI 0.13-0.55] vs 0.97 [95% CI0.76-0.93] p<0.0001
Garg et al., 2016 [25]	34/79 (43) LABC	22 (28)	14 (18)	13 (17)	1 (1) Isolated contralateral axillary and supraclavicula	N/A	N/A	14/79 (18)	14/79 (18) from surgery with or without prior	NR

		Prevalence of metastases by site				Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
Author	Unsuspected metastases (%)	Bone (%)	Liver (%)	Lung (%)	Other (%)	Stage I (%)	Stage II (%)	Stage III (%)		
					r lymphadenopathy				NAC to systemic CT	
Nursal et al., 2016 [18]	42/419 (10)	NR	NR	NR	NR	3/104 (3)	39/315 (12) 19/199 (1 0): A 20/116 (17): B	N/A	NR	NR
Hogan et al., 2015 [14]	ILC 12*/146 (8)	10 (7)	1 (0.7)	NR	DN 2 (1)	0/8 (0)	2/50 (4)	30/177 (17) 10/88 (11)	NR	NR
	IDC 20/89 (23)	17 (19)	2 (2)	2 (2)	DN 3 (3) Pleural 1 (1)	NA	NA	20/89 (23)		
Hulikal et al., 2015 [27]	10/38 (26) 14 metastatic sites	4 (11)	4 (11)	6 (16)	NR	NA	NA	10/38 (26)	10 patients with metastases received palliative care and 28 w/o metastases received NAC	NR
Krammer et al., 2015 [51]	16/101 (16)	13 (13)	5 (5)	5 (5)	DN 6 Adrenal gland 3 Soft tissue 2	N/A	NR	NR	4/101 (4) One patient underwent extended field or RT, a second patient palliative CT with bisphosphonate therapy, and the other two patients underwent	NR

* Nine demonstrated F-FDG-avid metastases. The remaining 3 patients were upstaged only by the CT component of the PET/CT study (these 3 patients were initially stage III ILC)

		Prevalence of metastases by site				Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
Author	Unsuspected metastases (%)	Bone (%)	Liver (%)	Lung (%)	Other (%)	Stage I (%)	Stage II (%)	Stage III (%)		
									palliative approach with systematic CT	
Groheux et al., 2015 [6]	11/85 (13)	5 (6)	3 (4)	3 (4)	DN 8 (9)	N/A	0/32 (0)	11/53 (21)	NR	<u>2-year DSS among patients with DM</u> 18.2% Significantly shorter than in those without DM on baseline PET/CT *P<0.001*
Ng et al., 2015 [10]	17/154 (11) LABC	7 (4)	2(1)	2 (1)	Mediastinal and/or DN 7 (5)	NA	5/101 (5) 1/20 (5) A 4/81 (5) B 1 TNBC 4 ER+PR+HER2-	12/53 (23) 7/43 (16) A 2/7 (29) B 3/3 (100) C 3 TNBC 4 ER+PR+HER2- 1 ER+PR-HER2+ 2 ER+PR+HER2+ 2 ER-PR-HER2+	These patients' intent to treat was subsequently changed from curative to palliative, and adjuvant radiation therapy was omitted	NR
Riedl et al., 2014 [19]	20/134 (15) Receptor phenotype was not found to relate to distant metastases	16 (12)	5 (4)	2 (1)	DN 6 (4)	1/20 (5)	10/91 (11) 2/44 (5): A 8/47 (17): B	9/23 (39) 4/13 (31) 4/8 (50) 1/2 (50)	NR	
Jeong et al., 2014 [15]	0/178	0	0	0	0	0/178	NR	NR	NR	0/178

		Prevalence of metastases by site				Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
Author	**Unsuspected metastases (%)**	**Bone (%)**	**Liver (%)**	**Lung (%)**	**Other (%)**	**Stage I (%)**	**Stage II (%)**	**Stage III (%)**		
Cochet et al., 2014 [3] 2006-2010	25/142 (18)	15 (11)	4 (3)	4 (3)	DN 4 (3)	NA	6/79 (8) 2/22 (9) A 4/57 (7) B	6/46 (13) 0/12 (0) A 4/19 (21) B 2/15 (13) C	11 (8) from curative to palliative care; 4 (3) from palliatice to curative treatment after PET/CT suggested absence of distant lesions	2-year PFS DM detected by CI vs. PET/CT 63% vs 40%
Manohar et al., 2013 [9]	10/43 (23) LABC	3 (7): IIIB	2 (5): IIIB	4 (9): IIIB	Sternum 2 (5) DN 3 (7)	NA	1/3 (33) B	9/40 (23) 1/15 (7) A 8/24 (33) B 0/1 (0) C	10/43 (23) One patient with initial clinical stage IIB, one with IIIC, and eight with IIIC	NR
Groheux et al., 2013 [26]	43/117 (37) 16/35 (46) IBC 27/82 (33) NIBC *P=0.18*	30 (26) 10 IBC 20 NIBC	10 (9) 4 IBC 6 NIBC	6 (5) 3 IBC 3 NIBC	DN 19 (16) 8 IBC, 11 NIBC Pleura 2 (2) 0 IBC, 2 NIBC	N/A	N/A	43/117 (37)		3-year DSS 40 M1 vs. 64 M0 53% vs. 78% *P=0.002*
Sen et al., 2013 [20]	12/77 (16) Early post-operative period	2 (3)	3 (4)	3 (4)	DN 7 (9)	1/19 (5)	4/38 (11)	7/18 (39)	Therapy decision changed either from RT to medical treatment or from CT to hormonal treatment	

	Prevalence of metastases by site					Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
Author	**Unsuspected metastases (%)**	**Bone (%)**	**Liver (%)**	**Lung (%)**	**Other (%)**	**Stage I (%)**	**Stage II (%)**	**Stage III (%)**		
Gunalp et al., 2012 [13]	Pre-op 40/141(29) Post-op 24/195 (12)	Pre-op 28 (20) Post-op 18 (9)	Pre-op 6 (4) Post-op 2 (1)	Pre-op 4 (3) Post-op 4 (2)	Pre-op 4 (3) Post-op 3 (2)	Pre-op 1/19 (5)	Pre-op 30/100 (30) 10/51(20) A 20/49(40) B	Pre-op 9/14 (64) 7/12 (58) A 2/2 (100) B	Post-op Post-operative chemotherapy was adapted to the metastatic disease in 24 (12%) patients	NR
Bernsdorf et al., 2012 [52]	6/103 (6)	5 (5)	N/A	1 (1)	0	NR	NR	NR	Therapy decision changed from adjuvant an treatment to a metastatic approach with/or without bisphosphonate	
Groheux et al., 2012 [8]	53/254 (21) 28/130 ER+HER2- 13/51 HER2+ 11/69 TNBC	35 (14)	13 (5)	9 (4)	DN 20 (8) Pleura 2 (1)	N/A	7/100 (7) 1/44 (2) A 6/56 (11) B	46/154 (30) 11/63 (18) A 27/74 (37) B 8/17 (47) C	NR	3-year DSS among 189 pts with stage IIB or higher: 47 M1 vs. 142 M0 57% vs 88% *P<0.001*
Garami et al., 2012 [5]	8/115 (7)	2 (2)	1 (0.9)	2 (2)	DN 3 (3)	2/63 (3)	6/49 (12)	NA	Lung resection (1), palliative chemotherapy (1), palliative surgery followed by	NR

		Prevalence of metastases by site				Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
Author	Unsuspected metastases (%)	Bone (%)	Liver (%)	Lung (%)	Other (%)	Stage I (%)	Stage II (%)	Stage III (%)		
									aggressive chemotherapy (4), and palliative oncologic treatment (2)	
Groheux et al., 2011 [7]	15/131 (12)	11 (8)	3 (2)	5 (4)	DN and pleura 2 (2)	N/A	5/84 (6) 1/36 (3) A 4/48 (8) B	10/47 (21) A	Treatment was adapted to the metastatic disease	NR
Alberini et al., 2009[1][2]	18/59 (31)	7/59 (12)	5/59 (9)	4/59 (7)	Mediastinum 12/59 (20) Peritoneum 3/59 (5)	N/A	N/A	18/59 (31)	NR	NR
Carkaci et al., 2009[1,2][2]	20/41 (49)	9/41 (22)	6/41 (15)	4/41 (10)	Mediastinum 10/41 (24)	NA	NA	20/41 (49)	NR	NR
Heusner et al., 2008[1][2]	10/40 (25)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Groheux al., 2008[1][2]	4/39 (10)	3/39 (8)	0/39	1/39 (3)	NA	NA	1/25 (4)	3/14 (21)	NR	NR
Van der Hoeven et al., 2004[1][2]	4/48 (8)	2/48 (4)	2/48 (4)	0	NR	NA	NA	4/48 (8)	NR	NR

Abbreviations: CI, confidence interval; CT, chemotherapy; DFS, disease-free survival; DN, distant lymph node; DSS, disease-specific survival; ER, estrogen receptor; FDG, fluorodeoxyglucose; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LABC, locally advanced breast cancer; NAC, neoadjuvant chemotherapy; NR, not reported; OS, overall survival; PET/CT, positron emission tomography/computed tomography; pre-op, preoperative; post-op, postoperative; RT, radiotherapy; TNBC, triple-negative breast cancer

[1] From "Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastasis in newly diagnosed breast cancer" by M.E. Brennan and N. Houssami, 2012, The Breast Journal, 21(2):112-13.

[2] Includes some cases with symptoms suggesting metastatic disease

Table 4-4. Unsuspected Distant Metastasis Detected by Conventional Imaging in Women with Newly Diagnosed Primary Breast Cancer

Author	Imaging Modality	Prevalence of metastases by site					Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
		Unsuspected metastases (%) pts	Bone (%)	Liver (%)	Lung (%)	Other (%)	Stage I (%)	Stage II (%)	Stage III (%)		
Gajjala et al., 2018 [28]	Bone CT, Chest X-ray, abdominal US, abdominal CT	13/61(21)	7 (12)	2 (3)	9 15)	DN 4 (7)	NR	NR	NR	NR	NR
Bychkovsky et al., 2016 [11]	Body CT	5/237 (2)	NR	NR	NR	NA	NA	5/237 (2) ER+/PR+ 3/135 (2) HER2+ 1/54 (2) TNBC 1/48 (2)	NR	NR	NR
Garg et al., 2016 [25]	Chest X-ray, abdominal US, bone scintigraphy	20/79 (25)	12 (15)	7 (9)	6 (8)				20/79 (25)		
Krammer et al., 2015 [51]	Abdominal US, chest X-ray, bone scan	13/101 (13)	11 (11)	4 (4)	1 (1)	NR	NR	NR	NR	NR	NR
Hulikal et al., 2015 [27]	CECT/BS	6/38 (16)	2 (5)	1 (3)	4 (11)				6/38 (16)		

Author	Imaging Modality	Prevalence of metastases by site					Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
		Unsuspected metastases (%) pts	Bone (%)	Liver (%)	Lung (%)	Other (%)	Stage I (%)	Stage II (%)	Stage III (%)		
Chen et al., 2014 [12]	Bone scan, liver US, chest x-ray	Number of patients with metastases was not reported	46 (1) 30 ER+ 16 ER- 25 PR+ 21 PR- 20 HER2+ 26 HER2-	14 (0.4) 4 ER+ 10 ER- 5 PR+ 9 PR- 8 HER2+ 6 HER2-	7 (0.2) 2 ER+ 5 ER- 2 PR+ 5 PR- 1 HER2+ 6 HER2-	0	8/411 (2) 5 bone, 2 liver, 1 lung	48/2561 (2) 33 bone, 10 liver, 5 lung	11/439 (3) 8 bone, 2 liver, 1 lung	NR	NR
Groheux et al., 2013 [26]	Bone scan, chest X-ray or CT, abdomino-pelvic ultrasound and/or CT, bone scintigraphy	30/117 (26)	19 (16)	9 (8)	7 (6)	DN 10 (9) Pleura 1 (1)					
Tanaka et al., 2012 [21]	CECT	26*/483 (5) 20/381 (5) ER+ 5/100 (5) ER- 15/314 (5) PR+ 10/167 (6) PR- 3/65 (5) HER2+ 21/393 (5) HER2-	13 (3)	11 (2)	18 (4)	NR	0/155 (0)	5/261 (2)	21/67 (31)	NR	2-year OS 99% and 74% for patients with normal findings and patients with metastases
Kim et al., 2011[1] [2]	Chest CT	26/1703 (2)	N/A	9 (0.5)	23 (1)	N/A	1/448 (0.2)	0/838 (0)	25/417 (6)	NR	3-year OS

* CECT detected 65 patients with abnormal findings, including true- and false-positive results

Author	Imaging Modality	Prevalence of metastases by site					Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
		Unsuspected metastases (%) pts	Bone (%)	Liver (%)	Lung (%)	Other (%)	Stage I (%)	Stage II (%)	Stage III (%)		
											98% and 52% for patients with normal CT and patients with metastases findings, respectively P<0.001
Barrett et al., 20091 [2]	Bone scan, chest x-ray, liver Us, CT	42/2612 (2)	23/373 (6)	6/339 (2)	3/1556 (0.2)		0/992 (0)	12/1041 (1)	26/224 (12)	NR	NR
Lee et al., 20051 [2]	Bone scan	28/1939 (1)	28/1939 (1)	NA	NA	NA	4/586 (1)	6/958 (1)	11/237 (5)	NR	NR
Puglisi et al., 20051 [2]	Liver US, chest x-ray, bone scan	33/516 (6)	26/412 (6)	3/412 (0)	4/428 (1)	NR	12/236 (5)	7/159 (4)	14/67 (21)	NR	NR
Kasem et al., 20061 [2]	Bone scan, liver US	7/221 (3)	6/221 (3)	3/221 (1)	NA	NR	1/61 (2)	8/18 (5)	NR	NR	NR
Koizumi et al., 20011 [2]	Bone scan	118/5538 (2)	118 (2)	NA	NA	NA	1/1212 (0)	34/3120 (1)	67/673 (10)	NR	NR
Dillman et al., 20001 [2]	Bone scan	26/947 (3)	20/601 (3)	20/601 (3)	23/635 (4)	Brain 2/2 (9)	1/502 (0)	13/367 (4)	12/78 (15)	NR	NR

Abbreviations: BS, bone scan; CECT, contrast enhanced computed tomography; CT, chemotherapy; DN, distant lymph node; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NA, not available; NR, not reported; OS, overall survival; PR, progesterone receptor; TNBC, triple-negative breast cancer; US, ultrasound

[1] From “Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastasis in newly diagnosed breast cancer” by M.E. Brennan and N. Houssami, 2012, The Breast Journal, 21(2):112-13.

Table 4-5. Unsuspected Distant Metastasis Detected by Combined Imaging Modalities (Conventional Imaging and/or PET/CT) in Women with Newly Diagnosed Primary Breast Cancer

Author	Imaging Modality	Prevalence of metastases by site					Prevalence of metastases by Stage (Upstaged to IV)			Change in Management	OS / PFS
		Unsuspected metastases (%) pts	Bone (%)	Liver (%)	Lung (%)	Other (%)	Stage I (%)	Stage II (%)	Stage III (%)		
Piatek et al., 2016 [53]	CT, bone scan, PET	21/362 (6)	14 (4)	6 (2)	8 (2)	DN 2 (0.6) Chest 1 (0.3)	NR	NR	NR	20/362 (6)	NR
Linkugel et al., 2015 [17]	Chest, abdominal and/or pelvis CT, bone CT, PET	11/882 (1.3)	4 (0.5)	1 (0.1)	3 (0.3)	NR	1/312 (0.3)	10/570 (1.8)	NA	NR	NR
Chu et al., 2012 [55]	Chest X-ray, bone scan, CT, PET	40/256 (16)	NR	NR	NR	NR	NA	NA	40/256 (16) 24/158 (15) N2 16/98 (16) N3	NR	NR for those in which metastases was detected
Botsikas et al., 2016 [54]	FDG-PET/MR	2/58 (4)	2/58	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; MR, magnetic resonance; NA, not available; NR, not reported; OS, overall survival; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival

Table 4-6. Prevalence of Bone, Liver, and Lung Metastases by Initial Clinical Stage as Detected by Different Imaging Modalities

Initial Stage / Reference [Modality]	Distant metastases/Sample population by Stage (%)								
	Stage I			Stage II			Stage III		
	Bone	Liver	Lung	Bone	Liver	Lung	Bone	Liver	Lung
Ng et al. 2015 [10] [PET/CT]				1/101 (0.9)	1/101 (0.9)	0/101 (0)	6/53 (11)	1/53 (1.9)	2/53 (3.7)
Chen et al. 2014 [12] [CI*]	5/411 (1.2)	2/411 (0.5)	1/411 (0.2)	33/2561 (1.3)	10/2561 (0.4)	5/2561 (0.2)	8/439 (1.8)	2/439 (0.5)	1/439 (0.2)
Manohar et al. 2013 [9] [PET/CT]				0/3 (0)	0/3 (0)	0/3 (0)	3/40 (7.5)	2/40 (5)	4/40 (10)
Tanaka et al. 2012 [21] [CT]	0/155 (0)	0/155 (0)	0/155 (0)	4/261 (1.5)	1/261 (0.4)	2/261 (0.8)	9/67 (13)	10/67 (15)	16/67 (24)
Gunalp et al. 2012 [13] Pre-op Setting [PET/CT]	1/19 (5)	0/19 (0)	0/19 (0)	21/100 (21)	4/100 (4)	2/100 (2)	6/14 (43)	2/14 (14)	2/14 (14)

Abbreviations: PET/CT, positron emission tomography/computed tomography; Pre-op, preoperative

* Bone scan, liver US, chest x-ray

Ongoing, Unpublished, or Incomplete Studies

One relevant trial was listed as recruiting in the U.S. National Library of Medicine www.ClinicalTrials.gov. The Ontario Clinical Oncology Group and CCO are collaborating on a trial titled "*Impact of 18-F-FDG PET-CT Versus Conventional Staging in the Management of Patients Presenting With Clinical Stage III Breast Cancer*". This trial is being conducted to determine the impact of whole body FDG PET-CT versus conventional imaging in the management of patients presenting with clinical stage IIb (T3N0) and III (T0N2, (T1N2, T2N2, T3N1, T3N2, or T4) breast cancer. For more information about this trial, please see registration # NCT02751710.

DISCUSSION

Over 7000 women will develop breast cancer each year in the province of Ontario [36]. While appropriate staging investigations in patients with newly diagnosed breast cancer can aid in expediting appropriate care, overuse can lead to unnecessary invasive biopsies, unnecessary exposure to potentially harmful radiation from the tests, psychological distress, heightened anxiety, and possible delays to treatment [44,45]. We sought to answer the question of which groups of primary diagnosed, asymptomatic breast cancer patients should routinely undergo staging investigations, and what are the optimal imaging modalities.

Our systematic review of over 5600 articles resulted in 32 studies for analysis. All studies reported an overall prevalence of asymptomatic distant metastases with a median prevalence of 14%, with the most common distant metastases sites as bone, lung, and liver, in that order. Excluding PET/CT, the detection of distant metastasis in stage I and II breast cancer patients with anatomic staging imaging tests was 1.0% (range, 0-1.9%) and 1.9% (range, 1.9-2.1%) respectively. This exceedingly low rate of distant metastasis in stages I and II does not warrant routine use of staging imaging.

On the other hand, results were more significant for stage III asymptomatic patients, as the median prevalence of distant metastases reported by conventional imaging was 21% (range, 3-31%), which is why routine systemic imaging is recommended. Overall, our recommendations agree with National Comprehensive Cancer Network (NCCN) updated 2018 [57], European Society for Medical Oncology (ESMO) 2015 [32], and ASCO Choosing Wisely guidelines [58] in that routine systemic imaging in asymptomatic patients should only be considered in patients who present locally advanced (stage III, T3 N1-3) disease.

Our current recommendations differ as compared to our previous CCO guideline published in 2011 in that "*we no longer recommend routine bone scan for stage II patients, even if they have node positive disease*". As more prospective studies became available, the low incidence of bone, lung, and liver metastasis was confirmed such that we no longer felt the need for a routine body imaging for the initial evaluation of women with stage II breast cancer and showing no symptoms for distant metastasis. Our current guidelines also differ from the latest Alberta Health Services (2012) and Eastern Health (2011) staging guidelines, both of which recommend a routine baseline bone scan and CT scan of chest/abdomen should be performed in all patients with node positive disease.

In regard to PET/CT imaging, the data did show overall additional detection rates across all stages. However, for stage I and II asymptomatic patients, the added prevalence of metastatic disease detection was highly variable, ranging from an additional 1-10%; and none of the studies were RCTs. For stage III asymptomatic patients, the average prevalence of distant metastases with PET/CT studies was more significant at 26% (13% to 64%). As such, we felt that PET/CT could be considered as method of staging for distant metastasis in stage III patients. The results of the Ontario PET-ABC study, an RCT of asymptomatic stage III patients comparing routine use of PET/CT versus conventional imaging would supplement this recommendation. However, for stage II patients, we struggled with whether to recommend routine use of PET/CT,

as some of us felt that a 10% prevalence of distant metastasis was not to be ignored. We therefore looked to literature guidance on this issue. Interestingly, while ASCO considers PET/CT as credible imaging modality for stage III patients, it recommends against its use in stage I and II asymptomatic patients. The NCCN panel recommended against its use in stages I to III, stating the high false negative rate for lesions that are small and/or low grade, the low probability of these patients having detectable metastatic disease, and the high rate of false positive scans. On the contrary, they recommend the use of PET/CT only as an adjunct to conventional imaging modalities when findings are suspicious or equivocal, especially in the setting of locally advanced or metastatic disease. Furthermore, results from a multicentre, prospective, diagnostic accuracy study reported that PET is not sufficiently specific to accurately identify distant metastasis in asymptomatic patients with primary breast cancer (I and II) [59]. Apart from staging investigation in patients with newly diagnosed breast cancer, the diagnostic value of PET in detecting distant metastasis in the initial staging of breast cancer was determined to be beyond the scope of this guideline.

There are limitations to the interpretation of the data based on the substantial heterogeneity in the design and quality of the studies. In general, the evidence is sparse and drawn mainly from single-institutional retrospective and prospective studies, reflecting the need for a prospective RCT. There was a substantial variability in the quality of the reference standard test used to confirm suspected metastasis as not all patients received histopathological confirmation, and no form of reference standard test was used to confirm negative results (misclassification bias). For many of the studies it was unknown whether or not the clinicians interpreting the results of the reference test were blinded to the results of the index test. Furthermore, when comparing imaging modalities, of the eight studies that examined the use of conventional imaging as staging tests, five used chest x-ray/ultrasound, two used CT scan, and one used either ultrasound or CT scan. None study compared the outcome of CT versus ultrasound and chest x-ray; therefore, no explicit recommendation can be made about which modality to use, based on the evidence review.

In addition, we focused on imaging detection of systemic disease, without the ability to determine to any meaningful degree whether the detection of metastasis affected outcome or treatment decisions, as information on treatment and survival by initial stage was not integrated into these imaging studies. Finally, it should be noted that for the purposes of our proposed imaging recommendations, staging can be based on clinical (in the patient undergoing neoadjuvant therapy) or pathological/anatomic stage assessment (in the postoperative patient). The new 8th revision to the AJCC Breast Cancer Staging System has incorporated tumour biology (grade, ER status, PR status, and HER2 status) and combined them with tumour-nodal-metastasis (TNM) categories into prognostic stage groups. Although this new prognostic staging system is supposed to be a better representation of prognosis and outcome, we have not incorporated it into our guidelines, simply because of a lack of available studies using this classification. It should be noted that up to 30% to 40% of patients can be reassigned to a different prognostic stage group than the one assigned on the basis of anatomic staging. We acknowledge that the studies included in this review used the AJCC 7th edition for staging which was based solely on anatomic stage groupings. The AJCC 8th edition was reviewed to determine whether new, clinical and pathologic prognostic stage groupings would affect the recommendations. In the new staging system, some anatomic stage II patients would be reclassified to stage III (e.g., high-grade, triple-negative disease). Additionally, some anatomic stage III patients (e.g., low-grade, ER+) would be downstaged to stage II in the new classification. Thus, there is some risk that our recommendations for stage II patients would result in understanding under the new clinical and pathologic prognostic stage groupings. On the other hand, the evidence review of specific studies that considered biomarker profile for selecting patients for distant metastasis staging did not show a greater prevalence of metastasis compared

to anatomic staging alone. Until further studies are performed delineating the evidence of staging in this new classification system, differences between the AJCC 7th and 8th classification systems in clinical and pathological staging should be taken into consideration when interpreting this guideline. We are aware that additional pre-operative imaging that may not be routine (MR imaging), if applied would also have the potential to upstage patients. We look forward to adjusting our systemic imaging recommendations in the future with emerging evidence on the prevalence of distant metastasis with the new AJCC classification system (8th edition) as well as additional pre-operative imaging modalities.

CONCLUSIONS

This guideline is intended to provide recommendations for the use of imaging tests to detect distant metastases in women with newly diagnosed breast cancer who are otherwise asymptomatic. Unless a patient has clinical or pathologic stage III breast cancer, this evidence based guideline recommends against the routine use of staging investigations, regardless of biomarker profile.

Baseline Staging Imaging for Distant Metastasis in Women with Stage I, II, and III Breast Cancer

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the six members of the GDG Expert Panel, five members cast votes and one abstained, for a total of 83% response in May 2019. Of those that cast votes, five approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel

Comments	Authors' Responses
1. The main argument against the routine use of PET is the quality of the studies and this aspect should be more strongly highlighted. Also, a value judgement needs to be made about what detection rate of an imaging modality would make the modality useful in staging. For example, is 10% detection in stage II such a detection rate? Either some type of cost-benefit assessment or oncologist survey or other literature would be required.	The following sentence was added: "The members of the Working Group believe that the anticipated benefits associated with baseline imaging investigation for distant metastasis are small and outweighed by the risk of anxiety, radiation exposure, cost, and false positive patients who would receive unnecessary and more aggressive treatment (i.e., systemic therapy rather than conserving surgery). Therefore, a 10% detection rate for distant metastasis was considered a reasonable threshold for considering baseline imaging investigation for distant metastasis. The members of the Working Group considered that this 10% threshold was determined as the best estimate of the infliction point where the risks-benefits ratio of testing patients with asymptomatic early stage breast cancer changes from being harmful to being beneficial". Cost-benefit assessment or oncologist surveys were not considered in this evidentiary base as such literature is out of the scope of the PEBC review.
2. Needs to be clear that the authors are referring to the old staging. Perhaps, in the recommendations, instead of stage I, II and III, use TN staging?	It has been clarified that all the included studies used the clinical and/or pathological Staging System for Breast cancer from the 7th Edition of the AJCC.
3. Should patients with clinical stage I or II TNBC or HER+ breast cancer treated with neoadjuvant chemotherapy undergo staging at initial diagnosis?	No evidence was found to support staging based on biomarker profile. It is stated under the qualifying statement for Recommendation 1, that the benefits and risks of the routine use of biomarker profiles to assess for distant metastasis is still unclear, and,

	thus, its use to guide decisions on imaging staging for clinical early-stage breast cancer is not recommended.
4. Under Recommendation 1, stage II breast cancer – Not even T3N0/stage IIB = locally advanced breast cancer?	The studies that were included in this systematic review were classified based on clinical stage. We are aware that locally advanced breast cancers can be stage IIB. Overall, there was no benefit observed for this group.
5. Under the qualifying statement for Recommendation 2, it is stated that is prudent to wait for the results of the trial before adopting imaging modalities as standard of practice, but the interpretation of the evidence stated that it is reasonable to use PET/CT for screening. I believe that If there was not an ongoing trial, the recommendation for PET/CT would be stronger. I am not sure we should be delaying the use of PET/CT. I would favour removing or modifying the sentence from the qualifying statement.	Imaging modalities have been recommended in women newly diagnosed with stage III breast cancer. The sentence under the qualifying statement refers to which modality (anatomical or functional) should be adopted as standard of practice.
6. Are the recommendations applicable to women all ages?	The studies included in this evidentiary base recruited a population with a median age of 51 years, which is a slighter younger population than the expected average breast cancer population, as median age of diagnosis in Ontario is approximately 61 years. However, since there was no restriction by age in any of the studies, the members of the Working Group believe that the recommendations are applicable to women of all ages.
7. Should women with a very high risk for breast cancer be managed based on this document? The lead panel should provide guidance on this issue.	This recommendation has been based on asymptomatic women and since risk assessment was not a factor for stratification, we cannot make recommendations specifically for women based on risk. Although women with triple-negative and HER2+ breast cancer have an increased risk of disease recurrence, the association of distant metastasis and biomarker profile in early-stage breast cancer has not been adequately studied in prospective studies of staging investigation.
8. A small percentage of women with stage II showed distant metastasis. Were these women really stage II? In other words, if they were diagnosed by MR imaging their staging may have been upgraded. Perhaps there is no information in the literature, but should this be listed as a limitation with regard to the literature to explain this small population with distant metastasis?	Almost all the studies used preoperative staging (some used postoperative/pathological staging). Generally, the preoperative staging was done by clinical examination and routine breast imaging (mammography and breast ultrasound); there may have been patents who were also staged according to MR imaging. In the Discussion section, we have listed the limitations of this document to describe the small population of women that may have been understaged preoperatively.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in April 2019. The RAP approved the document on April 22, 2019. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP

Comments	Authors' Responses
1. In Recommendation 1, it would be appropriate to clarify what "conventional" refers to.	What conventional refers to has been clarified and it now reads as: *"Staging tests using conventional anatomic (chest X-ray, liver ultrasound, chest-abdomen-pelvis CT scan)……."*
2. Under the qualifying statement for Recommendation 1 (second bullet), the authors discouraged the use of PET/CT as part of the baseline staging imaging in women clinically diagnosed breast cancer I and II. Based on the lack of evidence, "recommended" rather than "discouraged" should be used.	The members of the Working Group agreed with this comment and the change is reflected in the document.
3. Under the qualifying statement for Recommendation 1 (third bullet), the sentence below about biomarkers is not clear. "The benefit and risks of routine imaging by biomarker profile is still unclear and, thus, it is not recommended"	The sentence has been changed and it now read as: *"The benefit and risks of the routine use of biomarker profiles to assess for distant metastasis is still unclear and, thus, its use to guide decisions on imaging staging for clinical early-stage breast cancer is not recommended".*
4. Why does the Discussion section call out care at tertiary and associated cancer centres?	The members of the Working Group agreed with the comment, and the sentence was removed.
5. Under data extraction and assessment of quality and potential for bias, an explicit statement of the value of judgement of priority given to the outcome of distant metastasis should be provided, including rate of detecting distant metastasis.	The following sentence was added: "The members of the Working Group believe that the anticipated benefits associated with baseline imaging investigation for distant metastasis are small and outweighed by the risk of anxiety, radiation exposure, cost, and false positive patients who would receive unnecessary and more aggressive treatment (i.e., systemic therapy rather than conserving surgery). Therefore, a 10% detection rate for distant metastasis was considered a reasonable threshold for considering baseline imaging investigation for distant metastasis. The members of the Working Group considered that this 10% threshold was determined as the best estimate of the infliction point where the risks-benefits ratio of testing patients with asymptomatic early stage breast cancer changes from being harmful to being beneficial".
6. It may be worthwhile to include information about oligometastasis in the Discussion. It could be stated that it is an emerging field	The members of the Working Group are aware of the issue of oligometastasis as a subject of patients who are identified with metastatic disease that have a better prognosis. This guideline is about performing

and that there are insufficient data to intensify investigations based at this time.	staging investigations on patients expected not to have metastatic disease. The members of the Working Group are not clear about the relevance of oligometastatic disease as a factor in influencing the decision on whether to perform staging.
7. Would the authors consider dividing up Table 4-2 to align with Tables 4-3 and 4-4?	Table 4-2 has been modified to align with Tables 4-3 and 4-4.
8. Some comments were made to clarify definitions.	The members of the Working Group agreed with the comments, and changes are reflected in the document.

Table 5-3. Summary of the Working Group's responses to comments from the patient representative

Comments	Authors' Responses
1. The recommendations require a level of health/medical literacy which the general target patient population might not have. The general target population would have some difficulty understanding these recommendations depending on healthcare experiences and tests undertaken as part of their care. Given the fact that the target audience is health care professionals, policy makers, program planners and institutions, I anticipate thet the recommendations are manageable by this target audience.	The systematic review presented in section 2 and its companion recommendations are intended to promote evidence-based practice by the mentioned target audience in Ontario, Canada. It is anticipated that clinicans provide patients with clear information regarding baseline staging imaging after a new diagnosis of early stage breast cancer.
2. The recommendations consider issues and/or address outcomes that are important to patients and members of the public. However, patient specific material needs to be developed to educate patients on the choices made on the use of imaging tests to detect distant metastases based on staging. Patient anxiety needs to be managed through clear and transparent information-qualitative and quantitative as to the value/risk associated with choice of imaging test based on staging. 3. With effective patient centric education, patients will be better able to understand the choices being made by their healthcare providers. Patients should be given the necessary benefit/cost information including prevalence of distant metastases given staging and/or presence of triple negative and human epidermal growth factor receptor 2-positive [HER2+] breast cancer.	The members of the Working Group agreed with these comments, and they are now documented in Section 2, under "Implementation Considerations".

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Five targeted peer reviewers from who are considered to be clinical and/or methodological experts on the topic were identified by Staging in Early Stage Breast Cancer Working Group. Two agreed to be the reviewers (Appendix 1). Two responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-4. Responses to nine items on the targeted peer reviewer questionnaire

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	1				1
2. Rate the guideline presentation.			1	1	
3. Rate the guideline recommendations.	1			1	
4. Rate the completeness of reporting.			1		1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	
6. Rate the overall quality of the guideline report.			1	1	
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			1	1	
8. I would recommend this guideline for use in practice.			1	1	

9. What are the barriers or enablers to the implementation of this guideline report?

The guideline provides clear recommendations regarding the use of diagnostic imaging to investigate for the possibility of distant metastasis. Unfortunately, the guidelines bases this decision on clinical/pathologic staging derived from the AJCC 7th edition breast cancer staging manual. However, new staging classification is available (8th edition). The guideline does not give instruction as how the clinicians would handle changes in the staging classification when AJCC staging guidelines updates occur. Alternatively, the ESMO guideline defines high-risk patients not using staging criteria: 1) clinically positive lymph nodes, 2) large tumour (e.g., >5 cm); aggressive biology and clinical signs, symptoms or laboratory values suggesting presence of metastasis. Perhaps, a high risk definition not using specific staging classification, which may change over time, would have been helpful.

Table 5-5. Responses to comments from targeted peer reviewers

Comments	Authors' Responses
1. The guidelines are consistent with the evidence and clinical practice guidelines addressing this issue. My main suggestions would be to review the wording regarding "Recommendation 2". I would have thought a	The members of the Working Group agreed with this comment and the change is reflected in the document.

stronger recommendation would be warranted. For example, "In women newly diagnosed with stage III breast cancer, baseline staging tests, using either anatomic (chest X-ray, liver ultrasound, chest-abdomen-pelvis CT scan) and/or metabolic imaging modalities (PET/CT, PET/MR, bone scintigraphy), should be considered regardless of whether the patient is symptomatic for distant metastasis or not, and regardless of biomarker profile.	
2. I wonder whether the clinical practice guideline should state more definitely which conventional diagnostic imaging modalities are preferred versus not-preferred for breast cancer staging (e.g., CT scans of chest, abdomen/pelvis and bone scan). Given their lower sensitivity, should chest X-ray and ultrasound of the liver even be recommended unless contraindications for CT staging and/or bone scan exist? The evidence for PET was clearly outlined; however, I would have appreciated more explicit recommendation for use of differing conventional imaging modalities.	When comparing imaging modalities, of the eight studies that examined the use of conventional imaging as staging tests, five used chest X-ray/ultrasound, two used CT scan, and one used either ultrasound or CT scan. None of the studies compared the outcome of CT versus ultrasound and chest X-ray; therefore, no explicit recommendation can be made about which modality to use based on the evidence review. This statement has been incorporated in the Discussion section for clarification.
3. Given the increased risk of neoadjuvant chemotherapy, the guideline may wish to address the utility of staging in high-risk stage II breast cancer patients undergoing preoperative therapy. CT staging may give a more accurate assessment of locoregional disease, which may impact treatment after chemotherapy. Currently, the guideline advises not to stage under this circumstance, which would not follow standard current clinical practice where the vast majority of neoadjuvant breast cancer patients receive staging. Obviously, data on this issue are limited. I would have liked to see a more definitive comment on high-risk stage II breast cancer patients who are selected for neoadjuvant chemotherapy.	In reviewing the evidence, the Working Group members do not believe that staging TN or HER2+ patients with clinical stage II breast cancer who are having neoadjuvant chemotherapy is warranted.
4. The guideline bases this decision on clinical/pathologic staging derived from the AJCC 7th edition breast cancer staging manual. However, new staging classifications are available (8th edition). The guideline does not give instruction as the how clinicians would handle changes in the staging classification when AJCC staging guidelines updates occur. Alternatively, the ESMO guideline defines high-risk patients not using staging criteria: 1) clinically positive lymph nodes, 2) large tumour (e.g., >5 cm); aggressive biology and clinical signs, symptoms or laboratory values suggesting presence of metastasis. Perhaps, a high risk definition not using specific staging	The members of the Working Group acknowledge that the studies included in this review used the AJCC 7th edition for staging, which was based solely on anatomic stage groupings. The members of the Working Group reviewed the AJCC 8th edition to determine whether new clinical and pathologic prognostic stage groupings would affect the recommendations. In the new staging system, some anatomic stage II patients would be reclassified to stage III (e.g., high-grade, triple- negative disease). Additionally, some anatomic stage III patients (e.g., low-grade, ER+) would be downstaged to stage II in the new classification. Thus, there is some risk that our recommendations for stage II patients would result in understanding under the new clinical and

classification, which may change over time, would have been helpful.	pathologic prognostic stage groupings. On the other hand, the evidence review of specific studies that considered biomarker profile for selecting patients for distant metastasis staging did not show a greater prevalence of metastasis compared to anatomic staging alone. Differences between the AJCC 7th and 8th classification systems in clinical and pathological staging should be taken into consideration when interpreting this guideline. This statement has been incorporated in the Discussion section for clarification.
5. The guideline uses the terms "stage 1 / 2" and "newly diagnosed breast cancer". In the past, newly diagnosed meant newly diagnosed and treated and axillary staged. Now with neoadjuvant treatment we treat newly diagnosed cancers with chemotherapy - some of which are clinically staged N0 or N+ without knowing what pathological stage they are. Therefore, the guideline should be clarified with respect to clinical stage I or II and or pathologic stage I or II. Most of the papers use pathological stage I or II and look back at how many staging scans were positive. Fewer have accurate data on clinical stage I or II (and then patient selection biases come into play).	The members of the Working Group recognize that patients with neoadjuvant treatment may not have less accurate staging and that is a limitation of the guideline.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All medical oncologists, surgical oncologist, and radiation oncologist in the PEBC database were contacted by email to inform them of the survey. Two hundred oncologists were contacted and 49 responses were received. Twenty-three stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 26 participants are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-6. Responses to four items on the professional consultation survey

	Number (N=26)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1	10	15
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.		1	1	6	18
3. I would recommend this guideline for use in practice.			2	6	18

4. **What are the barriers or enablers to the implementation of this guideline report?**

The enablers mentioned included the clear and detailed evidence and guidance to discuss with patients, which helps to demonstrate that in many cases extensive testing is not required. Therefore, it may provide patients with the comfort needed to avoid additional work-up when asymptomatic at diagnosis. Information for patients to access on role and indications for staging (educational material) would be beneficial as the request often comes from patients and this can support physicians in their discussions with patients and families.

Potential barriers to implementation of this guideline may include:

- Confusion between risk of recurrence over time and risk of de novo metastatic presentation. The difference between these risks needs to be highlighted. This is especially true for TNBC, which has a high risk of recurrence over time, but does not have a significantly elevated risk of de novo metastatic presentation.
- Inertia. Many practices include reflex staging and will need to be convinced of the need to stop such practice.
- Need good communication strategy, especially in view of some leadership changes at CCO at the regional levels.
- Patient perceptions that more testing needs to be done.
- Limited data on outcomes incorporating molecular markers into new staging system.
- Staging is based on the AJCC 7th edition when new classification is available in the AJCC 8th edition.
- Availability of timely access to imaging.
- Dissemination to surgeons who often order staging before sending patient to medical oncology.
- Physician habits of practice.

Table 5-7. Modifications/Actions taken/Responses regarding main written comments from professional consultants

Comments	Authors' Responses
1. While overall, the guideline is written well, I am surprised that the literature review did not identify a large Californian population-based study that explored frequency of de novo metastatic presentation based on biomarkers (Tao L et al. Cancer Causes Control. 2016 Sep;27(9):1127-38.). This study of more than 120,000 women showed higher rates of de novo metastatic presentation in HER2+ patients (as high as 8.8% in ER-/HER2+). The increased risk of de novo metastasis appeared independent of stage and other established risk factors. These data provide a counter argument to the	The study by Tao et al., 2016 aimed to examine the occurrence and outcomes of the novo metastatic (stage IV) breast cancer, rather than on imaging investigations in women with newly diagnosed primary breast cancer who are otherwise asymptomatic. For this reason the study was considered outside the scope of the guideline.

recommendations that biomarkers should not influence baseline staging.	
2. The search strategy consisted of including papers on patients with early-stage breast cancer. I think an argument could be made that stage III patients (including those with inflammatory breast cancer), who were included, don't exactly fit the early-stage group. Perhaps that could be explained a bit clearer.	The members of the Working Group agreed with this comment and it has been clarified in the document.
3. Stage II patients comprise a very heterogeneous group, ranging from a patient with a 4 mm primary and a 3 mm focus in one lymph node to the patient with a 4.5 cm tumour and 23 positive lymph nodes. It does not seem appropriate to lump these two groups into one basket.	The members of the Working Group disagree with this comment.
4. There is a contradiction between the guideline, which says that T3N0 patients do not require imaging to look for asymptomatic metastasis, and the Ontario Clinical Oncology Group PET-ABC study that is including these patients for routine screening. Why the guideline update now and not wait until the results of that study are available?	The members of the Working Group believe that when the results of the PET-ABC study become available, the guideline will be updated.
5. While stratifying patients per biomarkers was discussed, there was no mention of the use of bloodwork, such as alkaline phosphatase or liver enzymes, to identify at-risk patients.	Stratification of patients by biomarkers is out of the scope of this guideline.
6. If staging imaging is not done based on clinical stage, and the patients subsequently qualifies based on pathological findings that 'upstage' her, then I would assume that imaging is indicated. This should be clarified in the guideline.	The members of the Working Group think that it is clear in the guideline that staging was based on either clinical or pathological stage assessment.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

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CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors (Working Group and Expert Panel members), and the internal and external reviewers were asked to disclose potential conflicts of interest. Seven members of the Working Group declared no conflicts and one declared potential conflicts (AE). AE declared that she had helped CCO to develop and promote a quality indicator for the Cancer System Quality Index (CSQI) on breast cancer.

For the Expert Panel, four Internal Reviewers declared no conflicts and one declared potential conflicts (MT). MT declared that she owns stock in RNA diagnosis valued at $500 or more, and also had received grant support for fellows from Genomic Health, Roche, ESSAIS.

Members of the RAP declared that they had no conflicts of interest.

Two Targeted Peer Reviewers declared potential conflicts (DM, PB). DMcC indicated that he received $500 or more in a single year from Mammoprint for acting in a consulting capacity. PB declared that he has been acting as a principal investigator for the PET ABC trial aimed to investigate the use of PET scan in locally advanced breast cancer.

The COIs declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca

Appendix 2: Literature Search Strategies

Systematic reviews

*Database(s): **EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to May 10, **Embase** 1974 to 2017 May 12, **OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present,** 2017*

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1 exp Breast Neoplasms/ or exp breast tumor/ or exp breast cancer/ or exp metastasis/ or exp neoplasm metastasis/ or exp recurrence/ or exp cancer recurrence/

2 ((cancer? or carcinoma? or neoplasm? or tumo?r) and (breast? or mammary)).tw.

3 or/1-2

4 exp neoplasm staging/ or exp cancer staging/

5 (change in stage or change in management or stage migration or upstag$ or downstag$).tw.

6 or/4-5

7 (systematic adj (review: or overview:)).mp.

8 (meta-analy: or metaanaly:).mp.

9 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.

10 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.

11 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.

12 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.

13 or/7-12

14 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.

15 (stud: adj1 select:).ab.

16 14 and 15 and review.pt.

17 13 or 16

18 (comment or letter or editorial or news or newspaper article or case report or historical article).pt.

19 17 not 18

20 3 and 6 and 19

21 limit 20 to (english language and yr="2000 -Current") [Limit not valid in CDSR; records were retained]

22 Animals/

23 Humans/

24 22 not 23

25 21 not 24

26 remove duplicates from 25

Primary Literature

Database(s): Embase 1996 to 2017 June 5, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

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1 exp Breast Neoplasms/ or exp breast tumor/ or exp breast cancer/ or ((exp metastasis/ or exp neoplasm metastasis/ or exp recurrence/ or exp cancer recurrence/ or exp neoplasm recurrence/) and breast.mp.) or ((cancer? or carcinoma? or neoplasm? or tumo?r) and (breast? or mammary)).tw. or exp.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, ui, sy]

2 exp cancer staging/ or (change in stage or change in management or stage migration or upstag$ or downstag$).tw.

3 1 and 2

4 3 not (comment or letter or editorial or news or newspaper article or case report or historical article).pt.

5 exp computer assisted tomography/ or exp echography/ or exp nuclear magnetic resonance imaging/ or exp bone scintiscanning/ or exp thorax radiography/ or exp positron emission tomography/ or exp tomography, X-ray computed/ or exp ultrasonography/ or exp magnetic resonance imaging/ or exp mass chest x-ray/

6 (computed assisted tomography or ct scan* or tomography or x-ray computed or cat scan*).ti,kw.

7 (echography or ultrasonic or ultrasound or ultrasonography).ti,kw.

8 (nuclear magnetic resonance imaging or magnetic resonance imaging or mri or mri imaging or nmr or nmr imaging or mr or mr imaging).ti,kw.

9 (bone scintiscanning or bone scan* or bone scintigraphy).ti,kw.

10 (thorax radiography or mass chest x-ray or chest x-ray or chest radiography or chest xray).ti,kw.

11 (positron emission tomography or pet or pet scan* or pet-ct or pet-ct scan* or pet-ct imaging).ti,kw.

12 or/5-11

13 4 and 12

14 animals/

15 humans/

16 14 not 15

17 13 not 16

18 limit 17 to yr="2000 -Current"

19 Remove duplicates from 18

Appendix 3: Quality Assessment of Included Systematic Review (AMSTAR)

(Yes/No/CA/NA)

AMSTAR Tool	Brennan et al., 2012 [2]
Q1. Was an '*a priori*' design provided?	Yes
Q2. Was there duplicate study selection and data extraction?	Yes
Q3. Was a comprehensive literature search performed?	Yes[1]
Q4. Was the status of the publication used as an inclusion criterion?	Yes[2]
Q5. Was a list of studies (included and excluded) provided?	No (Only included)
Q6. Were the characteristics of the included studies provided?	Yes
Q7. Was the scientific quality of the included studies assessed and documented?	No
Q.8 Was the scientific quality of the included studies used appropriately in formulating conclusions?	CA
Q9. Were the methods used to combine the findings of studies appropriate?	Yes
Q10. Was the likelihood of publication bias assessed?	No
Q11. Was the conflict of interest stated?	Yes

Abbreviations: CA (cannot answer); NA (not applicable)

[1] MEDLINE and reference lists from eligible studies
[2] Only primary search studies published in English were eligible

Appendix 4: QUADAS-2 Quality Assessment of Included Observational Study

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Referene Standard	Flow and Timing	Patient Selection	Index Test	Reference Stadard
Lebon et al. [16] PET/CT	L	L	L	L	L	L	L
Ulaner et al. [23] PET/CT	L	L	L	L	L	L	L
Evangelista et al. [4] PET/CT	L	L	L	L	L	L	L
Ulaner et al. [22] PET/CT	L	L	L	L	L	L	L
Garg et al. [25] PET/CT and CI	L	L	L	L	L	L	L
Nursal et al. [18] PET/CT	L	L	U	U	L	L	L
Piatek et al. [53] CI (CT, bone scan, PET)	L	L	U	U	L	L	L
Bychkovsky et al. [11] CI (body CT)	L	L	U	H	L	L	L
Botsikas et al. 2016 [54] PET/MRI	L	L	L	L	L	L	L
Linkugel et al. [17] CI (CT scan, PET)	L	L	U	L	L	L	L
Hulikal et al.[27] PET/CT and CI (CECT/BS)	L	L	U	L	L	L	L
Krammer et al. [51] PET/CT and CI	L	L	L	L	L	L	L
Hogan et al. [14] PET/CT	L	L	L	L	L	L	L
Groheux et al. [6] PET/CT	L	L	L	L	L	L	L
Ng et al. [10] PET/CT	L	L	U	L	L	L	L
Riedl et al. [19] PET/CT	L	L	L	L	L	L	L
Jeong et al. [15] PET/CT	U	L	L	L	L	L	L
Chen et al. [12]	L	L	U	L	L	L	L

CI (bone scan, liver US, chest X-ray)							
Cochet et al. [3] PET/CT	L	L	U	L	L	L	L
Groheux et al. [26] PET/CT and CI	L	L	L	U	L	L	L
Manohar et al. [9] PET/CT	L	L	U	L	L	L	L
Sen et al. [20] PET/CT	L	L	U	L	L	L	L
Tanaka et al. [21] CI (CECT)	L	L	U	U	L	L	L
Chu et al., 2012 [55] CI (chest X-ray, bone scan, CT, PET)	U	L	L	U	L	L	L
Gunalp et al. [13] PET/CT	L	L	U	L	L	L	L
Bernsdorf et al. [52] PET/CT	L	L	L	L	L	L	L
Groheux et al. [8] PET/CT	L	L	L	L	L	L	L
Garami et al. [5] PET/CT	L	L	U	L	L	L	L
Groheux et al. [7] PET/CT	L	L	L	U	L	L	L

CECT, contrast enhanced computed tomography; CI, conventional imaging; CT, computed tomography; L, low; H, high; PET, positron emission tomography; U, uncertain; US, ultrasound

Appendix 5: Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original Version Feb 2000	1996 - 1998	Full Report	Peer review publication Web publication	Search updated Mar 1999, Nov 1999, and Apr 2000
Update Apr 2003	2000 - 2003	No new data was added to original Full Report	Updated web publication	New search yielded no additional studies
Version 2 November 2011	2003 - 2009	PET and PET/CT data was added	Updated web publication	New PET data were incorporated in the guideline 2000 recommendations were endorsed.
Version 3 Sept 2019	2000 - 2019	Full Report	Updated web Publication	Research question focused on Imaging staging only
Version 3 Sept 2019	2000 - 2019	Full Report	Updated web Publication	Recommendation 2 was updated as RCT results were avalibale.