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PRACTICE GUIDELINE

Baseline staging imaging for distant metastasis in women with stages I, II, and III breast cancer

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ABSTRACT

Background 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 disease. This guideline addresses baseline imaging investigations for women with newly diagnosed primary breast cancer who are otherwise asymptomatic for distant metastasis.

Methods The MEDLINE and EMBASE databases were systematically searched for evidence from January 2000 to April 2019, and the best available evidence was used to draft recommendations relevant to the use of baseline imaging investigation in women with newly diagnosed primary breast cancer who are otherwise asymptomatic. Final approval of this practice guideline was obtained from both the Staging in Early Stage Breast Cancer Advisory Committee and the Report Approval Panel of the Program in Evidence-Based Care.

Recommendations These recommendations apply to all women with newly diagnosed primary breast cancer (originating in the breast) who have no symptoms of distant metastasis

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

In women newly diagnosed with stage III breast cancer, baseline staging tests using either anatomic imaging (chest radiography, liver ultrasonography, chest–abdomen–pelvis CT) or metabolic imaging modalities (PET/CT, PET/MRI, bone scintigraphy) should be considered regardless of whether the patient is symptomatic for distant metastasis and regardless of biomarker profile.

Key Words Baseline staging; imaging; distant metastases; breast cancer, early-stage

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INTRODUCTION

More than 7000 women will develop breast cancer (BCa) each year in the province of Ontario[1]. The incidence of distant metastatic disease in even the most common metastatic sites—such as lung, liver, and bone—is exceedingly rare (<1% in all patients with early-stage BCa), questioning the need for universal intensive staging at baseline[2–5].

A recent population-based study of patients with early-stage BCa in Ontario demonstrated significant overuse of diagnostic imaging tests for the purposes of staging, with approximately 80% of patients receiving such tests[6]. Additional imaging tests expose patients to potentially harmful radiation, psychological distress, heightened anxiety, and possibly, 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 Quality-Based Procedures at Ontario Health (Cancer Care Ontario) [OH(CCO)][7,8] aim to limit overuse of practices that have little evidence of efficacy and that are potentially harmful. The Cancer Quality Council of Ontario has advocated for efforts

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to enhance awareness among physicians and patients and to use knowledge translation to increase adherence to recommendations.

To standardize clinical practice across the province of Ontario and to expedite, in cancer centres, the assessment and treatment of patients with biopsy-confirmed early-stage primary BCa, the Staging in Early Stage Breast Cancer Working Group developed the present guideline, which addresses the research question "Should women with newly diagnosed primary BCa receive imaging staging tests to rule out distant metastases? If so, when should those tests be performed? And what are the optimal imaging modalities for staging?"

METHODS

The present guidance document, produced by the Program in Evidence-Based Care (PEBC) and approved by OH(CCO)'s Staging in Early Stage Breast Cancer Advisory Committee, was developed through a systematic review of the available evidence using the methods of the practice guidelines development cycle[9,10]. The PEBC is editorially independent of the Ontario Ministry of Health.

The guidance document was prepared in 3 planned stages, including a search for existing guidelines, followed by a search for systematic reviews and primary literature.

The electronic search for existing guidelines focused on baseline imaging investigations for distant metastases in the electronic databases MEDLINE (Ovid) and EMBASE (Ovid) and in the Standards and Guidelines Evidence Directory of Cancer Guidelines. That search was undertaken before any search for systematic reviews or primary literature. The goal was to identify existing guidelines for adaptation or endorsement so as to avoid duplication of guideline development efforts across jurisdictions.

Subsequently, the Cochrane Database of Systematic Reviews and MEDLINE (Ovid) and EMBASE (Ovid) were searched from January 2000 to May 2017 for systematic reviews. Any systematic reviews identified were assessed for quality using AMSTAR[11], and the results of the AMSTAR assessment were used to determine whether the existing systematic review should be included as part of the evidence base.

Assuming that no existing guidelines or systematic reviews were identified, a systematic review of the primary literature was also planned. If a suitable guideline or systematic review were to have been found, a systematic review of the primary literature would be conducted from the date of the previously reported search, only to update the evidence that informed the existing guideline or that appeared in any identified systematic reviews. The search strategy included a logical combination of terms for the condition (breast tumour, metastasis), the intervention (imaging modalities), and studies of interest [systematic reviews, clinical trials, and nonrandomized prospective (30 participants minimum) or retrospective (50 participants minimum) studies]. Relevant articles were assessed by 3 reviewers (NPV, AE, AA), and the reference lists from those sources were searched for additional trials. A data audit procedure was conducted by 2 independent individuals (Ananya Nair, Megan Smyth) to verify the accuracy of the information obtained from the studies included in the guideline.

RESULTS

Literature Search

Thirty-two studies assessing imaging modalities [anatomic: chest radiography, liver ultrasonography, chest–abdomen–pelvis computed tomography (CT); metabolic: integrated positron-emission tomography (PET)/CT, integrated PET/magnetic resonance imaging (MRI), bone scintigraphy] for staging in women with newly diagnosed BCa and reporting the outcomes of interest were retained: one systematic review[12], fourteen prospective cohort studies[13–26], and seventeen retrospective studies[27–43]. The study population comprised women with all presentations of BCa (including locally advanced BCa[14,15,17,20,21,26], inflammatory BCa[21], and invasive lobular and ductal carcinoma[35]) and a mixed population of newly diagnosed BCa. All studies reported data about the overall prevalence of asymptomatic distant metastases and 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, HER2 (human epidermal growth factor receptor 2)]: one using conventional imaging[40] and three using PET/CT[15,27,29].

The identified systematic review was published in 2012 by 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. That review not only significantly overlapped in scope with the objectives of the present work, but also provided a comprehensive summary, to June 2011, of the best available evidence concerning imaging used for staging investigations to detect asymptomatic distant metastases in women with newly diagnosed BCa[12]. It was assumed by the members of the Working Group that any relevant document published entirely within the review's search dates (1995 to June 2011) would have been identified. Therefore, the STEP systematic review was determined to be the main evidence source for the accompanying guideline, to be supplemented with additional data from relevant studies identified in the primary literature search. Only primary literature published from June 2011 onward (corresponding to the end date of the search in the 2012 STEP systematic review) was considered.

The STEP systematic review is summarized in the next subsection, and Table I depicts the characteristics of the newly identified observational studies.

STEP Systematic Review

The 2012 STEP systematic review included twenty-two studies: nine reporting on conventional imaging only (one prospective and eight retrospective studies); eight reporting on fluorodeoxyglucose (FDG)–PET or FDG–PET/CT, or both (five prospective, two retrospective, and one with an unreported study design); and five reporting on both conventional imaging and FDG–PET or FDG–PET/CT.

The study population included women with all presentations of BCa: locally advanced (three studies), inflammatory (two studies), and large-tumour BCa (>30 mm in diameter, one study), and a mixed population of stages and presentations (eighteen studies). Characteristics of

TABLE I Characteristics of included observational studies assessing imaging investigation for distant metastases in breast cancer

Reference (timeframe)	Study design	Population *(n)*
Integrated PET/CT		
Groheux *et al.,* 2011[25] (2006–2010)	Prospective	131
	Age (years): Median, 48; range, 26–81	
	Initial stage determination: Physical examination, mammography, breast and axilla ultrasonography, breast MRI	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* IIA, 36 (27); IIB, 48 (37); IIIA, 47 (36)	
	Verification of metastases: Surgery, histology, patient follow-up, and MRI for bone foci	
	Outcomes: Unsuspected distant metastases	
Bernsdorf *et al.,* 2012[24] (2008–2010)	Prospective	103
	Age (years): Median, 55; range, 24–81	
	Initial stage determination: Physical examination, mammography, ultrasonography (chest wall and axilla), chest radiography, blood parameters	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* I, 11 (11), 1 missing; II, 54 (52); III, 37 (34)	
	Verification of metastases: Histology or follow-up imaging (PET/CT or others)	
	Outcomes: Unsuspected distant metastases	
Garami *et al.,* 2012[23] (2008–2010)	Prospective	115
	Age (years): Median, 56	
	Initial stage determination: Physical examination, mammography, breast and abdominal ultrasonography, chest radiography, bone scintigraphy	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* I, 63 (55); II, 49 (43)	
	Verification of metastases: Direct sampling (pulmonary resection, liver biopsy), follow-up imaging (CT, MRI)	
	Outcomes: Unsuspected distant metastases and change in management	
Groheux *et al.,* 2012[22] (2006–2011)	Prospective	254
	Age (years): Not reported	
	Initial stage determination: Physical examination, mammography, breast MRI, breast and locoregional ultrasonography	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* IIA, 44 (17); IIB, 56 (22); IIIA, 63 (25); IIIB, 74 (29); IIIC, 17 (7)	
	Verification of metastases: Histopathology, imaging follow-up	
	Outcomes: Unsuspected distant metastases, change in management, disease-specific survival	
Gunalp *et al.,* 2012[41]	Retrospective	336 (preoperative, 141; postoperative, 195)
	Age (years): Preoperative: median, 47; range, 28–78; postoperative: median, 48; range, 25–75	
	Initial stage determination: Physical examination, mammography, breast and axilla ultrasonography, breast MRI Clinical stage III underwent conventional imaging: bone scan, abdominal and pelvic CT (or ultrasonography or MRI), chest imaging	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* Preoperative: I, 19 (14); IIA, 51 (36); IIB, 49 (35); IIIA, 12 (9); IIIB, 2 (2); IV, 8 (6)	
	Verification of metastases: Histopathology or patient follow-up; for bone foci, MRI was performed instead of biopsy	
	Outcomes: Unsuspected distant metastases	
Groheux *et al.,* 2013[21]	Prospective	117 LABC, stage III (35 IBC, 82 NIBC)
	Initial stage determination: Physical examination, mammography, breast and axilla ultrasonography, breast MRI	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* IBC: IIIB, 29 (83); IIIC, 6 (5)	
	Verification of metastases: Histopathology, further work-up or patient follow-up, and MRI imaging for bone foci	
	Outcomes: Distant metastases, change in management	
Manohar *et al.,* 2013[20]	Prospective	43 LABC (40 IDC, 1 AMC, 1 PC, 1 ASC)
	Age (years): Median, 49; range, 28–80	
	Initial stage determination: Physical examination, chest radiography, abdominal ultrasonography, whole body bone scintigraphy	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* IIB, 3 (7); IIIA, 15 (35); IIIB, 24 (56); IIIC, 1 (2)	
	Verification of metastases: Histopathology, clinical or imaging at a mean follow-up of 8 months	
	Outcomes: Unsuspected distant metastases	
	Notes: Distant metastases missed by conventional imaging	

TABLE I Continued

Reference (timeframe)	Study design	Population *(n)*
Integrated PET/CT (continued)		
Sen *et al.*, 2013[39] (2009–2012)	Retrospective	77 Postoperative patients with histologically proven breast cancer who underwent surgery with no previous CT or radiography
	Age (years): Median, 52; range, 26–87	
	Initial stage determination: Abdominal ultrasonography, CT (chest, abdomen), bone scan	
	Only 47 patients were assessed for metastatic disease through conventional imaging.	
	Imaging modality: FDG PET/CT performed in the early postoperative period (7–57 days after mastectomy or breast-conserving surgery) and before systemic therapy	
	*Stage distribution [*n *(%)]:* I, 19 (25); II, 38 (49); III, 18 (23)	
	Verification of metastases: Histopathology, clinical and follow-up data, imaging follow-up including FDG PET/CT	
	Outcomes: Postoperative distant metastases that were previously undetected	
Cochet *et al.*, 2014[19] (2006–2010)	Prospective	142
	Age (years): Median, 51; range, 25–85	
	Initial stage determination: Physical examination, mammography or breast and liver ultrasonography (or both), chest radiography, bone scintigraphy, CT	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* IIA, 22 (15); IIB, 57 (40); IIIA, 12 (9); IIIB, 19 (13); IIIC, 15 (11); IV, 17 (12)	
	Verification of metastases: Imaging and clinical follow-up, or pathology, or both	
	Outcomes: Distant metastases, change in management	
	Notes: Four patients were downstaged by PET/CT from stage IV to stage II or III	
Jeong *et al.*, 2014[37] (2010–2013)	Retrospective	178 Clinical negative axillary nodal involvement
	Age (years): Median, 55; range, 33–82	
	Initial stage determination: Clinical examination, mammography, breast and abdominal ultrasonography, chest radiography, MRI	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* I, 178 (100)	
	Verification of metastases: Histopathology, follow-up imaging	
	Outcomes: Unsuspected distant metastases	
	Notes: Patients with no sign of axillary lymph node metastasis by conventional diagnostic modalities (breast ultrasonography or MRI)	
Riedl *et al.*, 2014[36] (2003–2012)	Retrospective	134 (75 ER+, HER2–; 26 HER2+; 28 TNBC; 5 unspecified)
	Age (years): Median, 36; range, 22–40	
	Initial stage determination: According to AJCC: Physical exam, mammography, breast ultrasonography and MRI	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* I, 20 (15); IIA, 44 (33); IIB, 47 (35); IIIA, 13 (10); IIIB, 8 (6); IIIC, 2 (1)	
	Verification of metastases: Histopathology	
	Outcomes: Unsuspected distant metastases	
Groheux *et al.*, 2015[18] (2006–2012)	Prospective	85 TNBC
	Age (years):	
	Initial stage determination: According to AJCC: Physical exam, mammography, breast ultrasonography and MRI	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* II, 32 (38); III, 53 (62)	
	Verification of metastases: Histopathology or imaging follow-up	
	Outcomes: Unsuspected distant metastases	
Hogan *et al.*, 2015[35] (2006–2013)	Retrospective (MSKCC-HIS, single-institution)	235 (ILC, 146; IDC, 89)
	Age (years): Median, 57; range, 34–92	
	Initial stage determination: Physical examination, mammography, breast ultrasonography, breast MRI or surgical findings	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* ILC—I, 8 (5); II, 50 (35); III, 88 (60); IDC—I, 0 (0); II, 0 (0); III, 89 (100)	
	Verification of metastases: Histopathology	
	Outcomes: Unsuspected distant metastasis	

TABLE I Continued

Reference (timeframe)	Study design	Population *(n)*
Integrated PET/CT (continued)		
Hulikal *et al.,* 2015[17] (2013–2014)	Prospective	38 LABC (stage III)
	Age (years): Median, 38; range, 27–73	
	Initial stage determination: According to AJCC	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* IIIA, 10 (26); IIIB, 25 (65); IIIC, 3 (9)	
	Verification of metastases: Histopathology	
	Outcomes: Unsuspected distant metastases, change in management	
Krammer *et al.,* 2015[16] (2010–2013)	Prospective	101 (91 preoperative[a]; 10 postoperative[b]; 67 ER+; 37 ER–; 56 PgR+; 48 PgR–; 56 HER2+; 48 HER2–)
	Age (years): Mean, 54±10	
	Initial stage determination: Clinical examination, mammography, breast and local lymph node ultrasonography	
	Imaging modality: FDG PET/CT	
	Stage distribution [n (%)]: As detected by CT/BS: preoperative—IIA, 47 (52); IIB, 23 (25); IIIA, 6 (7); IIIB, 5 (6); IV, 10 (11); postoperative—IIA, 5 (50); IIIA, 3 (30); IIIC, 1 (10); IV, 1 (10)	
	Verification of metastases: Histopathology, follow-up imaging	
	Outcomes: Unsuspected distant metastases, change in management	
	Notes: Preoperative patients with clinical tumour stage T2 or greater, or positive lymph nodes; postoperative patients with clinical node-negative stage T1 tumours, if positive for malignant cells after sentinel lymph node biopsy	
Ng *et al.,* 2015[15] (2004–2014)	Prospective	154 LABC (99 ER+, 55 ER–, 86 PgR+, 68 PgR–, 52 HER2+, 102 HER2–)
	Age (years): Median, 49; range, 26–70	
	Initial stage determination: Physical examination; breast mammography; ultrasonography; tumour core biopsy; chest, abdomen, and pelvis CT; whole-body bone scan	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* IIA, 20 (13); IIB, 81 (53); IIIA, 43 (28); IIIB, 7 (5); IIIC, 3 (2)	
	Verification of metastases: PET/CT results were compared with initial CT/BS results. In selected patients, follow-up imaging or biopsy (or both) was performed to confirm metastatic disease	
	Outcomes: Unsuspected distant metastases	
Garg *et al.,* 2016[14] (2014–2015)	Prospective	79 LABC (stage III)
	Age (years): Median, 50; range, 18–80	
	Initial stage determination: According to AJCC	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* LABC III, 79	
	Verification of metastases: 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[c]; MRI was undertaken in suspicious skeletal lesions	
	Outcomes: Unsuspected distant metastasis, upstaging, change in management	
Nursal *et al.,* 2016[31] (2012–2014)	Retrospective	419
	Age (years): Mean, 51±10	
	Initial stage determination: Physical exam, mammography, breast MRI, and ultrasonography	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* I, 104 (25); II, 315 (75)	
	Verification of metastases: MRI, biopsy	
	Outcomes: Distant metastases	
Ulaner *et al.,* 2016[29] (2007–2013)	Retrospective (MSKCC-HIS, single-institution)	232 TNBC
	Age (years): Median, 51; range, 25–93	
	Initial stage determination: According to the AJCC: some combination of physical exam, mammography, breast ultrasonography, breast MRI, and surgical findings	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* I, 23 (10); IIA, 82 (35); IIB, 87 (38); IIIA, 23 (10); IIIB, 14 (6); IIIC, 3 (1)	
	Verification of metastases: Histopathology; if not available, follow-up imaging was used	
	Outcomes: Unsuspected distant metastases, upstaging, survival	

TABLE I Continued

Reference (timeframe)	Study design	Population *(n)*
Integrated PET/CT (continued)		
Evangelista *et al.,* 2017[13] (2011–2015)	Prospective	275 TNBC or HER2+ (preoperative, 149; postoperative, 126)
	Age (years): Median, 53; range, 27–89	
	Initial stage determination: According to the AJCC: some combination of physical examination, mammography, breast ultrasonography, breast MRI, and surgical findings	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* I, 8 (5); II, 68 (46); III, 72 (48); I, 26 (21); II, 44 (35); III, 56 (44)	
	Verification of metastases: Histopathology if available; otherwise, follow-up imaging	
	Outcomes: Unsuspected distant metastasis	
	Notes: Of patients in the postoperative setting, 15% had symptoms suspicious for metastasis; mean interval between surgery and PET/CT was 45±22 days	
Lebon *et al.,* 2017[28] (2006–2015)	Retrospective	214 (<40 years: 107; ≥40 Years: 107; 34% HR+, HER2–; 33% HER2+; 33% TNBC)
	Age (years): <40 Years: mean, 34.5±4; ≥40 years: mean, 56±10.7	
	Initial stage determination: According to the AJCC: clinical examination, mammography, breast MRI, ultrasonography	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* <40 Years: I, 12 (11); IIA, 32 (30); IIB, 30 (28); III, 33 (31); ≥40 years: I, 12 (11); IIA, 32 (30); IIB, 30 (28); III, 33 (31)	
	Verification of metastases: For small number of patients, all PET/CT imaging was reinterpreted by an interpreter who was unaware of the original PET/CT report or any other imaging, follow-up imaging, and pathology	
	Outcomes: Unsuspected distant metastases	
	Notes: Suspicious metastases on PET/CT was not confirmed by histology because the main goal of the study was to compare the distant metastasis rates in women ≥40 and <40 years of age	
Ulaner *et al.,* 2017[27] (2011–2014)	Retrospective (MSKCC-HIS, single-institution)	483 (245 HER2+; 238 ER+, HER2–)
	Age (years): ER+, HER2–: median, 55; range, 27–89; HER2+: median, 50; range, 24–87	
	Initial stage determination: According to the AJCC: some combination of physical exam, mammography, breast ultrasonography, breast MRI, and surgical findings	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* ER+, HER2–: I, 15 (6); IIA, 71 (30); IIB, 95 (40); IIIA, 23 (10); IIIB, 26 (11); IIIC, 8 (3); HER2+: I, 21 (9); IIA, 72 (29); IIB, 93 (38); 3 IIIA, 2 (13); IIIB, 21 (6); IIIC, 6 (3)	
	Verification of metastases: Histopathology (imaging follow-up was used in 2 patients because histology was not available)	
	Outcomes: Unsuspected distant metastases, upstaging	
Gajjala *et al.,* 2018[26]	Prospective	61 LABC (stage III)
	Age (years): Median, 51; range: 27–78	
	Initial stage determination: According to the AJCC: clinical examination, mammography, breast MRI, ultrasonography	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* IIIA, 14 (23); IIIB, 42 (68); IIIC, 5 (9)	
	Verification of metastases: Biopsy or fine needle aspiration cytology, or MRI of the spine	
	Outcomes: Unsuspected distant metastases	
Yararbas *et al.,* 2018[43]	Retrospective	234 (preoperative, 114; postoperative, 120)
	Age (years): Median not reported; range, 23–87	
	Initial stage determination: Histopathology results: 125 According to the AJCC: physical examination, breast and axillary ultrasonography, and MRI in a few cases (*n*=109)	
	Imaging modality: FDG PET/CT	
	*Stage distribution [*n *(%)]:* I, 3 (1); IIA, 43 (18); IIB, 66 (28); IIIA, 82 (35); IIIB, 16 (7); IIIC, 24 (10)	
	Verification of metastases: Judgment of two experienced nuclear medicine physicians, histopathology, MRI, ultrasonography	
	Outcomes: Distant metastasis (unclear if symptomatic)	

TABLE I Continued

Reference (timeframe)	Study design	Population *(n)*
Conventional anatomic imaging (chest radiography, liver ultrasonography, chest–abdomen–pelvis CT)		
Tanaka *et al.,* 2012[40] (2006–2011)	Prospective	483 (<50 years: 108; ≥50 years: 375; 381 ER+; 100 ER–; 314 PgR+; 167 PgR–; 65 HER2+; 393 HER2–)
	Initial stage determination: Physical examination	
	Imaging modality: Contrast-enhanced CT	
	*Stage distribution [*n *(%)]:* I, 155 (32); II, 261 (54); III, 67 (14)	
	Verification of metastases: Follow-up CT (plain or contrast-enhanced) within 3–4 months, or further imaging follow-up (PET, MRI)	
	Outcomes: Unsuspected distant metastases	
Groheux *et al.,* 2013[21]	Prospective	117 LABC, stage III (IBC, 35; NIBC, 82)
	Initial stage determination: Physical examination, mammography, breast and axilla sonography, breast MRI	
	Imaging modality: Bone scan, chest radiography or CT, abdominopelvic ultrasonography or CT (or both), bone scintigraphy	
	*Stage distribution [*n *(%)]:* IBC: IIIB, 29 (83); IIIC, 6 (5)	
	Verification of metastases: Histopathology, further work-up or patient follow-up, and MRI imaging for bone foci	
	Outcomes: Distant metastases, change in management	
Chen *et al.,* 2014[38] (2000–2010)	Retrospective	3411 (2094 ER+; 1317 ER–; 2280 PgR+; 1131 PgR–; 771 HER2+; 2640 HER2–)
	Age (years): Median, 60; range, 18–75	
	Initial stage determination: According to AJCC: physical exam, mammography, breast ultrasonography and MRI	
	Imaging modality: Bone scan, liver ultrasonography, chest radiography	
	*Stage distribution [*n *(%)]:* I, 411 (12); II, 2561 (75); III, 439 (13)	
	Verification of metastases: Bone metastases indicated by bone scan were confirmed by CT or MRI; liver metastases indicated by liver ultrasonography were confirmed by liver dual-phase CT; lung metastases indicated by chest radiography were confirmed by chest CT or MRI	
	Outcomes: Unsuspected distant metastases by site	
Hulikal *et al.,* 2015[17] (2013–2014)	Prospective	38 LABC, stage III
	Age (years): Median, 38; range, 27–73	
	Initial stage determination: According to AJCC	
	Imaging modality: Chest and abdominal contrast-enhanced CT, bone scan	
	*Stage distribution [*n *(%)]:* IIIA, 10 (26); IIIB, 25 (65); IIIC, 3 (9)	
	Verification of metastases: Histopathology	
	Outcomes: Unsuspected distant metastases, change in management	
Krammer *et al.,* 2015[16] (2010–2013)	Prospective	101 (preoperative[d], 91; postoperative[e], 10; 67 ER+; 37 ER–; 56 PgR+; 48 PgR–; 56 HER2+; 48 HER2–)
	Age (years): Mean, 54±10	
	Initial stage determination: Clinical examination, mammography, breast and local lymph node ultrasonography	
	Imaging modality: Abdominal ultrasonography, chest radiography, bone scan	
	*Stage distribution [*n *(%)]:* As detected by CT/BS: preoperative—IIA, 47 (52); IIB, 23 (25); IIIA, 6 (7); IIIB, 5 (6); IV, 10 (11); postoperative—IIA, 5 (50); IIIA, 3 (30); IIIC, 1 (10); IV, 1 (10)	
	Verification of metastases: Histopathology. follow-up imaging	
	Outcomes: Unsuspected distant metastases, change in management	
	Notes: Preoperative patients with clinical tumour stage T2 or greater, or positive lymph nodes; postoperative patients with clinical node-negative stage T1 tumours, if positive for malignant cells after sentinel lymph node biopsy	
Bychkovsky *et al.,* 2016[32] (2006–2007)	Retrospective, multicentre (2 academic centres in Boston, MA, U.S.A.)	237 (135 ER+ or PgR+; 54 HER2+; 48 TNBC)
	Age (years): Median, 52; range, 23–90	
	Initial stage determination: According to AJCC	
	Imaging modality: Body CT	
	*Stage distribution [*n *(%)]:* IIA, 130 (55); IIB, 107 (45)	

TABLE I Continued

Reference (timeframe)	Study design	Population *(n)*
Conventional anatomic imaging (chest radiography, liver ultrasonography, chest–abdomen–pelvis CT) (continued)		
Garg *et al.,* 2016[14] (2014–2015)	Prospective	79 LABC, stage III
	Age (years): median, 50; range, 18–80	
	Initial stage determination: According to AJCC	
	Imaging modality: Chest radiography, abdominal ultrasonography, bone scintigraphy	
	*Stage distribution [*n *(%)]:* LABC III, 79	
	Verification of metastases: 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[f]; MRI was undertaken in suspicious skeletal lesions	
	Outcomes: Unsuspected distant metastasis, upstaging, change in management	
Gajjala *et al.,* 2018[26]	Prospective	61 LABC, stage III
	Age (years): Median, 51; range, 27–78	
	Initial stage determination: According to the AJCC: clinical examination, mammography, breast MRI, ultrasonography	
	Imaging modality: Bone scan, abdomen and pelvis ultrasonography	
	*Stage distribution [*n *(%)]:* IIIA, 14 (23); IIIB, 42 (68); IIIC, 5 (9)	
	Verification of metastases: Biopsy or fine-needle aspiration cytology, or MRI of the spine; histology (*n*=12); follow-up imaging	
	Outcomes: Unsuspected distant metastases	
Conventional anatomic and metabolic imaging modalities, combined or separately		
Chu *et al.,* 2012[42] (1998–2010)	Retrospective	256 (158 N2, 98 N3)
	Age (years): N2: median, 59; range, 27–86; N3: median, 57; range, 31–84	
	Initial stage determination: According to AJCC	
	Imaging modality: Bone scan, 62; CT, 78; PET, 39	
	*Stage distribution [*n *(%)]:* III, 256 (158 N2, 98 N3)	
	Verification of metastases: Judgment of multidisciplinary tumour board and histopathology in most of the cases	
	Outcomes: Distant metastases at time of diagnosis or within 1 month after definitive surgery	
Linkugel *et al.,* 2015[34] (1998–2012)	Retrospective	882
	Age (years): Median, 55.0	
	Initial stage determination: Clinical examination	
	Imaging modality: PET; some combination of chest, abdomen, and pelvis CT; bone scintigraphy	
	*Stage distribution [*n *(%)]:* I, 312 (35); II, 570 (65)	
	Verification of metastases: Histopathology, follow-up imaging (radiography, CT, bone scan, ultrasonography, MRI, or PET)	
	Outcomes: Unsuspected distant metastases	
Botsikas *et al.,* 2016[33] (2010–2014)	Retrospective	58
	Age (years): Mean, 47.4±11.2	
	Initial stage determination: Clinical examination and conventional imaging	
	Imaging modality: FDG PET/MRI	
	*Stage distribution [*n *(%)]:* I, 13 (22); II, 30 (52); III, 12 (21); IV, 1 (2)	
	Verification of metastases: Follow-up imaging, biopsy	
	Outcomes: Unsuspected distant metastases	

TABLE I Continued

Reference (timeframe)	Study design	Population *(n)*
Conventional anatomic and metabolic imaging modalities, combined or separately (continued)		
Piatek *et al.*, 2016[30] (2000–2010)	Retrospective, multicentre (university of California Norris Comprehensive Cancer Center, Los Angeles County–University of Southern California Medical Center	362 stage III
	Age (years): Not reported	
	Initial stage determination: History, physical exam, chest radiography	
	Imaging modality: CT, bone scan, PET	
	Stage distribution [n (%)]: IIIA, 175 (42); IIIB, 105 (25); IIIC, 140 (33)	
	Verification of metastases: Only 362 underwent routine staging imaging studies; judgment of radiologist or physician, or subsequent imaging or histology	
	Outcomes: Unsuspected distant metastasis, change in management, relapse-free survival; imaging abnormalities were not routinely biopsied	

[a] Patients with clinical tumour stage T2 or greater, or positive lymph nodes, were included preoperatively.
[b] Patients who were clinically node-negative, with stage T1 tumours, were included postoperatively if, after sentinel lymph node biopsy, they were positive for malignant cells.
[c] Multiple lung nodules or lytic or marrow lesions in the skeleton.
[d] Patients with clinical tumour stage T2 or greater, or positive lymph nodes, were included preoperatively.
[e] Patients who were clinically node-negative, with stage T1 tumours were included postoperatively if, after sentinel lymph node biopsy, they were positive for malignant cells.
[f] Multiple lung nodules or lytic or marrow lesions in the skeleton.

PET = positron-emission tomography; CT = computed tomography; MRI = magnetic resonance imaging; FDG = fluorodeoxyglucose; LABC = locally advanced breast cancer; IBC = inflammatory breast cancer; NIBC = non-inflammatory breast cancer; IDC = invasive ductal carcinoma; AMC = atypical medullary carcinoma; PC = papillary carcinoma; ASC = adenosquamous carcinoma; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; AJCC = American Joint Committee on Cancer staging; MSKCC = Memorial Sloan Kettering Cancer Center; HIS = Healthcare Information System; ILC = invasive lobular carcinoma; PgR = progesterone receptor; CT/BS = chest–abdomen–pelvis CT, whole-body bone scintigraphy.

the studies such as author, publication year, timeframe, study design, mean or median age, stage distribution, and the outcomes of interest were summarized and presented in evidence tables. All studies reported data about the overall prevalence of asymptomatic distant metastasis and the prevalence of metastasis by site and stage of disease.

Based on the AMSTAR criteria, the methodologic quality of the systematic review was considered to be good.

Primary Literature

The quality of the primary literature was assessed using the QUADAS-2 tool. For all studies, concerns about applicability were judged to be low. For domains relating to bias, three studies were unclear about whether they avoided the inclusion of patients with symptoms of distant metastasis, and there is therefore an unknown risk of bias for patient selection[37,42,43].

The reference standard was considered on the basis of clinical and short-term follow-up imaging of metastatic lesions, or on the judgment of a multidisciplinary tumour board when biopsy or histopathology was not feasible, or both, because no "gold standard" for the detection of real metastases has been established. 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[15,17,19,20,23,26,30–32,34,38–41,43], and the risk for bias is related to the potential influence of previous knowledge on test interpretation[44].

Seven studies were identified to have concerns about 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 might lead to verification bias[32]. The other six studies did not provide sufficient information to determine whether suspicious findings were confirmed by the reference standard or whether all patients with suspected metastasis received the same reference standard[21,25,30,31,40,42].

Overall, the evidence quality was considered to range from low to moderate because it was derived mainly from retrospective studies with bias concerns.

Outcomes

Detection of Distant Metastasis by Initial (at Diagnosis) Staging of BCa and by Site of Metastasis

Systematic Review (All Stages): The systematic review by Brennan and Houssami[12] reported a low median prevalence of distant metastasis in women initially diagnosed with stages I and II BCa, with a much higher prevalence in those initially diagnosed with stage III disease. For stage I, the median prevalence from seven studies, all based on conventional imaging alone, was 0.2% (range: 0%–5%). For stage II BCa, the overall median prevalence was reported to be 1.2% (range: 0%–34%): 1.1% with conventional imaging alone (seven studies), 3.3% with PET/CT (one study), and 34.3% with both (one study).

TABLE II Unsuspected distant metastasis detected in women with newly diagnosed primary breast cancer

Reference	Unsuspected metastases [*n* (%)]	Prevalence of metastases (%)							Change in management	OS or PFS
		By site				By stage (upstaged to IV)				
		Bone	Liver	Lung	Other	I	II	III		
Integrated PET/CT										
Van der Hoeven *et al.*, 2004[a]	4/48 (8)	2/48 (4)	2/48 (4)	0	NR	NA	NA	4/48 (8)	NR	NR
Groheux *et al.*, 2008[a]	4/39 (10)	3/39 (8)	0/39	1/39 (3)	NA	NA	1/25 (4)	3/14 (21)	NR	NR
Heusner *et al.*, 2008[a]	10/40 (25)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alberini *et al.*, 2009[a]	18/59 (31)	7/59 (12)	5/59 (9)	4/59 (7)	Mediastinum: 12/59 (20) Peritoneum: 3/59 (5)	NA	NA	18/59 (31)	NR	NR
Carkaci *et al.*, 2009[a,b]	20/41 (49)	9/41 (22)	6/41 (15)	4/41 (10)	Mediastinum: 10/41 (24)	NA	NA	20/41 (49)	NR	NR
Groheux *et al.*, 2011[25]	15/131 (12)	11 (8)	3 (2)	5 (4)	Distant LN and pleura: 2 (2)	NA	5/84 (6) A: 1/36 (3) B: 4/48 (8)	A: 10/47 (21)	Tx adapted to the metastatic disease	NR
Bernsdorf *et al.*, 2012[24]	6/103 (6)	5 (5)	NA	1 (1)	0	NR	NR	NR	Therapy decision changed from adjuvant Tx to a metastatic approach with or without bisphosphonate	
Garami *et al.*, 2012[23]	8/115 (7)	2 (2)	1 (0.9)	2 (2)	Distant LN: 3 (3)	2/63 (3)	6/49 (12)	NA	Lung resection (*n*=1), palliative CTx (*n*=1), palliative surgery followed by aggressive CTx (*n*=4), and palliative oncologic Tx (*n*=2)	NR
Groheux *et al.*, 2012[22]	53/254 (21)	35 (14)	13 (5)	9 (4)	Distant LN: 20 (8) Pleura: 2 (1)	NA	7/100 (7)	46/154 (30)	NR	3-Year disease-specific survival for 189 patients staged IIB or higher: 47 M1 vs. 142 M0 57% vs. 88% (p<0.001)
ER+, HER2–	28/130						1/44 (2)	11/63 (18)		
HER2+	13/51						6/56 (11)	27/74 (37)		
TNBC	11/69							8/17 (47)		
Gunalp *et al.*, 2012[41]										
Preoperative	40/141(29)	28 (20)	6 (4)	4 (3)	4 (3)	1/19 (5)	30/100 (30) A: 10/51(20) B: 20/49(40)	9/14 (64) A: 7/12 (58) B: 2/2 (100)		NR
Postoperative	24/195 (12)	18 (9)	2 (1)	4 (2)	3 (2)				Postoperative CTx was adapted to metastatic disease in 24 patients (12%)	

TABLE II Continued

Reference	Unsuspected metastases [*n* (%)]	Prevalence of metastases (%)							Change in management	OS or PFS
		By site				By stage (upstaged to IV)				
		Bone	Liver	Lung	Other	I	II	III		
Integrated PET/CT (continued)										
Groheux *et al.*, 2013[21] IBC NIBC	43/117 (37) 16/35 (46) 27/82 (33) (p=0.18)	30 (26) 10 20C	10 (9) 4 6	6 (5) 3 3	Distant LN: 19 (16) (8 IBC, 11 NIBC) Pleura: 2 (2) (0 IBC, 2 NIBC)	NA	NA	43/117 (37)		3-Year disease-specific survival: 40 M1 vs. 64 M0 53% vs. 78% (p=0.002)
Manohar *et al.*, 2013[20]	LABC: 10/43 (23)	IIIB: 3 (7)	IIIB: 2 (5)	IIIB: 4 (9)	Sternum: 2 (5) Distant LN: 3 (7)	NA	B: 1/3 (33)	9/40 (23) A: 1/15 (7) B: 8/24 (33) C: 0/1 (0)	10/43 (23) 1 Patient with initial clinical stage IIB, 1 with IIIC, and 8 with IIIC	NR
Sen *et al.*, 2013[39]	12/77 (16) Early postoperative period	2 (3)	3 (4)	3 (4)	Distant LN: 7 (9)	1/19 (5)	4/38 (11)	7/18 (39)	Therapy decision changed either from RT to medical Tx or from CTx to hormonal Tx	
Cochet *et al.*, 2014[19] (2006–2010)	25/142 (18)	15 (11)	4 (3)	4 (3)	Distant LN: 4 (3)	NA	6/79 (8) A: 2/22 (9) B: 4/57 (7)	6/46 (13) A: 0/12 (0) B: 4/19 (21) C: 2/15 (13)	11 (8%) Changed from curative to palliative care, and 4 (3%) changed from palliative to curative Tx after PET/CT suggested absence of distant lesions	2-Year PFS: distant metastases detected by CT/BS vs. PET/CT—63% vs. 40%
Jeong *et al.*, 2014[37]	0/178	0	0	0	0	0/178	NR	NR	NR	0/178
Riedl *et al.*, 2014[36]	20/134 (15) Receptor phenotype was not found to relate to distant metastases	16 (12)	5 (4)	2 (1)	Distant LN: 6 (4)	1/20 (5)	10/91 (11) A: 2/44 (5) B: 8/47 (17)	9/23 (39) 4/13 (31) 4/8 (50) 1/2 (50)	NR	
Groheux *et al.*, 2015[18]	11/85 (13)	5 (6)	3 (4)	3 (4)	Distant LN: 8 (9)	NA	0/32 (0)	11/53 (21)	NR	2-Year disease-specific survival for patients with distant metastases: 18.2% Significantly shorter than in those without distant metastases on baseline PET/CT (p<0.001)
Hogan *et al.*, 2015[35]								30/177 (17)	NR	NR
ILC	12[c]/146 (8)	10 (7)	1 (0.7)	NR	Distant LN: 2 (1)	0/8 (0)	2/50 (4)	10/88 (11)		
IDC	20/89 (23)	17 (19)	2 (2)	2 (2)	Distant LN: 3 (3) Pleura: 1 (1)	NA	NA	20/89 (23)		

TABLE II Continued

Reference	Unsuspected metastases [*n* (%)]	Prevalence of metastases (%)							Change in management	OS or PFS
		By site				By stage (upstaged to IV)				
		Bone	Liver	Lung	Other	I	II	III		
Integrated PET/CT (continued)										
Hulikal *et al.*, 2015[17]	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 without metastases received neoadjuvantCTx	NR
Krammer *et al.*, 2015[16]	16/101 (16)	13 (13)	5 (5)	5 (5)	Distant LN: 6 Adrenal gland: 3 Soft tissue: 2	NA	NR	NR	4/101 (4) 1 Patient underwent extended-field RT; 1 patient received palliative CTx with bisphosphonate therapy; 2 patients underwent a palliative approach with systematic CTx	NR
Ng *et al.*, 2015[15]	LABC: 17/154 (11)	7 (4)	2(1)	2 (1)	Mediastinal or distant LN: 7 (5)	NA	5/101 (5) A: 1/20 (5) B: 4/81 (5)	12/53 (23) A: 7/43 (16) B: 2/7 (29) C: 3/3 (100)	Intention to treat for these patients was subsequently changed from curative to palliative, and adjuvant RT was omitted	NR
TNBC							1	3		
ER+, PgR+, HER2–							4	4		
ER+, PgR–, HER2+								1		
ER–, PgR+, HER2+								2		
ER–, PgR–, HER2+								2		
Garg *et al.*, 2016[14]	LABC: 34/79 (43)	22 (28)	14 (18)	13 (17)	1 (1) Isolated contralateral axillary and supraclavicular lymphadenopathy	NA	NA	14/79 (18)	14/79 (18) changed from surgery with or without prior neoadjuvant CTx to systemic CTx	NR
Nursal *et al.*, 2016[31]	42/419 (10)	NR	NR	NR	NR	3/104 (3)	39/315 (12) A: 19/199 (10) B: 20/116 (17)	NA	NR	NR
Ulaner *et al.*, 2016[29]	TNBC: 30/232 (13)	11 (5)	8 (3)	7 (3)	Pleura: 1 (0.4) Distant LN: 8 (3) >1 Site: 5 (2)	0/23 (0)	17/169 (10) A: 4/82 (5) B: 13/87 (15)	13/40 (33) A: 4/23 (17) B: 8/14 (57) C: 1/3 (33)	NR	3-Year Kaplan–Meier estimate: patients initially staged IIB upstaged to IV (13/87) vs. not upstaged—0.33 (95% CI: 0.13 to 0.55) vs. 0.97 (95% CI: 0.76 to 0.93), $p<0.0001$

TABLE II Continued

Reference	Unsuspected metastases [*n* (%)]	Prevalence of metastases (%)							Change in management	OS or PFS
		By site				By stage (upstaged to IV)				
		Bone	Liver	Lung	Other	I	II	III		
Integrated PET/CT (continued)										
Evangelista *et al.*, 2017[13]					3/34 (9)	8/112 (7)	18/126 (14)			
Preoperative	22/149 (15)	14 (9)	6 (4)	5 (3)	Distant LN: 40 (27%)	TNBC: 1/8 (13)	4/68 (6)	17/70 (24)	15/149 (10%) Enlarged surgical approach (*n*=1), systemic Tx (*n*=12), systemic plus local Tx (*n*=2)	3.6-Year Kaplan–Meier estimate: 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)
Postoperative	7/126 (5)	5 (4)	—	3 (2)	—	2/26	4/44	1/56 (2)	18/126 (14%) Further surgery (*n*=3), additional external-beam RT (*n*=8), more aggressive systemic Tx or a combination of local and systemic therapies (*n*=7)	No differences found between patients with positive and negative PET/CT findings (OS and DFS both p>0.05)
Lebon *et al.*, 2017[28]						2/24 (8)	16/124 (13)	29/66 (44)	NR	NR
<40 Years	23/107 (21)	11 (10)	NR	2 (2)	Distant LN: 6 (6)	1/12 (8)	A: 3/32 (9) B: 5/30 (17)	14/33 (42)		
≥40 Years	24/107 (22)	7 (7)	3 (3)	1 (0.9)	Distant LN: 6 (6)	1/12 (8)	A: 4/32 (13) B: 4/30 (13)	15/33 (45)		
Ulaner *et al.*, 2017[27]	61/483 (13)	46 (10)	13 (3)	8 (2)	Distant LN: 7 (2)	1/36 (3)	32/331 (10) A: 6/143 (4) B: 26/188 (14)	28/116 (24) A: 7/55 (13) B: 18/47 (38) C: 3/14 (21)	NR	NR
ER+, HER2–	32/238 (13)	27 (11)	4 (2)	4 (2)	Pleura: 1 (0.4) Distant LN: 3 (1) >1 Site: 6 (3)	1/15 (7)	A: 3/71 (4) B: 13/95 (14)	A: 2/23 (9) B: 12/26 (46) C: 1/8 (13)		
HER2+	29/245 (12)	19 (8)	9 (4)	4 (2)	Distant LN: 4 (2) >1 Site: 7 (3)	0/21 (0)	A: 3/72 (4) B: 13/93 (14)	5/32 (16) 6/21 (29) 2/6 (33)		
Gajjala *et al.*, 2018[26]	20/61 (33)	11 (18)	6 (10)	7 (11)	Distant LN: 11 (18) Brain: 1 (2)	NA	NA	20/61 (33)	20/61 (33)	NR
Yararbas *et al.*, 2018[43]	64/234 (27)	43 (18)	9 (4)	16 (7)	Distant LN: 37 (16) Pleura: 3 (1) Surrenal: 4 (2)	0	25/109 (23)	39/122 (32)	64/234 (27)	NR

TABLE II Continued

Reference	Unsuspected metastases [*n* (%)]	Prevalence of metastases (%)							Change in management	OS or PFS
		By site				By stage (upstaged to IV)				
		Bone	Liver	Lung	Other	I	II	III		
Conventional anatomic imaging (chest radiography; liver ultrasonography; chest, abdomen, and pelvis CT)										
Dillman *et al.*, 2000[a] (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
Koizumi *et al.*, 2001[a] (bone scan)	118/5538 (2)	118 (2)	NA	NA	NA	1/1212 (0)	34/3120 (1)	67/673 (10)	NR	NR
Lee *et al.*, 2005[a] (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.*, 2005[a] (liver ultrasonography, chest radiography, 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.*, 2006[a] (bone scan, liver ultrasonography)	7/221 (3)	6/221 (3)	3/221 (1)	NA	NR	1/61 (2)	8/18 (5)	NR	NR	NR
Barrett *et al.*, 2009[a] (bone scan, CT, chest radiography, liver ultrasonography)	42/2612 (2)	23/373 (6)	6/339 (2)	3/1556 (0.2)		0/992 (0)	12/1041 (1)	26/224 (12)	NR	NR
Kim *et al.*, 2011[a] (chest CT)	26/1703 (2)	NA	9 (0.5)	23 (1)	NA	1/448 (0.2)	0/838 (0)	25/417 (6)	NR	3-Year OS: 98% for patients with normal CT;52% for patients with metastases findings (p<0.001)
Tanaka *et al.*, 2012[40] (contrast–enhanced CT)	26[d]/483 (5)	13 (3)	11 (2)	18 (4)	NR	0/155 (0)	5/261 (2)	21/67 (31)	NR	2-Year OS: 99% for patients withnormal findings; 74% for patients with metastases
ER+	20/381 (5)									
ER–	5/100 (5)									
PgR+	15/314 (5)									
PgR–	10/167 (6)									
HER2+	3/65 (5)									
HER2–	21/393 (5)									
Groheux *et al.*, 2013[21] (bone scan; chest radiography or CT; abdominopelvic ultrasonography or CT, or both; bone scintigraphy)	30/117 (26)	19 (16)	9 (8)	7 (6)	Distant LN: 10 (9) Pleura: 1 (1)					

TABLE II Continued

Reference	Unsuspected metastases [*n* (%)]	Prevalence of metastases (%)							Change in management	OS or PFS
		By site				By stage (upstaged to IV)				
		Bone	Liver	Lung	Other	I	II	III		
Conventional anatomic imaging (chest radiography; liver ultrasonography; chest, abdomen, and pelvis CT) (continued)										
Chen *et al.*, 2014[38] (bone scan, liver ultrasonography, chest radiography)	Patients (*n*) with metastases NR	46 (1)	14 (0.4)	7 (0.2)	0	8/411 (2) Bone (*n*=5), liver (*n*=2), lung (*n*=1)	48/2561 (2) Bone (*n*=33), liver (*n*=10), lung (*n*=5)	11/439 (3) Bone (*n*=8), liver (*n*=2), lung (*n*=1)	NR	NR
ER+		30	4	2						
ER–		16	10	5						
PgR+		25	5	2						
PgR–		21	9	5						
HER2+		20	8	1						
HER2–		26	6	6						
Hulikal *et al.*, 2015[17] (contrast-enhanced CT and bone scan)	6/38 (16)	2 (5)	1 (3)	4 (11)				6/38 (16)		
Krammer *et al.*, 2015[16] (abdominal ultrasonography, chest radiography, bone scan)	13/101 (13)	11 (11)	4 (4)	1 (1)	NR	NR	NR	NR	NR	NR
Bychkovsky *et al.*, 2016[32] (body CT)	5/237 (2)	NR	NR	NR	NA	NA	5/237 (2)	NR	NR	NR
ER+ or PgR+, or both							3/135 (2)			
HER2+							1/54 (2)			
TNBC							1/48 (2)			
Garg *et al.*, 2016[14] (chest radiography, abdominal ultrasonography, bone scintigraphy)	20/79 (25)	12 (15)	7 (9)	6 (8)				20/79 (25)		
Gajjala *et al.*, 2018[26] (bone CT, chest radiography, abdominal ultrasonography, abdominal CT)	13/61 (21)	7 (12)	2 (3)	9 (15)	Distant LN: 4 (7)	NR	NR	NR	NR	NR

TABLE II Continued

Reference	Unsuspected metastases [*n* (%)]	Prevalence of metastases (%)							Change in management	OS or PFS
		By site				By stage (upstaged to IV)				
		Bone	Liver	Lung	Other	I	II	III		
Conventional anatomic and metabolic imaging modalities, combined or individually										
Chu *et al.*, 2012[42] (chest radiography, bone scan, CT, PET)	40/256 (16)	NR	NR	NR	NR	NA	NA	40/256 (16)	NR	Patients in whom metastases were detected NR
N2								24/158 (15)		
N3								16/98 (16)		
Linkugel *et al.*, 2015[34] (chest, abdomen, and 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
Botsikas *et al.*, 2016[33] (FDG PET/MRI)	2/58 (4)	2/58	NR	NR	NR	NR	NR	NR	NR	NR
Piatek *et al.*, 2016[30] (CT, bone scan, PET)	21/362 (6)	14 (4)	6 (2)	8 (2)	Distant LN: 2 (0.6) Chest: 1 (0.3)	NR	NR	NR	20/362 (6)	NR

[a] From Brennan and Houssami, 2012[12].
[b] Includes some cases with symptoms suggesting metastatic disease.
[c] In 9 patients, ^{18}F-FDG–avid metastases were demonstrated. The remaining 3 patients were upstaged only by the CT component of the PET/CT study. The latter 3 patients were initially diagnosed with stage III invasive lobular cancer.
[d] Contrast-enhanced CT detected 65 patients with abnormal findings, including true- and false-positive results.

OS = overall survival; PFS = progression free-survival; PET = positron-emission tomography; CT = computed tomography; NR = not reported; NA = not available; LN = lymph nodes; Tx = treatment; CTx = chemotherapy; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; IBC = inflammatory breast cancer; NIBC = noninflammatory breast cancer; LABC = locally advanced breast cancer; CT/BS = chest–abdomen–pelvis CT, whole-body bone scintigraphy; ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma; RT = radiation therapy; DFS = disease-free survival; PgR = progesterone receptor; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging.

For women initially diagnosed with stage III BCa, the median prevalence was reported to be 8% (six studies) with conventional imaging, 26% (four studies) with PET or PET/CT, and 34% (one study) with both. Two studies that included only cases of inflammatory BCa reported a prevalence of 30.5% (conventional imaging) and 48.8% (PET or PET/CT).

Primary Literature: Stage I: Detection of distant metastases in stage I disease (Table II), was 3.0% (range: 0%–8.8%) from twelve studies of PET/CT[13,23,27–29,31,35–37,39,41,43], 1.0% (range: 0%–1.9%) from two studies of conventional imaging[38,40], and 0.3% from one study reporting on both (conventional imaging and PET/CT)[34].

For conventional imaging, the median from two studies that reported detection of metastasis by site was 2.5% for bone, 1.0% for liver, and 0.5% for lung[38,40]. Only one study of PET/CT in 19 women initially diagnosed with stage I BCa reported distant metastasis detection rates of 5% for bone, 0% for liver, and 0% for lung[41].

Figure 1 depicts the detection of distant metastasis by imaging modality in women initially diagnosed with stage I BCa, including studies from the systematic review by Brennan and Houssami[12]. In two studies of PET/CT reporting by biomarker status in primary BCa, unsuspected distant metastasis was detected in 7%, 0%, and 0% of patients with ER+, HER2–; HER2+; and triple-negative BCa respectively[27,29].

As expected, survival or disease-free survival, or both, were reported to be significantly shorter for patients with distant metastasis than for those without distant metastasis[21,22,29].

Stage II: For stage II BCa, the median prevalence was 10% (range: 0%–33%) from seventeen studies of PET/CT[13,15,18–20,22,23,25,27–29,31,35,36,39,41,43], 1.9% (range: 1.9%–2.1%) from three studies of conventional imaging[32,38,40], and 1.8% from one study reporting on both PET/CT and conventional imaging[34] (Table II).

The median prevalence of metastasis from three studies of PET/CT was 1.0% in bone (range: 0%–21%), 1.0% in liver (range: 0%–4.0%), and 0% in lung (range: 0%–2%)[15,20,41]. In two studies of conventional imaging, the median prevalence was 1.4% for bone, 0.4% for liver, and 0.5% for lung[38,40].

Figure 2 depicts the detection of distant metastasis by imaging modality in women initially diagnosed with stage II BCa, including studies from the systematic review

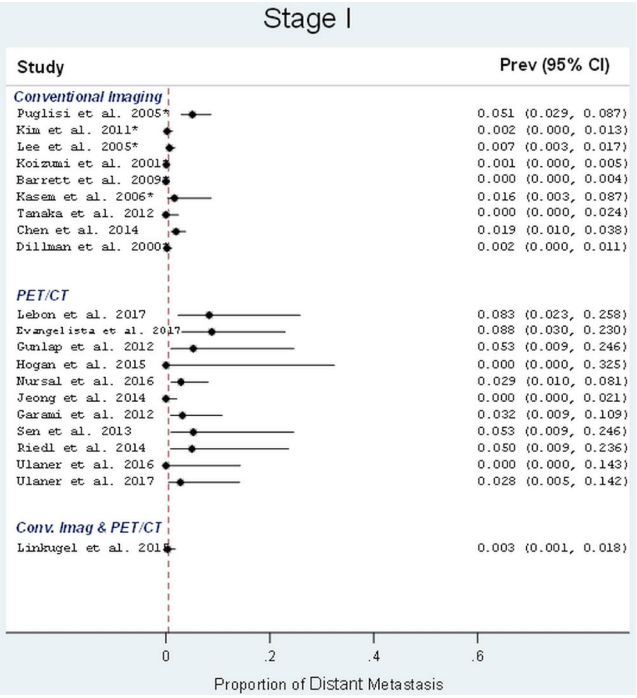

FIGURE 1 Plot of individual studies and pooled prevalence of distant metastasis, by imaging modality, in women initially diagnosed with stage I breast cancer, including 95% confidence intervals (95% CIs). * From the systematic review by Brennan and Houssami, 2012[12]. Prevalence of distant metastasis detected by conventional imaging and by integrated positron-emission tomography/computed tomography (PET/CT) 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 between the studies (I^2: 52% for PET/CT and >75% for conventional imaging).

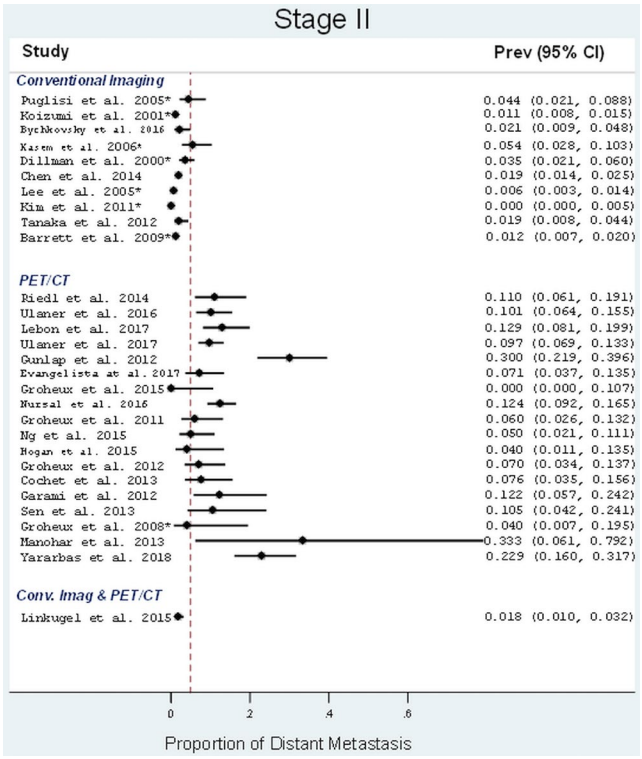

FIGURE 2 Plot of individual studies and pooled prevalence of distant metastasis, by imaging modality, in women initially diagnosed with stage II breast cancer, including 95% confidence intervals (95% CIs). * From the systematic review by Brennan and Houssami, 2012[12]. Prevalence of distant metastasis detected by conventional imaging and by integrated positron-emission tomography/computed tomography (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^2: 67% for PET/CT and >75% for conventional imaging).

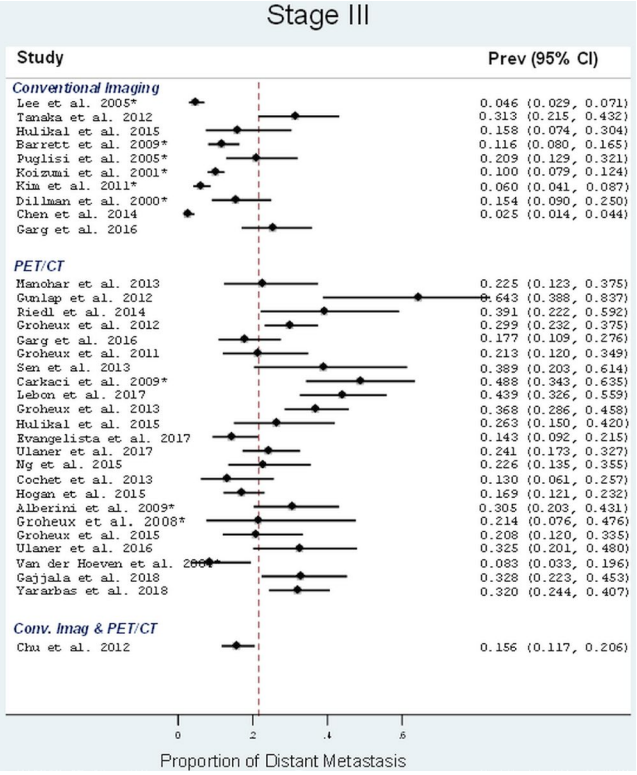

FIGURE 3 Plot of individual studies and pooled prevalence of distant metastasis, by imaging modality, in women initially diagnosed with stage III breast cancer, including 95% confidence intervals (95% CIs). * From the systematic review by Brennan and Houssami, 2012[12]. Prevalence of distant metastasis detected by conventional imaging and by integrated positron-emission tomography/computed tomography (PET/CT) ranged from 2.5% to 31.3% and from 8.3% to 64% respectively. Conventional imaging and integrated 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^2: 74.4% for PET/CT and >75% for conventional imaging).

by Brennan and Houssami[12]. In two studies of PET/CT reported by biomarker, unsuspected distant metastasis was detected in 10% of each of these groups: ER+, HER2–; HER2+; and triple-negative BCa[27,29].

Stage III: For stage III BCa, the prevalence of distant metastases was reported in nineteen studies of PET/CT[13–15,17–22,25–29,35,36,39,41,43], four studies of conventional imaging[14,17,38,40], and one study of both imaging modalities[42].

The median prevalence of distant metastases detected by studies of PET/CT was 26% (range: 13%–64%). Studies reporting on the detection of distant metastasis reported median detection rates of 21% for conventional imaging (range: 3%–31%) and 16% when both conventional imaging and PET/CT were used (Table II).

The median prevalence of metastasis from three studies of PET/CT was 11% in bone (range: 7.5%–43%), 5% in liver (range: 1.9%–14%), and 10% in lung (range: 3.8%–14%)[5,20,41]. The median prevalences of metastasis from two studies of conventional imaging was 7.6% in bone, 7.7% in liver, and 12.1% in lung[38,40].

Figure 3 depicts the detection of distant metastasis by imaging modality in women initially diagnosed with stage III BCa, including studies from the systematic review by Brennan and Houssami[12].

In two PET/CT studies reporting by biomarker, unsuspected distant metastasis was detected in 26% of ER+, HER2–; 22% of HER2+; and 32% of triple-negative BCa[27,29].

Timing of Baseline Staging: Pre- Compared with Post-Treatment: Two studies addressed the issue of the timing of staging investigations in the evaluation of patients newly diagnosed with BCa[13,41].

In the nonrandomized study by Evangelista *et al.*[13], 275 patients with stages I–III triple-negative or HER2+ BCa were staged either before neoadjuvant systemic therapy and surgery (54%), or after surgery (45%). Almost one quarter of the patients with stage III disease receiving pretreatment staging were upstaged to stage IV. Outcomes were worse in all patients who were upstaged before treatment compared with those who were not upstaged. Change in treatment was reported in 15 patients: 1 patient received a more aggressive surgical approach, 12 patients received systemic treatment only, and 2 patients received a combination of systemic and local treatment. For patients who underwent staging imaging after surgery, the upstaging rate was lower (10%), and no difference in prognosis was observed in those who were upstaged compared with those who were not.

The retrospective study by Gunalp *et al.*[41] retrospectively examined 341 patients who were referred for PET/CT staging after a diagnosis of BCa. Patients had clinical stages I–IV BCa and underwent PET/CT pre- or postoperatively. The paper did not indicate whether any of the patients received neoadjuvant systemic therapy, and the specific distribution of clinical stages in the pre- and postoperative groups was not reported.

Given the design limitations of the two studies, no conclusions can be drawn about the value of pre- compared with posttreatment staging. Because many patients in Ontario with clinical stage III disease will receive neoadjuvant systemic therapy with curative intent[45], it makes sense to perform staging investigations for that group before treatment initiation.

PET/CT Considerations in Stage III Disease: As identified in the present review, the prevalence of distant metastases in patients with clinical stage III BCa who undergo PET/CT is high and greater than that seen with conventional imaging. Because upstaging patients to stage IV would likely alter treatment intent in their cases, it is important to accurately identify the presence of distant metastases. In Ontario, PET/CT is not currently funded for the staging of patients with BCa on the basis that the existing evidence consists largely of observational, retrospective, single-institution studies. To generate better-quality evidence, the Ontario Clinical Oncology Group initiated a randomized trial of PET/CT compared with conventional imaging in patients who present with clinical stage III invasive ductal cancer. In the same study, a cohort of patients with similarly staged invasive lobular cancer will be staged using both modalities. The primary outcome of the study will be the proportion of patients who are upstaged to stage IV disease. Secondary

endpoints include final treatment intent, 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 for a 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 as the standard of practice.

DISCUSSION

Although appropriate staging investigations in patients with newly diagnosed BCa can aid in expediting appropriate care, overuse can lead to unnecessary invasive biopsies, unnecessary exposure to potentially harmful radiation from the imaging, psychological distress, heightened anxiety, and possible delays to treatment[46,47]. We sought to answer the question of which groups of patients diagnosed with asymptomatic primary BCa should routinely undergo staging investigations, and what the optimal imaging modalities are.

Our systematic review of more than 5600 articles resulted in 32 studies for analysis. All analyzed studies reported an overall prevalence of asymptomatic distant metastases. The median prevalence was 14%, with the most common sites of distant metastasis being bone, lung, and liver, in that order. Excluding PET/CT, the detection of distant metastasis with anatomic imaging for staging in patients with stages I and II BCa was 1.0% (range: 0%–1.9%) and 1.9% (range: 1.9%–2.1%) respectively. Those exceedingly low rates of distant metastasis in stages I and II disease do not warrant routine use of staging imaging.

Results were more significant for asymptomatic patients with stage III disease, with a median prevalence of distant metastases reported by conventional imaging of 21% (range: 3%–31%)—which is why routine systemic imaging is recommended. Overall, our recommendations agree with those published by the U.S. National Comprehensive Cancer Network (updated in 2018)[48], the European Society for Medical Oncology (2015)[49], and the American Society of Clinical Oncology's Choosing Wisely guidelines[50], in that routine systemic imaging in asymptomatic patients should be considered only in patients who present with locally advanced (stage III, T3N1–3) disease.

Our current recommendations differ from the earlier OH(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 routine body imaging in the initial evaluation of women with stage II BCa who show no symptoms of distant metastasis. Our current guidelines also differ from the latest Alberta Health Services (2012) and Eastern Health (2011) staging guidelines, both of which recommend that a routine baseline bone scan and CT of chest and abdomen should be performed in all patients with node-positive disease.

With respect to PET/CT imaging, the data overall did show additional detection rates at all stages. However, for asymptomatic patients with stage I or II disease, the added prevalence of metastatic disease detection was highly variable (ranging from an additional 1% to 10%), and no study was a randomized controlled trial. For asymptomatic patients with stage III disease, the average prevalence of distant metastases in studies of PET/CT was more significant at 26% (range: 13%–64%). Given that finding, we felt that PET/CT could be considered as a method of staging for distant metastasis in patients stage III disease. The results of the Ontario PET-ABC study, a randomized controlled trial that investigated the routine use of PET/CT compared with conventional imaging in asymptomatic patients with stage III disease supplements that recommendation.

On the other hand, for patients with stage II disease, we struggled with whether to recommend routine use of PET/CT, because some of us felt that a 10% prevalence of distant metastasis was not to be ignored. We therefore looked to the literature for guidance on the issue. Interestingly, although the American Society of Clinical Oncology considers PET/CT to be a credible imaging modality for patients with stage III disease, it recommends against its use in asymptomatic patients with stage I or II disease. The U.S. National Comprehensive Cancer Network panel recommended against its use in stages I–III disease, citing the high false-negative rate for lesions that are small or low-grade (or both), the low probability of those patients having detectable metastatic disease, and the high rate of false positives. In contrast, 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 prospective multicentre diagnostic accuracy study reported that PET is not sufficiently specific to accurately identify distant metastasis in asymptomatic patients with primary BCa (stages I and II)[51].

Apart from staging investigations in patients with newly diagnosed BCa, the diagnostic value of PET in detecting distant metastasis in the initial staging of BCa was determined to be beyond the scope of the present guideline.

Interpretation of the data from the analyzed studies has associated limitations based on substantial heterogeneity in design and quality. In general, the evidence is sparse and drawn mainly from single-institution retrospective and prospective studies, reflecting the need for a prospective randomized controlled trial. Substantial variability was observed in the quality of the reference-standard test used to confirm suspected metastasis, because not all patients received histopathologic 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 the clinicians interpreting the results of the reference test had been 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 radiography or ultrasonography, two used CT, and one used either ultrasonography or CT. No study compared the outcomes of CT, ultrasonography, and chest radiography, and therefore, based on the evidence review, no explicit recommendation can be made about which modality to use.

We also focused on the imaging detection of systemic disease without the ability to determine to any meaningful degree whether the detection of metastasis affected outcome or treatment decisions, because information on treatment and survival by initial stage was not integrated into the analyzed 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 pathologic or anatomic stage assessment (in the postoperative patient). The new 8th revision to the American Joint Committee on Cancer (AJCC) BCa staging system has combined tumour biology (grade, ER status, progesterone receptor status, and HER2 status) with 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 the resulting classification. It should be noted that up to 30%–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, for staging, the studies included in this review used the AJCC 7th edition, which was based solely on anatomic stage. We reviewed the AJCC 8th edition to determine whether new clinical and pathologic prognostic stage groupings would affect our recommendations. In the new staging system, some patients at anatomic stage II would be reclassified to stage III (for example, high-grade triple-negative disease). Additionally, some patients at anatomic stage III (for example, low-grade ER+ disease) would be downstaged to stage II in the new classification. Thus, there is some risk that our recommendations for patients with stage II disease would result in misunderstandings when using the new clinical and pathologic prognostic stage groupings. On the other hand, the evidence review of specific studies that considered biomarker profile in the selection of patients for distant metastasis staging did not, compared with anatomic staging alone, show a greater prevalence of metastasis. Until further studies delineating the evidence for staging under this new classification system are performed, differences between the AJCC 7th and 8th classification systems in clinical and pathologic staging should be taken into consideration when interpreting the guideline. We are aware that additional preoperative imaging that might not be routine (MRI), if applied, would also have the potential to upstage patients. We look forward to adjusting our systemic imaging recommendations in the future as evidence emerges about the prevalence of distant metastasis with the new (8th edition) AJCC classification system and about additional preoperative imaging modalities.

CONCLUSIONS

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

REVIEW PROCESS

The health research methodologist (NPV), in collaboration with the lead author (AA), wrote the initial recommendations and qualifying statements pertaining to the use of imaging tests to detect distant metastases in women newly diagnosed with BCa. The guideline was circulated to the members of the Staging in Early Stage Breast Cancer Working Group and discussed during a teleconference, after which the draft recommendations were generated. The ensuing guideline was reviewed by the PEBC's Report Approval Panel (scientific director, the PEBC assistant director, and two health research methodologists) to ensure that the guideline development was methodologically rigorous and that the evidence-based recommendations are indeed supported by the evidence in a transparent way. The refined guideline was then presented to the Staging in Early Stage Breast Cancer Advisory Committee to ensure the clinical relevance and utility of the recommendations, and to obtain a final approval.

After internal review, feedback on the approved draft guideline was obtained from content experts and the target users through two processes. In the targeted peer review, two individuals with content expertise were asked to review and provide feedback on the guideline document. In the professional consultation, 26 relevant care providers and other potential users of the guideline provided feedback on the guideline recommendations through a brief online survey. The latter consultation was intended to facilitate the dissemination of the final guideline to Ontario practitioners.

Practice guidelines and recommendation reports developed by the PEBC are reviewed and updated as needed. Please visit the OH(CCO) Web site (https://www.cancercare ontario.ca/) for the full guideline and subsequent updates.

PRACTICE GUIDELINE

Evidence from a systematic search of the primary literature, consensus of expert opinion, feedback obtained through a review process, and final approval given by the Staging in Early Stage Breast Cancer Advisory Committee and the PEBC's Report Approval Panel collectively form the basis of this guideline, completed in October 2019.

Target Population

The target population for this guideline is women with newly diagnosed primary BCa (originated in the breast) who have no symptoms of distant metastasis.

Recommendation 1

Staging tests using conventional anatomic (chest radiography, liver ultrasonography, chest–abdomen–pelvis CT) or metabolic imaging modalities (PET/CT, PET/MRI, bone scintigraphy), or both, should not be ordered routinely for women newly diagnosed with clinical stage I or II BCa who have no symptoms of distant metastasis, regardless of biomarker status.

Qualifying Statements

Baseline conventional anatomic imaging modalities (chest radiography, liver ultrasonography, bone scan,

chest–abdomen–pelvis CT) should not be ordered routinely in women with newly diagnosed stage I or II BCa because this population shows an extremely low prevalence of asymptomatic distant metastasis.

Although PET/CT might improve the detection rate, the prevalence of distant metastasis in women with early stage I or II BCa is very low, and PET/CT might unnecessarily increase anxiety and resource use. The use of PET/CT as part of baseline staging in women clinically diagnosed with early-stage BCa (I, II) and with no symptoms of distant metastasis is therefore not recommended at this time.

Although women with triple-negative and HER2+ BCa have an increased risk of disease recurrence, the association of distant metastasis with biomarker profile in early-stage BCa has not been adequately assessed in prospective studies of staging investigation. 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 about staging imaging for clinical early-stage BCa is not recommended regardless of whether the patient will be receiving neoadjuvant therapy.

Recommendation 2

In women newly diagnosed with stage III BCa, baseline staging tests using either anatomic (chest radiography, liver ultrasonography, chest–abdomen–pelvis CT) or metabolic (PET/CT, PET/MRI, bone scintigraphy) imaging modalities, or both, should be considered regardless of whether the patient is symptomatic for distant metastasis and regardless of biomarker profile.

Qualifying Statements

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

A prospective randomized trial (see NCT02751710 at https://ClinicalTrials.gov/) of PET/CT compared with conventional anatomic imaging in patients with clinical stage III disease who will receive neoadjuvant therapy is currently underway in Ontario. The goal of the trial is to determine the rate of upstaging to stage IV with each modality. Given that the existing evidence is based largely on retrospective, observational, and single-institution studies, members of the Working Group believe that it is prudent to wait for the results of the trial before making a recommendation on the choice between anatomic or functional imaging modalities as the standard of practice for staging in such patients.

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The PEBC at OH(CCO) is sponsored by the Ontario Ministry of Health. The full guideline is available on the OH(CCO) Web site, in the Guidelines and Advice section at https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1096.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: 7 members of the Working Group declared that they had no conflicts to disclose; 1 (AE) declared potential conflicts in that she had helped OH(CCO) develop and promote a quality indicator on BCa for the Cancer System Quality Index. That conflict did not disqualify AE from performing her designated role in the development of this guideline.

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