STAGING INVESTIGATIONS FOR ASYMPTOMATIC AND NEWLY DIAGNOSED BREAST CANCER

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Last Revised: May 2012

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

BACKGROUND

Appropriate staging investigations in patients with newly diagnosed breast cancer can aid in expediting care at the tertiary and associate cancer centers. Treatment decisions can be made on day one at the cancer centre if the treating physicians are provided with baseline imaging and blood work. The purpose of this guideline is to provide recommendations that outline which tests should be included in the staging investigation of patients with asymptomatic, biopsy confirmed 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.

GUIDELINE QUESTIONS

1. What are the appropriate staging investigations (e.g. imaging and blood work) for patients with asymptomatic, newly biopsy-confirmed breast cancer?

2. Do staging investigations vary according to stage of disease or other factors at diagnosis?

DEVELOPMENT

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

SEARCH STRATEGY

A systematic search for clinical practice guidelines, systematic reviews, meta-analyses, and clinical studies was conducted of: MEDLINE, EMBASE, the Cochrane Library, Cancerviewcanada, and the National Guidelines Clearinghouse. The search terms included “breast cancer” and ”staging investigations.” The search covered the period between 1965 and 2011 April 18. A total of seven clinical practice guidelines, one meta-analysis, and 10 clinical studies were deemed relevant. Evidence tables, summarizing the information from these 18 sources, are included in the Appendix.

The guideline development panel, including medical oncologists, radiation oncologists, and breast surgeons, initially reviewed the evidence in between May 2010 and October 2010. A draft document was subsequently developed, distributed for review, and discussed with the Breast Tumour Team at the annual meeting in January 2011. After a review of existing guidelines and clinical consensus recommendations were agreed upon.

In April 2012, the American Society of Clinical Oncology published five practices or interventions that are widely used, but not supported by high-level clinical evidence. The recommendation against performing PET, CT, and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis has been added to this guideline.

TARGET POPULATION

This guideline on staging investigations was developed for the management of patients with asymptomatic, biopsy-confirmed breast cancer, prior to referral to the cancer centre.

RECOMMENDATIONS

All patients should have the appropriate medical history and physical examination performed by a qualified health care practitioner.

1. Baseline Investigations

- Stage 0: bilateral mammography
- Stage I: bilateral mammography and laboratory investigations *
- Stage II: bilateral mammography, chest x-ray, laboratory investigations *, and optional abdominal imaging
- Stage III: bilateral mammography, chest x-ray or chest CT †, abdominal imaging (U/S or CT †), bone scan, and laboratory investigations *
- Stage IV: chest x-ray or chest CT †, abdominal imaging (U/S or CT †), bone scan, and laboratory investigations *
- Unless metastatic disease is suspected from symptoms and/or physical exam, staging tests can be performed after surgery.
- All staging tests will be reviewed at the cancer centre and subsequently followed up, based upon the results of the tests.

2. Investigations Prior to Adjuvant Chemotherapy

- For anthracycline-based chemotherapy (e.g. lymph node positive patients): MUGA or ECHO
- For trastuzumab (e.g. HER2+ patients): MUGA or ECHO
- For adjuvant chemotherapy (e.g. lymph node positive patients, high risk, lymph node negative patients, stage III patients, or stage IV patients): laboratory investigations *
- Laboratory and/or baseline cardiac investigations (if required) for subsequent adjuvant therapy can be arranged at the time of the cancer centre triage review.

3. TNM Classification

The TNM staging system developed by the American Joint Committee on Cancer [(1)] is used to group patients with respect to prognosis. TNM staging definitions are included in Appendix A.

DISCUSSION

Several relevant clinical practice guidelines were reviewed and their recommendations on imaging tests and blood work were summarized (Table I, Appendix B). Recommendations on bone scan, ultrasound, x-ray, MRI, CT, and blood work were included. Clinical studies on these imaging modalities were then summarized as well (Table II, Appendix B).

Guidance from Cancer Care Ontario, Program in Evidence-Based Care (CCO, 2003),[(2)] the British Columbia Cancer Agency (BCCA, 2005),[(3)] the National Comprehensive Cancer Network (NCCN, 2011),[(4)]

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* Laboratory investigations include CBC, ALT, AP, total bilirubin, albumin, calcium, and LDH.

† CT is preferred for inflammatory breast cancer.

the European Society for Medical Oncology (ESMO, 2010),[5, 6] the New Zealand Guidelines Group (NZGG, 2009),[7] the National Institute for Health and Clinical Excellence (NICE, 2009),[8, 9] and the National Health and Medical Research Council, Australia (NHMRC, 2001)[10] all agree that that for early stage breast cancer patients, bone scan, is not necessary. For stage II disease, a bone scan has been recommended as part of the work-up by CCO;[2] however, while others have recommended it only for patients with positive nodes,[3, 6] and several groups did not include it at all.[4, 7-9] The Alberta Provincial Breast Tumour Team has adopted ASCO's recommendation that states PET, CT and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis should not be performed.[11,12] For patients with positive nodes and/or those with stage III or IV disease, a bone scan has been recommended by all groups.[2-5, 7-10] In addition, a bone scan has been recommended by several groups, for specific indications (e.g. elevated alkaline phosphatase, localized bone pain).[3, 4, 10] Clinical studies support these recommendations. A retrospective study by Morris, et al. (2009) showed that bone metastasis is not common among patients with early stage disease (42 of 266 patients; 15.8%) and typically presents with symptoms, as less than five percent of cases with bone metastasis were asymptomatic.[13] Focusing on stage I-II node negative patients only, the reported rates of bone metastasis are quite low (e.g. 0.2-0.9%).[14-18] However, in patients with node positive and/or stage III disease, bone metastasis rates of as high as 16% have been reported.[15, 17-19]

Regarding liver ultrasound, there is general consensus that this imaging is not necessary in patients with early stage (e.g. stage 0-I) disease.[2-10] However, in stage II disease with four or more positive nodes or stage III disease, CCO, ESMO, and NICE recommend liver ultrasonography,[2,5,6,8,9] whereas NCCN recommends considering liver ultrasonography (or CT liver or MRI abdomen +/- pelvis) for stage III only, or if there are specific symptoms (e.g. abdominal symptoms, elevated liver function tests, elevated alkaline phosphatase).[4] Others recommend this imaging only if the physical examination and history suggest metastases and/or liver function tests are abnormal.[3, 10] Liver metastasis has been found in only a small proportion of breast cancer patients overall (<1% to 9%), most of which were those with advanced stage disease.[13, 15, 16, 18, 19]

Pulmonary metastasis is not common (i.e. 0.6% to 0.93%) among patients with early stage (i.e. stage 0-III) node negative breast cancer.[15, 19] Among early stage patients with pulmonary metastasis, the majority are stage III.[19] Hence, chest x-ray is typically not recommended for patients with stage 0-I disease. CCO recommends chest x-ray for patients with stage II disease with four or more positive nodes or stage III disease.[2] BCCA and ESMO recommend chest x-ray for node positive, advanced stage disease, if the history and physical exam are suspicious for metastasis or as per chest symptoms.[3, 5, 6] The NCCN recommends chest x-ray for patients with stage III-IV disease, inflammatory breast cancer, or as per chest symptoms.[4] Other groups have put forth similar recommendations.[7-10]

Magnetic resonance imaging (MRI) may be useful in special circumstances, rather than as part of routine imaging in breast cancer patients. Brennan, et al. (2009) conducted a meta-analysis comparing contralateral MRI with conventional imaging to detect contralateral breast cancer, among 3253 patients (any stage) from 22 studies. The positive predictive value for MRI was 47.9% (95% CI, 31.8% to 64.6%), with a true-positive to false-positive ratio of 0.92 (95% CI, 0.47 to 1.82). However, the incremental cancer detection rate was 4.1% (95% CI, 2.7% to 6.0%). Where reported, 35.1% of MRI-detected cancers were DCIS (mean 6.9 mm), 64.9% were invasive (mean 9.3 mm), and the majority were stage pTis or pT1 and node negative.[20] A subsequent randomized controlled trial by Turnbull, et al. (2010), designed to test whether the addition of MRI to conventional imaging would reduce the reoperation rate of breast cancer patients (n=1623; any stage) showed no impact of MRI; 153 patients (19%) needed reoperation in the MRI plus conventional imaging group and 156 patients (19%) needed reoperation in the conventional imaging only group (OR 0.96, 95% CI 0.75-1.24; p=0.77).[21] Some guidelines recommend that MRI could be used

in place of CT or U/S if indicated for abdominal symptoms or pelvic symptoms, or if the physical examination and history are suspicious for metastasis.[3, 4] Others recommend that MRI be used when other imaging is inconclusive.[9, 10] A full guideline on the use of MRI in breast cancer patients was developed by Alberta Health Services in 2010.[22]

Computed tomography (CT) can be used in place of chest x-ray or ultrasound, where those tests are indicated.[4-6] In addition, however, NCCN recommends a CT scan of the chest, abdomen, and pelvis in cases of inflammatory breast cancer[2] and ESMO recommends a CT scan +/- MRI scan of the brain for CNS symptoms suggestive of brain metastasis.[5, 6] NICE recommends a CT scan for patients with advanced stage disease, to assess for the presence/extent of bone or visceral metastasis, or to make a new diagnosis of metastasis if the imaging is suspicious.[8]

For stage I-III breast cancer patients, most groups do recommend bilateral mammography, with or without ultrasound,[3, 4, 6, 8-10] while others (e.g. CCO and NZGG) do not discuss this in their guidelines.[2, 7] The purpose of bilateral mammography is to assess for multiple primary tumours and to evaluate the extent of the lesion.[4]

In terms of laboratory investigations, CBC, ALT, AP, total bilirubin, albumin, calcium, and LDH are typically recommended for stage I-IV breast cancer patients.[3-7, 10] Renal function tests and urinary protein tests (as indicated) have also been included in some guidelines.[5-7] Most guideline groups do not recommend routine investigation with circulating tumour cells/markers (CTC) or state that CTC is currently an experimental test.[5-7, 10] BCCA, however, lists CTC as an optional test.[3] The clinical application of CTC has been questioned in the past.[23] However, recent data suggests that there may be specific applications for this test, including pre-chemotherapy assessment. Bidard, et al. (2010) prospectively detected CTC before and after neoadjuvant chemotherapy, in breast cancer patients diagnosed with large operable or locally advanced disease (n=115) and showed that CTC detection before chemotherapy was an independent prognostic factor for both distant metastasis-free survival (p=0.01; relative risk 5.0; 95% CI, 1.4-17) and overall survival (p=0.007; relative risk 9; 95% CI, 1.8-45) after a median follow-up of 36 months; CTC detection after chemotherapy was not significant (p=0.07 and 0.09, respectively).[24] Liu, et al. (2009) also prospectively showed that, among patients starting a new treatment regimen for metastatic breast cancer (n=68), a significant correlation was demonstrated between CTC and radiographic disease progression (at time of imaging, 3-5 weeks before imaging, and 7-9 weeks before imaging) in patients receiving chemotherapy or endocrine therapy.[25] Nevertheless, for the routine work up of newly diagnosed breast cancer patients, CTC is currently not recommended.

Other investigations may be necessary depending on the type of planned treatment. Anthracycline treatment has been shown to cause early cardiomyopathy and can produce late-onset ventricular dysfunction years after treatment, often leading to permanent myocardial damage and reduced functional reserve.[26] Trastuzumab has also been associated with cardiotoxicity, but not in all patients who use it; several risk factors for trastuzumab-related cardiotoxicity have been suggested, but there is currently no reliable way predict which patients will develop cardiotoxicity.[27] Therefore, for anthracycline-based chemotherapy (e.g. lymph node positive patients) or for trastuzumab chemotherapy (e.g. HER2+ patients), multigated radionuclide angiography (MUGA) or echocardiogram (ECHO) is recommended to monitor patients.[28, 29]

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ALT	alanine aminotransferase
AP	alkaline phosphatase
CBC	complete blood count
CI	confidence interval
CT	computed tomography
CTC	circulating tumour cells
ECHO	echocardiogram
HER2	human epidermal growth factor receptor 2
LDH	lactate dehydrogenase
MUGA	multigated radionuclide angiography
TNM	tumour, node, metastasis
U/S	ultrasound

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2013. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Breast Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services, Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Breast Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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APPENDIX A: AMERICAN JOINT COMMITTEE ON CANCER (AJCC) TNM STAGING DEFINITIONS

The following information was reproduced from the AJCC Cancer Staging Manual, 7th Edition (2010).

Primary Tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	DCIS
Tis (LCIS)	LCIS
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional Lymph Nodes (N)

Nx	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph nodes metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted OR metastases in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement OR metastases in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases OR metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

Pathologic (pN)

pNx	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically.

Note: ITCs are defined as small clusters of cells ≤0.2 mm, or single tumor cells, or a cluster of <200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by IHC methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i-)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) ≤0.2 mm (detected by H&E or IHC including ITC)
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases OR metastases in 1-3 axillary lymph nodes AND/OR metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1mi	Micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis >2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes OR metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least 1 tumor deposit >2 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in ≥10 axillary lymph nodes (at least 1 tumor deposit >2.0 mm) OR metastases in infraclavicular (level III axillary) lymph nodes OR metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes OR metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically OR metastases in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ≥10 axillary lymph nodes (at least 1 tumor deposit >2.0 mm) OR metastases in infraclavicular (level III axillary) lymph nodes
pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes OR metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Distant Metastases (M)

M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm

Anatomic Stage/Prognostic Groups

Stage	***T***	***N***	***M***
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

APPENDIX B: EVIDENCE TABLES

Table I. Existing guidelines on staging investigations for breast cancer.

Guideline, year	Stage	Bone scan	Ultrasound (U/S)	X-ray	MRI	CT	Blood tests
Cancer Care Ontario, PEBC April, 2003	DCIS & stage I	No	No	No	Not discussed	Not discussed	Not discussed
	Stage II <4 nodes	Yes	No	No			
	Stage II ≥4 nodes	Yes	Yes (liver)	Yes (chest)			
	Stage III	Yes	Yes (liver)	Yes (chest)			
	Stage IV	Not discussed	Not discussed	Not discussed			
	Treatment limited to tamoxifen, hormones, no therapy	No	No	No			
National Comprehensive Cancer Network, March, 2011	Stage I	No	No	No	Optional	No	CBC, platelets liver function tests (LFT), alkaline phosphatase (AP)
	Stage IIA/IIB	No	No	No	Optional	No	
	Stage IIIA	Yes	Consider; or CT or MRI (abdomen ± pelvis)	Yes (chest)	Consider; or U/S or CT (abdomen ± pelvis)	Consider; or U/S or MRI (abdomen ± pelvis)	
	Stage IV	Yes; plus bone x-ray to confirm	No	Yes (chest)	Consider; or CT (abdomen)	Consider; or MRI (abdomen)	
	As per symptoms	Yes; for localized bone pain, ↑ AP	Yes; or MRI or CT for abdominal symptoms, ↑ AP, abnormal LFT (abdomen ± pelvis)	Yes; for pulmonary symptoms (chest)	Yes; or U/S or CT if for abdominal symptoms, ↑ AP, abnormal LFT (abdomen ± pelvis)	Yes; or U/S or MRI for abdominal symptoms, ↑ AP, abnormal LFT (abdomen ± pelvis)	
	Inflammatory	Yes	No	Yes; for pulmonary symptoms (chest)	Optional	Yes (chest/abdomen/ pelvis)	

Guideline, year		Bone scan	Ultrasound (U/S)	X-ray	MRI	CT	Blood tests
BC Cancer Agency, July, 2005; July, 2006	Stage I, II, N0	No	Not discussed	Not discussed	Not discussed	Not discussed	Yes, if exam or Hx are suspicious or prior to chemo: CBC, LFT, AP OPTIONAL: tumour markers
	Node positive or locally advanced disease	Yes; if risk of bone mets	Yes, if phys exam and Hx suggest mets	Yes, if phys exam and Hx suggest mets	Yes, if phys exam and Hx suggest mets		
	Tumours >5 cm, or when palpable nodes	Yes if ↑ alkaline phosphatase	Yes, if phys exam and Hx suggest mets	Yes, if phys exam and Hx suggest mets	Yes, if phys exam and Hx suggest mets		
	As per symptoms	Yes, if ↑ alkaline phosphatase	Yes, if abnormal LFT (liver)	Yes, to assess if mets present	Not discussed		
European Society for Medical Oncology, February, 2010 February, 2010	Early stage (e.g. N0)	No	No	No	No	No	CBC, LFT renal function tests (RFT) AP, calcium Specific treatment-based tests (i.e. urinary protein) Circulating tumour cells is currently experimental
	To exclude mets if neo-adj systemic treatment is planned	Yes	Yes (abdominal)	Yes (chest)	Not discussed	Not discussed	
	Locally advanced (node positive, large tumour)	Yes	Yes (abdominal)	Yes (chest)	Not discussed	Not discussed	
	Locally advanced, to identify bone/ visceral mets	Yes; plus bone x-ray, CT, or MRI to confirm	Yes; or MRI or CT (abdominal)	Yes; or CT (chest)	Yes; or U/S or CT (abdominal)	Yes; or x-ray (chest); or MRI or U/S (abdominal)	
	Local advanced, to identify isolated mets	Not discussed	Not discussed	Not discussed	Not discussed	Yes	
	If clinical signs/ symptoms	Not discussed	Not discussed	Not discussed	Yes, ± CT for CNS symptoms	Yes, ± MRI for CNS symptoms	
New Zealand Guidelines Group, 2009	Early operable T1-2, N0-1	No	Not discussed	No	Not discussed	Not discussed	Advanced: CBC, RTF, LFT, calcium Biomarkers not recom-mended
	Advanced but operable T3, N1-2, if will affect treatment	Yes	Yes	Yes	Yes, if imaging is unreliable or inconclusive	Not discussed	

Guideline, year		Bone scan	Ultrasound (U/S)	X-ray	MRI	CT	Blood tests
National Institute for Health and Clinical Excellence, February, 2009	Advanced stage, to monitor disease or monitor response	No	Not discussed	Not discussed	Not discussed	No	Not discussed
	Early/locally advanced pre-op assessment of invasive or DCIS	No	Yes (scan of axilla) and as U/S-guided FNAC if abnormal nodes	No	No	No	
	Advanced stage, to assess presence/ extent of bone or visceral mets	Yes plus assess for fracture in proximal bones if bone mets	Yes	Yes plus assess for fracture in proximal bones if bone mets	Yes plus confirm bone mets if imaging equivocal plus assess for fracture in proximal bones if bone mets	Yes plus assess for fracture in proximal bones if bone mets plus to make a new diagnosis of mets if imaging suspicious	
National health and Medical Research Council, 2001	Early stage	No	No	No	No	No	Early stage (select) and advanced stage: CBC, serum biochemistry Serum antigens (CEA and CA 15.3) not recom-mended
	Advanced stage	Yes, to assess metastases, as appropriate (indications: bone pain/ tenderness)	Yes, to assess metastases as appropriate (indications: LFT, palpable liver)	Yes, to assess metastases as appropriate (indications: lung symptoms)	No	No, unless clinically indicated	

Table II. Clinical studies on staging investigations for breast cancer.

First Author	Year	Intervention	Number	Patients	Outcome Measures	Summary of results
Brennan	2009	*Meta-analysis* Contralateral MRI vs. conventional imaging to detect contralateral BCa	3253 (22 studies)	Any stage	Pos predictive value (PPV) True-pos: false-pos ratio (TP:FP) Incremental cancer detection rate (ICDR)	MRI detected contralateral disease in 131 pts. PPV: 47.9% (95% CI, 31.8% to 64.6%) TP: FP ratio: 0.92 (95% CI, 0.47 to 1.82) ICDR: 4.1% (95% CI, 2.7% to 6.0%) Where reported, 35.1% of MRI-detected cancers were DCIS (mean 6.9 mm), 64.9% were invasive (mean 9.3 mm), and majority were stage pTis or pT1 and node negative.
Turnbull	2010	*Prospective RCT* MRI (816) vs. no further imaging (807)	1623	Any stage; patients underwent triple assessment	Repeat surgery/ further mastectomy within 6 mos of randomization, or avoidable initial mastectomy	Addition of MRI to conventional triple assessment was not significantly associated with reduced reoperation rate, with 153 (19%) needing reoperation in the MRI group versus 156 (19%) in the no MRI group, (OR 0.96, 95% CI 0.75-1.24; p=0.77).
Barrett	2009	*Retrospective* Investigations for breast cancer (comparison of current practice to national guidelines)	2612	Stage I-IV	Presence of metastases	No patients with stage 0 or I disease had metastases (2.2% and 2.6%, respectively, had false positive results). Only 2 patients (0.3%) with stage II and ≤3 positive nodes had mets (3.8% false-positive). Occult mets were present in 5% of stage II (≥4 pos nodes), 13.9% of stage III, and 57% of stage IV patients.
Morris	2009	*Retrospective* Bone scan (266) and liver ultrasonography (261)	781	Early stage	Detection of metastases	Bone scan: mets in 42 of 266 (15.8%) patients; of these, 26 (61.9%) were symptomatic with pain; only two asymptomatic patients had skeletal mets (Euro 50,850 per case) Liver U/S: mets in 23 of 261 (8.8%) patients; of these, 19 (82.6%) had abnormal liver blood tests; only two patients had incidental hepatic mets (Euro 29,400 per case)
Abuzallouf	2007	*Retrospective* Bone scan, liver ultrasound, chest X-ray	785	Stage I-III	Detection of metastases	Distant mets found in 36 (4.6%) patients Bone mets found in 29 (3.7%) patients Pulmonary mets found in 6 (0.8%) patients Liver mets found in 5 (0.6%) patients Stage: 0.7% of stage I and II patients had mets vs. 16.2% of stage III patients (p=0.0001)

First Author	Year	Intervention	Number	Patients	Outcome Measures	Summary of results
Kasem	2006	*Retrospective* Bone scan (BS) and liver ultrasound (LU) plus liver function tests (LFT)	221	Any	Detection of metastases	BU: 32 patients had suspicious/positive scans; 6 confirmed positive on further investigations LU: 7 patients had suspicious ultrasound and underwent CT which confirmed liver mets in 2 patients (1 w/abnormal LFT) BS and liver US truly altered treatment in 3% of patients.
Puglisi	2005	*Prospective study* Bone scanning (BS), liver ultrasonography (LUS), chest radiography (CXR)	428	Stage I-III	Detection of metastases	BS detected skeletal mets in 6.31% of patients (26.9% were previously staged as clin stage III; stage III detection 14%) LUS detected liver mets in 0.72% of patients (all previously staged as clin stage III; stage III detection rate of 5.6%) CXR detected lung mets in 0.93% of patients (all previously staged as clin stage III; stage III detection rate of 7.2%)
Samant	1999	*Retrospective study* Routine bone scans and liver imaging	250	Stage I-II N0-1	Detection of metastases	25 (10.0%) diagnosed with mets: 5 were path stage T1-2 N0-1; 18 were stage T3-4 or N2 Of pts with mets, only 2 were diagnosed solely on bone scan; none were diagnosed solely on liver imaging (U/S or radionuclide isotope scan)
O'Hanlon	1995	*Retrospective study* Serial CA15-3 levels	168	Stage I	Detection of metastases	CA15-3 not elevated in pts w/ locoregional disease; sig elevated in pts w/ bony mets (mean lead time of 6.3 months over bone scintigraphy)
Cox	1992	*Prospective study* Bone scan (339 scans) and liver ultrasound (U/S; 309 scans)	358	Stage I-III	Detection of metastases	0.9% bone scans were positive in stage I and II patients; 16.2% were positive in stage III pts 0% U/S scans were positive for stage I or II pts, but 5.4% were positive for stage III pts
Glynne-Jones	1991	*Retrospective study* 99mTc bone scan; chest X-ray; liver function tests (including alkaline phos) & liver ultrasound (U/S)	398	Clinical stage I-III rec'd RT	Detection of metastasis at 3 months	9.3% total: 7.4% for skeletal scintigraphy; 2.6% for chest x-rays; 2.9% for liver U/S; 0.8% for alkaline phosphatase Skeletal scintigraphy alone identified 78% (29/37) of those with mets; skeletal scintigraphy and liver ultrasound will identify 95% (35/37)