



EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Directorate F - Health, Consumers & Reference Materials (Ispra)
Health in Society

European Commission Initiative on Breast Cancer (ECIBC): European guidelines on breast cancer screening and diagnosis

QUESTION	
Should conventional staging exams vs. no staging exams be used for patients with clinical stage II breast cancer without symptoms suggestive of metastases?	
POPULATION:	patients with clinical stage II breast cancer without symptoms suggestive of metastases
INTERVENTION:	conventional staging exams
COMPARISON:	no staging exams
MAIN OUTCOMES:	Detection rate: Combined tests (prevalence); False positive: Combined tests; Detection rate: Bone Scan; False positive: Bone Scan; Detection rate: CT Chest; False positive: CT Chest; Detection rate: CT pelvic; False positive: CT Pelvic; Detection rate: CT abdominal ; False positive: CT abdominal; Detection rate: RX Chest; False Positive: RX Chest ; Detection rate: US; False positive: US;
SETTING:	European Union
PERSPECTIVE:	Population (National Health System)
BACKGROUND:	The main cause of death from breast cancer is due to distant metastases. The diagnosis of distant metastases in patients with newly diagnosed breast cancer alters treatment and prognosis. If metastases are present, the prognosis worsens significantly and the treatment has to balance between prolongation of survival and quality of life since the disease is no longer curable. Therefore, the staging interventions aim to avoid overtreatment in patients with primarily metastasized breast cancer and, in some cases, to start treatments that are specific for metastases. However, the risk for metastases is lower in early detected (clinical stage I and II) breast cancer than in later stages (clinical stage III). Although, the staging interventions have the advantage of ensuring adequate treatment adapted to the tumour stage, it is also associated with some disadvantages like limited specificity, leading to false positive with consequent psychological stress for the women, unnecessary ascertainment and, when ascertainment is not possible leading to wrong treatment planning; furthermore some imaging techniques have procedure related consequences, in particular, radiation (depending on the used technique) and high costs.
CONFLICT OF INTEREST:	ColS for all Guidelines Development Group (GDG) members were assessed and managed by the European Commission Joint Research Centre (JRC) following an established procedure in line with the institutional rules. GDG member participation in the development of the recommendations was restricted, according to Col disclosure. Consequently, for this particular question, the following GDG members were recused from voting: Axel Gräwingholt. Miranda Langendam, as external expert, was also not allowed to vote, according to the ECIBC rules of procedure.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	<p>The detection of distant metastases in patients with newly diagnosed breast cancer alters treatment and prognosis. If metastases are present, the prognosis worsens significantly and the treatment has to balance between prolongation of survival and quality of life since the disease is no longer curable. Therefore, the staging interventions aim to avoid overtreatment in patients with primarily metastasized breast cancer and, in some cases, to start treatments that are specific for metastases.</p> <p>Although, the staging interventions have the advantage of ensuring adequate treatment adapted to the tumour stage, they are also associated with some disadvantages like limited specificity, leading to false positive with consequent psychological stress for the women, unnecessary ascertainment and, when ascertainment is not possible leading to wrong treatment planning; furthermore some imaging techniques have procedure related consequences, in particular radiation (depending on the used technique) and high costs.</p>	<p>The GDG prioritised this question for the ECIBC.</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																				
<div><div>○ Trivial</div><div>● Small</div><div>○ Moderate</div><div>○ Large</div><div>○ Varies</div><div>○ Don't know</div></div>	<div>Desirable Effects</div> <table><tr><th>Outcomes</th><th>Impact</th><th>No of participants (studies)</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Detection rate: Combined tests (prevalence)</td><td>Pooled detection rate: 25 per 1,000 examinations (95% CI: 13 - 41); n/N = 48/2,262</td><td>(6 RCTs)^{1,2,3,4,5,6}</td><td><div><div>⊕⊕○○</div><div>LOW^{a,b,c,d}</div></div></td></tr><tr><td>Detection rate: Bone Scan</td><td>Pooled detection rate: 21 per 1,000 examinations (95% CI: 9 - 38); n/N = 61/4,597</td><td>(5 RCTs)^{2,3,5,7,8}</td><td><div><div>⊕⊕○○</div><div>LOW^{a,b,d,e}</div></div></td></tr><tr><td>Detection rate: CT Chest</td><td>Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 0); n/N = 4/871</td><td>(2 RCTs)^{3,9}</td><td><div><div>⊕⊕○○</div><div>LOW^{a,b,d,e}</div></div></td></tr><tr><td>Detection rate: CT pelvic</td><td>Detection rate: 53 per 1,000 examinations</td><td>(1 RCT)³</td><td><div><div>⊕○○○</div></div></td></tr></table>	Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Detection rate: Combined tests (prevalence)	Pooled detection rate: 25 per 1,000 examinations (95% CI: 13 - 41); n/N = 48/2,262	(6 RCTs) ^{1,2,3,4,5,6}	<div><div>⊕⊕○○</div><div>LOW^{a,b,c,d}</div></div>	Detection rate: Bone Scan	Pooled detection rate: 21 per 1,000 examinations (95% CI: 9 - 38); n/N = 61/4,597	(5 RCTs) ^{2,3,5,7,8}	<div><div>⊕⊕○○</div><div>LOW^{a,b,d,e}</div></div>	Detection rate: CT Chest	Pooled detection rate: 0 per 1,000 examinations (95% CI: 0 - 0); n/N = 4/871	(2 RCTs) ^{3,9}	<div><div>⊕⊕○○</div><div>LOW^{a,b,d,e}</div></div>	Detection rate: CT pelvic	Detection rate: 53 per 1,000 examinations	(1 RCT) ³	<div><div>⊕○○○</div></div>	<div>Subgroup analysis.</div> <div>Stage IIA (2 studies)</div> <div>Pooled detection rate: 28 per 1,000 examinations (95% CI: 12 - 49); n/N = 11/337 (Dilman 2000, Kasem 2006).</div> <div>Stage IIB (2 studies)</div> <div>Pooled detection rate: 40 per 1,000 examinations (95% CI: 14 - 76); n/N 9/178 (Dilman 2000, Kasem 2006).</div> <div>In one study including 411 clinical stage II breast cancer patients (Bychkovsky 2016) evaluated by conventional imaging, the percentage of distant metastases did not differ by BC subtype: among ER/PR-positive and HER2-negative patients was 2.2% (95% CI, 0.5%–6.4%), for HER2+ patients was 1.9% (95% CI, 0%–9.9%), and in TNBC patients was 2.1% (95% CI, 0.1%–11.1%). Another study in 254 patients with BC clinical stage II and III evaluated by 18FDG-PET-CT (Groheux 2012), reported that the rates of distant metastases did not differ between TNBC (16 %), HER2- positive (26 %), and ER-positive (22 %) breast cancers subtypes (p =0.42).</div>
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	Detection rate: CT pelvic	Detection rate: 53 per 1,000 examinations	(1 RCT) ³	<div><div>⊕○○○</div></div>																		

	(95% CI: 6 - 177); n/N = 2/38		VERY LOW ^{a,b,d,e,f}	The GDG notes that for the women with additional detection, not all women will have a change in their course of treatment. In some cases chemotherapy may not be suggested if metastases are detected. However, the GDG noted that other differences may impact outcomes, for example: no surgical treatment, decision to initiate chemotherapy and anti-HER2 therapy, radiotherapy on metastases. The GDG judged by consensus that the desirable effects were small.
Detection rate: CT abdominal	Detection rate: 86 per 1,000 examinations (95% CI: 29 - 190); n/N = 5/58	(1 RCT) ³	⊕○○○ VERY LOW ^{a,b,d,e,f}	
Detection rate. RX Chest	Pooled detection rate: 12 per 1,000 examinations (95% CI: 2 - 28); n/N = 6/345	(2 RCTs) ^{2,3}	⊕○○○ VERY LOW ^{a,d,f}	
Detection rate: US	Pooled detection rate: 3 per 1,000 examinations (95% CI: 0 - 14); n/N = 2/372	(3 RCTs) ^{2,3,5}	⊕⊕⊕○ MODERATE ^{a,b,e}	
<div><div><div>1. Bychkovsky BL, Guo H,Sutton J, Spring L, Faig J, Dagogo-Jack I, Battelli C, Houlihan MJ, Yeh TC, Come SE, Lin NU.. Use and Yield of Baseline Imaging and Laboratory Testing in Stage II Breast Cancer.. Oncologist.; 2006.</div><div>2. Puglisi F, Follador A, Minisini AM, Cardellino GG, Russo S, Andreetta C, Di Terlizzi S, Piga A.. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications.. Ann Oncol.; 2005.</div><div>3. Dillman RO, Chico S.. Radiologic tests after a new diagnosis of breast cancer.. Eff Clin Pract.; 2000.</div><div>4. Ravaioli A, Tassinari D, Pasini G, Polselli A, Papi M, Fattori PP, Pasquini E, Masi A, Alessandrini F, Canuti D, Panzini I, Drudi G.. Staging of breast cancer: what standards should be used in research and clinical practice?. Ann Oncol. ; 1998.</div><div>5. Kasem AR, Desai A, Daniell S, Sinha P.. Bone scan and liver ultrasound scan in the preoperative staging for primary breast cancer.. Breast J. ; 2006.</div><div>6. Barret T, Bowden DJ, Greenberg DC, Brown CH, Wishart PD. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer; 2009.</div><div>7. Koizumi M, Yoshimoto M, Kasumi F, Ogata E.. What do breast cancer patients benefit from staging bone scintigraphy?. Jpn J Clin Oncol.; 2001.</div><div>8. Lee JE, Park SS, Han W, Kim SW, Shin HJ, Choe KJ, Oh SK, Youn YK, Noh DY, Kim SW.. The clinical use of staging bone scan in patients with breast carcinoma: reevaluation by the 2003 American Joint Committee on Cancer staging system.. Cancer. ; 2005.</div><div>9. Kim H, Han W, Moon HG, Min J, Ahn SK, Kim TY, Im SA, Oh DY, Han SW, Chie EK, Ha SW, Noh DY.. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma.. Breast Cancer Res Treat.; 2011.</div></div><div><div>a. Different reference standards were used, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition.</div><div>b. Some studies included retrospective case records where inclusion criteria cannot be properly assessed, in some cases the distribution of stages at diagnosis is not that expected in the population, in particular stage I and stage II are under-represented; this suggest that only a subpopulation of these cases entered in the study and that they could be those with higher suspicious of having distal metastases.</div><div>c. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimated the exams' performance. All studies reported to include follow-up of patients although with different time frame.</div><div>d. Some or most of the studies recruited consecutive patients from medical records (or prospectively) who</div></div></div>				

- could or could not have symptoms suggestive of metastases.
- e. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance measurements.
 - f. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests.

Undesirable Effects

Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)
False positive: Combined tests (prevalence)	Pooled false positive: 53 per 1,000 examinations (95% CI: 16 - 109); n/N = 72/1,600	(3 RCTs) ^{1,2,3}	⊕⊕○○ LOW ^{a,b,c,d}
False positive: Bone Scan	False positive: 101 per 1,000 examinations (95% CI: 62 - 160); n/N = 15/148	(1 RCT) ²	⊕⊕⊕○ MODERATE ^{a,b,e}
False positive: CT Chest	False positive: 144 per 1,000 examinations (95% CI: 122 - 170); n/N = 121/838	(1 RCT) ⁴	⊕⊕⊕○ MODERATE ^{a,e}
False positive: CT Pelvic - not reported		-	-
False positive: CT abdominal - not reported		-	-
False Positive: RX Chest - not reported		-	- ^{a,f}
False positive: US	False positive: 34 per 1,000 examinations (95% CI: 14 - 77); n/N = 5/148	(1 RCT) ²	⊕⊕⊕○ MODERATE ^{a,b,e}





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Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																
<div><div>○ Large</div><div>○ Moderate</div><div>○ Small</div><div>○ Trivial</div><div>● Varies</div><div>○ Don't know</div></div>	<div>Desirable Effects</div> <table><tr><th>Outcomes</th><th>Impact</th><th>Nº of participants (studies)</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Detection rate: Combined tests (prevalence)</td><td>Pooled detection rate: 25 per 1,000 examinations (95% CI: 13 - 41); n/N = 48/2,262</td><td>(6 RCTs)^{1,2,3,4,5,6}</td><td><div><div>⊕⊕○○</div><div>LOW^{a,b,c,d}</div></div></td></tr><tr><td>Detection rate: Bone Scan</td><td>Pooled detection rate: 21 per 1,000 examinations (95% CI: 9 - 38); n/N = 61/4,597</td><td>(5 RCTs)^{2,3,5,7,8}</td><td><div><div>⊕⊕○○</div><div>LOW^{a,b,d,e}</div></div></td></tr><tr><td>Detection rate: CT Chest</td><td>Pooled detection rate: 0 per 1,000</td><td>(2 RCTs)^{3,9}</td><td><div><div>⊕⊕○○</div></div></td></tr></table>	Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)	Detection rate: Combined tests (prevalence)	Pooled detection rate: 25 per 1,000 examinations (95% CI: 13 - 41); n/N = 48/2,262	(6 RCTs) ^{1,2,3,4,5,6}	<div><div>⊕⊕○○</div><div>LOW^{a,b,c,d}</div></div>	Detection rate: Bone Scan	Pooled detection rate: 21 per 1,000 examinations (95% CI: 9 - 38); n/N = 61/4,597	(5 RCTs) ^{2,3,5,7,8}	<div><div>⊕⊕○○</div><div>LOW^{a,b,d,e}</div></div>	Detection rate: CT Chest	Pooled detection rate: 0 per 1,000	(2 RCTs) ^{3,9}	<div><div>⊕⊕○○</div></div>	<div>Subgroup analysis.</div> <div>Stage IIA (1 study)</div> <div>Pooled false positive: 125 per 1,000 examinations (95% CI: 66 - 208); n/N = 12/96 (Kasem 2006).</div> <div>Stage IIB (1 study)</div> <div>Pooled false positive: 154 per 1,000 examinations (95% CI: 69 - 281); n/N = 8/52 (Kasem 2006).</div> <div>The GDG noted that a false positive may lead to further assessment and may not lead to unnecessary treatment. If a patient is assumed to have distant metastasis or qualify for endocrine therapy, detection of metastasis on conventional staging exams may mean they will be treated.</div>
	Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)														
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	examinations (95% CI: 0 - 0); n/N = 4/871		LOW ^{a,b,d,e}	<p>The GDG notes that the undesirable effects of false positives may include psychological distress and biopsy or further investigations.</p> <p>The GDG noted that the higher false positive rate for clinical stage IIb breast cancer may be secondary to bias with if the radiologist is aware that a patient has a clinical stage IIb breast cancer.</p> <p>The GDG judged that the undesirable effects varied.</p>
Detection rate: CT pelvic	Detection rate: 53 per 1,000 examinations (95% CI: 6 - 177); n/N = 2/38	(1 RCT) ³	 VERY LOW ^{a,b,d,e,f}	
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- in the study and that they could be those with higher suspicious of having distal metastases.
- c. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimated the exams' performance. All studies reported to include follow-up of patients although with different time frame.
 - d. Some or most of the studies recruited consecutive patients from medical records (or prospectively) who could or could not have symptoms suggestive of metastases.
 - e. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance measurements.
 - f. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests.

Undesirable Effects

Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)
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False positive: CT Pelvic - not reported		-	-
False positive: CT abdominal - not reported		-	-
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False positive: US	False positive: 34 per 1,000 examinations	(1 RCT) ²	⊕⊕⊕○

	<div> <div>(95% CI: 14 - 77); n/N = 5/148</div> <div>MODERATE^{a,b,e}</div> </div> <ol style="list-style-type: none"> Bychkovsky BL, Guo H,Sutton J,Spring L,Faig J,Dagogo-Jack I,Battelli C,Houlihan MJ,Yeh TC,Come SE,Lin NU.. Use and Yield of Baseline Imaging and Laboratory Testing in Stage II Breast Cancer.. Oncologist.; 2006. Kasem AR, Desai A,Daniell S,Sinha P.. Bone scan and liver ultrasound scan in the preoperative staging for primary breast cancer.. Breast J. ; 2006. Barret T, Bowden DJ,Greenberg DC,Brown CH,Wishart PD. Radiological staging in breast cancer: which asymptomatic patients to image and how. Br J Cancer; 2009. Kim H, Han W,Moon HG,Min J,Ahn SK,Kim TY,Im SA,Oh DY,Han SW,Chie EK,Ha SW,Noh DY.. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma.. Breast Cancer Res Treat.; 2011. <ol style="list-style-type: none"> Different reference standards were used, some included another imaging test without histological confirmation which is likely to incorrectly classify the condition. Some studies included retrospective case records where inclusion criteria cannot be properly assessed, in some cases the distribution of stages at diagnosis is not that expected in the population, in particular stage I and stage II are under-represented; this suggest that only a subpopulation of these cases entered in the study and that they could be those with higher suspicious of having distal metastases. The proportion of patients actually staging investigated with more than one imaging tests was variable which could underestimated the exams' performance. All studies reported to include follow-up of patients although with different time frame. Some or most of the studies recruited consecutive patients from medical records (or prospectively) who could or could not have symptoms suggestive of metastases. The assessment of each individual tests is based in the number of patients that were examined who are a subpopulation of all those subject at this stage which could overestimate its performance measurements. Judgement of imprecision was considered serious as one or both of the confidence interval limits reached detection rates threshold which could potentially change the decision about requesting staging tests. 	
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Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ● Low ○ Moderate ○ High ○ No included studies 		<p>The GDG notes that the risk of bias was perceived as serious due to the reference test used, given that not all cases were confirmed by pathology but with other imaging tests, in several cases which may lead to misclassification.</p> <p>The GDG notes that retrospective studies may lead to inclusion of population at higher risk of metastasis because assessment of distant metastases is not overall recommended.</p> <p>The GDG judged by consensus that there is low certainty</p>

		for evidence of test accuracy.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes 		<p>No systematic review for values and preferences regarding diagnostic exams was conducted.</p> <p>The GDG notes that due to the variety of diagnostic and treatment pathways the values and preferences for each may be very heterogeneous.</p> <p>The GDG notes that certain individuals will be reassured by staging exams that do not demonstrate evidence of metastases, while other individuals will experience stress waiting for follow-up if there is a false positive on staging exam. There is therefore important uncertainty or variability in how much people value the main outcomes.</p> <p>As consensus was not reached, voting was conducted: *17 members voted for 'possibly important uncertainty or variability';</p> <p>*5 members voted for 'important uncertainty or variability';</p> <p>*1 member voted for 'no known undesirable outcomes'</p>
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 		<p>The GDG considered the balance of effects separately for clinical Stage IIa and IIb.</p> <p>For clinical Stage IIa breast cancer, agreement within the GDG could not be reached by consensus, voting among the members without Col was conducted:</p> <p>*14 members voted 'probably favours the comparison', *8 members voted 'does not favour either the intervention or the comparison',</p>

		<p>*1 member voted 'don't know'.</p> <p>For clinical Stage IIb breast cancer, agreement within the GDG could not be reached by consensus, voting among the members without Col was conducted:</p> <p>*12 members voted for 'probably favours the comparison',</p> <p>*8 members voted 'does not favour either the intervention or the comparison',</p> <p>*2 members voted 'favours the comparison', and</p> <p>*1 member voted 'probably favours the intervention'.</p>
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Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS															
<ul style="list-style-type: none">○ Large costs○ Moderate costs○ Negligible costs and savings○ Moderate savings○ Large savings● Varies○ Don't know	<p>Direct evidence: Mean cost and utilization</p> <p>One Italian study (DePlacido 2017) determined the relative costs of staging and follow-up tests in a population of breast cancer patients in a Southern Italian region. The number and type of tests per patient were recorded 3 months before and 12 months after the date diagnosis of nonmetastatic breast cancer from 2001 to 2010.</p> <table><tr><th rowspan="2">Type of tests</th><th colspan="3">Estimated annual variation (2001-2010)</th></tr><tr><th>Mean cost¹ of imaging tests per patient (Euros)</th><th>Imaging utilization, % (95% CI)</th><th>Imaging-related costs, % (95% CI)</th></tr><tr><td>Chest radiograph, abdominal ultrasound, bone scan, and mammograms</td><td>Remain constant at 250 €</td><td>Increase 0.1% (-0.1–0.3)</td><td>Decrease 0.1% (-0.9 to 0.6)</td></tr><tr><td>CT, PET, and MRI</td><td>Increased from 350 € in 2001 to 800 € in 2010</td><td>Increase 15.7% (14.2–17.2)</td><td>Increase 19.4% (15.9–23.0)</td></tr></table> <p>¹Prices were reported in 2011 Euros value.</p>	Type of tests	Estimated annual variation (2001-2010)			Mean cost ¹ of imaging tests per patient (Euros)	Imaging utilization, % (95% CI)	Imaging-related costs, % (95% CI)	Chest radiograph, abdominal ultrasound, bone scan, and mammograms	Remain constant at 250 €	Increase 0.1% (-0.1–0.3)	Decrease 0.1% (-0.9 to 0.6)	CT, PET, and MRI	Increased from 350 € in 2001 to 800 € in 2010	Increase 15.7% (14.2–17.2)	Increase 19.4% (15.9–23.0)	<p>Indirect evidence: One study from Canada and two studies from the USA reported costs of imaging tests. The Canadian study reported that patients with stage II incurred higher imaging costs than those with stage I: CAD 535 per capita compared with CAD 204 per capita (2015 Canadian dollars) (Thavorn2016). The USA studies reported that the unitary cost per chest x-rays was USD 96.9, abdominal ultrasound USD 285, CT chest with contrast USD 239 to USD 510, CT abdominal-pelvis with contrast USD 305 to USD 696, body bone scan USD 658 to USD 853.8 (2013-2014 US dollars) (Louie2015, Pellet2016).</p> <p>The GDG notes that for clinical stage IIa the cost would be approximately USD 100,000 per metastasis detected and for clinical stage IIb the cost would be approximately USD 50,000 per metastasis detected.</p> <p>The GDG notes that for clinical stage IIa there may be more imaging required to pick up an additional metastasis; whereas for clinical stage IIb less imaging may be required to detect an additional metastasis (for example if an initial liver ultrasound detects metastasis you may not need to proceed to other imaging modalities).</p> <p>The costs for clinical stage IIa were judged to be large and the costs for IIb were judged to be moderate by voting: 14 moderate.</p>
Type of tests	Estimated annual variation (2001-2010)																
	Mean cost ¹ of imaging tests per patient (Euros)	Imaging utilization, % (95% CI)	Imaging-related costs, % (95% CI)														
Chest radiograph, abdominal ultrasound, bone scan, and mammograms	Remain constant at 250 €	Increase 0.1% (-0.1–0.3)	Decrease 0.1% (-0.9 to 0.6)														
CT, PET, and MRI	Increased from 350 € in 2001 to 800 € in 2010	Increase 15.7% (14.2–17.2)	Increase 19.4% (15.9–23.0)														

Direct evidence: Unitary cost and cost of detecting metastatic disease

One UK study (Barret 2009) estimated the health-care costs of detecting metastases by stage of disease and mode of imaging staging in a population of 3,398 newly diagnosed breast cancer patients during 1999 to 2007. The estimation was based on local costing taking into consideration staffing, consumable and hardware expenses. Calculations were carried out based on the observed true-positive rates and the added expense generated by false-positive imaging results.

Type of tests	Unitary cost ¹ (British Pounds)	Cost ¹ of detecting 1 patient with metastatic disease by breast cancer stage	
		II-A	II-B
Chest radiograph	80 £	200,393 £	8,492 £
Ultrasound liver	176 £		
Bone scan	184 £		
CT (chest, abdomen, and pelvis)	271 £	119,744 £	5,074 £

¹Value prices were not clearly reported (data was collected from 1999 to 2007).

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ● Low ○ Moderate ○ High ○ No included studies 	<p>Low certainty of the evidence due to indirectness, and imprecision. Costs reported in the studies may not be representative of other European settings since they were performed only in Campania, Italy or in the UK. For the UK study, in addition, value prices were not reported (data was collected from 1999 to 2007) and may not represent current costs. Also, there is imprecision in the results since the cost of each test was not reported.</p>	<p>The cost requirement evidence was based only on two studies with serious concerns regarding the indirectness and imprecision. The GDG judged that the certainty of evidence of required resources was low.</p>

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies 	No relevant economic evaluations were identified	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know 		<p>The GDG notes that increasing the burden of tests on patients for staging exams may result in increased costs to patients depending on health care coverage of diagnostic tests for patients.</p> <p>If the wait time is long for publicly-funded staging exams is long, patients may opt to pay out of pocket for accelerated staging exams, therefore reducing health equity.</p> <p>The GDG judged by consensus that the impact on health equity varies.</p>

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 		<p>The GDG judged that the acceptability varied among women. Some women may strongly desire staging exams, while other women may be distressed by undergoing staging exams.</p> <p>Additionally, the GDG notes that the acceptability will also vary among policy-makers and healthcare providers depending on their perspective on the use of staging</p>

		<p>exams.</p> <p>The GDG therefore judged by consensus that the acceptability varies.</p>
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 		<p>The GDG notes that the intervention is feasible because it is already performed in many settings. However, the GDG notes that if staging exams were more widely used there would be even more significant difficulties with costs and wait times for staging exam imaging.</p> <p>The feasibility may also depend on whether there is a screening program in a particular setting. If there is a screening program there will likely be more clinical stage I presentations, and if there is no screening program there will be more symptomatic clinical stage II presentations. Therefore, this will affect the feasibility of the use of staging exams for patients with clinical stage II breast cancer.</p>

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
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CONCLUSIONS

Recommendation

The ECIBC's Guidelines Development Group suggests against using a staging exams with imaging in women with clinical stage IIa and IIb breast cancer (conditional recommendation, low certainty of the evidence).

Justification

Overall justification

The GDG reached consensus suggesting against the intervention of staging exams using imaging for women presenting with clinical stage II breast cancer.

Detailed justification

Desirable Effects

The GDG judged that the desirable effects were small.

Undesirable Effects

The GDG judged that the undesirable effects varied. For clinical stage IIa breast cancer the undesirable effects due to false positives were small. For clinical stage IIb breast cancer the undesirable effects due to false positives were moderate.

Values

The GDG did not conduct a systematic review for values and preferences regarding diagnostic exams. The GDG notes that due to the variety of diagnostic and treatment pathways the values and preferences for each may be very heterogeneous.

Resources required

The GDG judged that the resources required for clinical stage IIa breast cancer were large and for IIb breast cancer were moderate.

Feasibility

The feasibility may vary by setting. If there is a screening program in place there will likely be more clinical stage I breast cancer presentations, and if there is no screening program there will likely be more symptomatic clinical stage II breast cancer presentations. This will affect the volume of staging exams using imaging and therefore the feasibility.

Subgroup considerations

1. For clinical stage II breast cancers, the GDG notes that there is no evidence of an increased detection rate according to hormone receptor and HER2 status, although these results might influence the decision to conduct further imaging because of the possible impact on treatment strategies.
2. The GDG also notes that age and presence of comorbidities of the patient may be a consideration in the decision of whether to conduct staging exams with imaging as this may change the choice of treatment.
3. Subgroups based on histological and marker results may impact the need to conduct staging examinations using imaging.

Implementation considerations

1. The GDG notes that a positive on imaging staging exams may be managed differently in different settings and in different body sites; if the presence of a distant metastasis on staging exams results in initiation of treatment, the impact of false positives may be greater.
2. The GDG considered the definition of 'clinical stage' as pre-pathological clinical stage, in accordance with the definition listed in the ECIBC glossary.
3. The GDG notes that there is still uncertainty with the evidence of detection rate using staging exams with imaging.
4. Consultation with colleagues during the interdisciplinary cancer treatment team meetings may be helpful in limiting the need for staging exams.
5. Education of healthcare providers to limit the use of staging exams using imaging for clinical stage IIa/IIb breast cancer.

Monitoring and evaluation

1. The GDG suggests monitoring for compliance that routine staging exams using imaging are not conducted due to the undesirable effects, including increased false positives with small desirable effects.

Research priorities

1. The GDG notes that no research evidence was identified on how people value the main outcomes. The GDG suggests additional research on how people value the main outcomes of staging exams for detection of metastases.
2. The GDG suggests further research on marker results and the implications for using staging exams using imaging.
3. Further research on the psychological effects and values and preferences for women related to the consequences of staging and non-staging approaches.