



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 18F-FDG PET-CT staging exams vs. no PET 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:	18F-FDG PET-CT staging exams
COMPARISON:	no PET staging exams
MAIN OUTCOMES:	Detection rate; False positive;
SETTING:	European Union
PERSPECTIVE:	Population (National Health System)
BACKGROUND:	<p>The main cause of death from breast cancer is distant metastases. 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. However, the risk for metastases is lower in early detected (clinical stage 1 and 2) breast cancer than in later stages (clinical stage 3). 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 psychological stress of the women, radiation (depending on the used technique) and high costs.</p>
CONFLICT OF INTEREST:	<p>Colis 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.</p>

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 main cause of death from breast cancer is distant metastases. 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. However, the risk for metastases is lower in early detected (clinical stage I and II) breast cancer than in later clinical stages (stage 3). 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 psychological stress of the women, 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>	Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	<p>The GDG agreed to divide the judgements for stage II into stage IIA and stage IIB. The studies included based the staging on T (tumour) and N (nodules) preoperatively.</p> <p>Clinical stage IIA</p> <p><u>Pooled detection rate: 50 per 1000 examinations (95% CI: 29 - 76); n/N = 20/377 (5 studies).</u></p> <p>The GDG agreed the desirable effects were small for stage IIA</p> <p>Clinical stage IIB</p> <p><u>Pooled detection rate: 141 per 1000 examinations (95% CI: 109 - 176); n/N = 62/438 (5 studies).</u></p> <p>The GDG agreed the desirable effects were moderate for stage IIB. The GDG was less sure about the downstream consequences, clinical significance, compared to stage III.</p> <p>The subgroup analysis did not find difference in the rate of distant metastases (per 1000 examined patients) at clinical stage II, between women with triple negative breast cancer (TNBC) (DR: 72.3; 95% CI: 39.2 - 115.3) and the general breast cancer population (DR 81.8; 95% CI: 49.9 -</p>
	Detection rate	Pooled detection rate: 93 per 1000 examinations (95% CI 74 - 113) n/N = 85/880	(7 RCTs) ^{1,2,3,4,5,6,7}	<div><div>⊕⊕○○</div><div>LOW^{a,b,c,d}</div></div>	
<div><div><div>1. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging; Oct 2016.</div><div>2. Sen F, Akpınar AT, Ogur U, Duman G, Tamgac F, Alper E.. The impact of PET/CT imaging performed in the early postoperative period on the management of breast cancer patients. Nucl Med Commun; 2013.</div><div>3. Riedl CC, Slobod E, Jochelson M, Morrow M, Goldman DA, Gonen M, Weber WA, Ulaner GA.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med; 2014.</div><div>4. Lebon, V., Alberini, J. L., Pierga, J. Y., Dieras, V., Jehanno, N., Wartski, M.. Rate of Distant Metastases on 18F-FDG PET/CT at Initial Staging of Breast Cancer: Comparison of Women Younger and Older Than 40 Years. J Nucl Med; Feb 2017.</div><div>5. Hogan MP, Goldman DA, Dashevsky B, Riedl CC, Gonen M, Osborne JR, Jochelson M, Hudis C, Morrow M, Ulaner GA.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. J Nucl Med; 2015.</div><div>6. Groheux D, Hindié E, Delord M, Giacchetti S, Hamy AS, de Bazelaire C, de Roquancourt A, Vercellino L, Toubert ME, Merlet P, Espié M.. Prognostic impact of (18)FDG-PET-CT findings in clinical stage III and IIB breast cancer. J Natl Cancer Inst; 2012.</div></div></div>					

7. Ulaner, G. A.,Castillo,R.,Goldman,D. A. 18F-FDG-PET/CT for systemic staging of patients with newly diagnosed ER-positive and HER2-positive breast cancer. Eur J Nucl Med Mol ; 2017.
- a. Different reference standards were used across studies some included another imaging test without histological confirmation which is likely to incorrectly classify the condition. Additional follow up were not implemented in all cases.
- b. Some studies collected its data from medical registries on retrospective designs which preclude them from implementing standard procedures and quality of data.
- c. Judgement of imprecision depends on the panel decision about the detection rate threshold which leads to change decision.
- d. Overall studies included small sample sizes, therefore confidence interval are widen.

Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)
False positive	Pooled detection rate: 0.0 per 1000 examinations (95% CI 0 - 5) n/N = 0/394	(4 RCTs) ^{1,2,3,4}	⊕⊕○○ LOW ^{a,b,c,d}

1. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging; Oct 2016.
2. Riedl, C. C., Slobod, E., Jochelson, M., Morrow, M., Goldman, D. A., Gonen, M., Weber, W. A., Ulaner, G. A.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med; Oct 2014.
3. Hogan, M. P., Goldman, D. A., Dashevsky, B., Riedl, C. C., Gonen, M., Osborne, J. R., Jochelson, M., Hudis, C., Morrow, M., Ulaner, G. A.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. J Nucl Med; Nov 2015.
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119.8) (Test heterogeneity: *p* value = 0.71).

One study did not reveal significant difference in the rate of distant metastases at clinical stages I to III between breast cancer patients less than 40 years versus those ≥40 years (*p* value=1.0).

One study with 254 patients with BC clinical stage II and III evaluated by 18FDG-PET-CT (1), 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).

The clinical impact of detecting distant metastasis (in practice moving the patient to Stage IV) can be considered on two domains:

Survival

The 5-year relative survival rate for women with breast cancer by stage is approximately:

-Stage II breast cancer is about 93%. ·

-Metastatic, or stage IV breast cancers survival rate of about 22%.

Quality of life

This domain is influenced by the change of treatment plans in each clinical stage according to the presence of distant metastases :

-Clinical stage I and II not needing adjuvant chemotherapy (HER2 positive or triple negative breast cancer < 5 mm): potentially minor change or no change. Radiotherapy might or might not be indicated to primary lesion and in single cases of oligometastases.

-Clinical stage I and II that need adjuvant chemotherapy (HER2 positive or triple negative and tumour size ≥5 mm): potentially meaningful change depending on: 1) ER/PR positive/HER2 negative breast cancer: endocrine treatment only, no chemotherapy 2) HER positive: less intense chemotherapy regime; 3) triple negative: only mono-chemotherapy instead of poly-chemotherapy. Radiotherapy might or might not be indicated to primary lesion and in single cases of oligometastases. On those

		<p>HER2+ possibly addition of Pertuzumab to the anti-HER2 therapy.</p> <p>Glycolytic activity with 18F-FDG PET/CT, tumour biology, and prognosis ((2), Systematic Review)</p> <p><i>"Maximum standardized uptake value (SUVmax) increases with the biological aggressiveness of the tumors; high-grade, hormone receptor-negative, have higher SUVmax. However, a reproducible SUVmax cutoff that would predict tumor biology has yet to be established"</i></p> <p><i>"The prognostic impact of the SUVmax of the primary tumor is controversial. Whereas some authors found no association between tumor 18F-FDG uptake and prognosis, others reported that patients with high tumor uptake had worse outcomes. Furthermore, a single and reproducible SUVmax has yet to be established"</i></p>
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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>Outcomes</div>	<div>Impact</div>	<div>No of participants (studies)</div>	<div>Certainty of the evidence (GRADE)</div>	<div>The GDG was more concerned in stage II, than in Stage III, of diagnosis of metastases that would not give symptoms in the life of a patient.</div>
	<div>Detection rate</div>	<div>Pooled detection rate: 93 per 1000 examinations (95% CI 74 - 113) n/N = 85/880</div>	<div>(7 RCTs)^{1,2,3,4,5,6,7}</div>	<div><div><div>⊕⊕○○</div><div>LOW^{a,b,c,d}</div></div></div>	<div>Other undesirable effects considered were radiation exposure and the anxiety and inconvenience for patients.</div> <div>Two studies reported false positives rates for patients in clinical stage II and III as overall, from 7.6 (Groheux 2012) to 11.8 (Groheux 2011) per 1000 examined women.</div> <div><div>Clinical stage IIa</div><div>As there was disagreement among GDG members regarding whether the effects were large or moderate, voting took place among the GDG members without conflict of interest: nine members voted for "large" effects while eight voted for "moderate".</div><div>Therefore, the undesirable effects were considered large.</div><div><div>Clinical stage IIb</div><div>As there was disagreement among GDG members</div></div></div>
<div><div>1. Ulaner, G. A., Castillo, R., Goldman, D. A., Wills, J., Riedl, C. C., Pinker-Domenig, K., Jochelson, M. S., Gonen, M.. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging; Oct 2016.</div><div>2. Sen F, Akpinar AT,Ogur U,Duman G,Tamgac F,Alper E.. The impact of PET/CT imaging performed in the early postoperative period on the management of breast cancer patients. Nucl Med Commun; 2013.</div><div>3. Riedl CC, Slobod E,Jochelson M,Morrow M,Goldman DA,Gonen M,Weber WA,Ulaner GA.. Retrospective analysis of 18F-FDG PET/CT for staging asymptomatic breast cancer patients younger than 40 years. J Nucl Med; 2014.</div><div>4. Lebon, V., Alberini, J. L., Pierga, J. Y., Dieras, V., Jehanno, N., Wartski, M.. Rate of Distant Metastases on 18F-FDG PET/CT at Initial Staging of Breast Cancer: Comparison of Women Younger and Older Than 40 Years. J Nucl Med; Feb 2017.</div><div>5. Hogan MP, Goldman DA,Dashevsky B,Riedl CC,Gonen M,Osborne JR,Jochelson M,Hudis C,Morrow M,Ulaner GA.. Comparison of 18F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma. J Nucl Med; 2015.</div></div>					

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regarding whether the effects were large or moderate, voting took place among the GDG members without conflict of interest: 2 members voted for "large". 11 members voted for "moderate" effects, three voted for "small" and one voted for "varies".

Therefore, the undesirable effects were considered moderate.

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 evidence for correct diagnosis was considered low applying a testing framework.</p> <p>The GDG had low certainty that we are making the right diagnosis but was not really certain about the downstream consequences. That is, whether these women classified as stage III, based on detection, are now receiving the appropriate treatment (ie. will they receive bisphosphonates if they have bone metastases).</p> <p>The GDG was uncertain about the effect this diagnostic test result has on treatment and the effect of this treatment (downstream consequences), so the overall certainty was judged as very low.</p>

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>The GDG agreed by consensus that there was possibly important uncertainty or variability.</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 agreed the balance of effects favours the comparison for stage IIa.</p> <p>For stage IIb there was disagreement among GDG members regarding the balance of effects so voting took place among the GDG members without conflict of interest: 3 members voted "probably favours the comparison" and 14 members voted for "does not favour either".</p> <p>Therefore, the balance of effects does not favour either for stage IIb.</p>

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>The cost of receiving PET-CT per patient with stage II breast cancer is about EUR 1 500.</p> <p>Costs informed by the GDG Cost PET-CT</p> <table><tr><th>Test</th><th>Country, year value</th><th>Setting</th><th>Cost</th></tr><tr><td>PET-CT staging*</td><td>Germany, 2017</td><td>Hospital</td><td>1987,76 Euro</td></tr><tr><td>PET alone</td><td>Germany, 2017</td><td>Hospital</td><td>1337,04 Euro</td></tr><tr><td>PET alone</td><td>Italy, 2012-2016</td><td>Hospital</td><td>1286,00 Euro</td></tr></table> <p>* including all the cost for machine, radionuclide and the work of doctors and technicians</p> <p>Resources required PET-CT</p> <table><tr><th>Resources</th><th>Cost</th></tr><tr><td>PET-CT machine</td><td>2.5 million Euro</td></tr><tr><td>Reactor to make the radionuclide</td><td>NA</td></tr><tr><td>Nuclear medicine doctor</td><td>NA</td></tr><tr><td>Radiologist</td><td>NA</td></tr><tr><td>Nurse/technician running the machine</td><td>NA</td></tr><tr><td>Medical physicist</td><td>NA</td></tr></table>	Test	Country, year value	Setting	Cost	PET-CT staging*	Germany, 2017	Hospital	1987,76 Euro	PET alone	Germany, 2017	Hospital	1337,04 Euro	PET alone	Italy, 2012-2016	Hospital	1286,00 Euro	Resources	Cost	PET-CT machine	2.5 million Euro	Reactor to make the radionuclide	NA	Nuclear medicine doctor	NA	Radiologist	NA	Nurse/technician running the machine	NA	Medical physicist	NA	<p>The cost per patient with stage II breast cancer receiving PET-CT is about EUR 1 500, in this case, compared to stage III, there are a lot more women in stage II, so the GDG agreed the costs were large.</p>
Test	Country, year value	Setting	Cost																													
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	<p>One study performed in the Netherlands (3) reported the costs associated with implementing PET and PET/CT with FES or FDG as an upfront imaging test for diagnosing metastatic breast cancer in oestrogen receptor-positive women with symptoms. The reported unitary costs were:</p> <p>CT: EUR 199</p> <p>FES-PET: EUR 1 505</p> <p>FDG-PET: EUR 1 505</p> <p>The unit prices of the tests based on tariffs of The Dutch Healthcare Authority.</p>	
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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 	Moderate certainty of the evidence. Costs reported by the study from The Netherlands is consistent with those reported by hospital registries in Germany and Italy.	The GDG agreed the certainty of the resources evidence was moderate.

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 economic evaluations were identified	No studies were included.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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<input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know	No systematic review was carried out.	The GDG agreed that equity would probably be reduced. In many countries there may be problems providing PET to these patients.
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Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	No systematic review was carried out.	<p>The GDG agreed it would probably vary. On the one hand, for policy makers it would probably not be acceptable as there are many more exams to pay.</p> <p>For women it would also vary.</p>

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input checked="" type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	No systematic review was carried out.	The GDG agreed that the feasibility would vary, mainly due to the large number of women that would have to be tested.

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

For patients with clinical stage IIa breast cancer without symptoms suggestive of metastases, the ECIBC's Guidelines Development Group (GDG) suggests against using positron emission tomography-computed tomography (PET-CT) staging exams (conditional recommendation, very low certainty of the evidence).

For patients with clinical stage IIb breast cancer without symptoms suggestive of metastases, the ECIBC's Guidelines Development Group (GDG) suggests against using positron emission tomography-computed tomography (PET-CT) staging exams (conditional recommendation, very low certainty of the evidence).

Justification

The conditional recommendation for stage IIa, is a result of a balance that favours the comparison (no staging exams) with very low certainty of the evidence, so we are not very certain as to what the benefits are. In addition there are large costs, probably reduced equity and the intervention is probably not feasible. The GDG felt that very few situations would arise that would prompt conducting a PET-CT.

The conditional recommendation for stage IIb, is a result of a balance that does not favour PET-CT, with very low certainty of the evidence. In addition, the same as in stage IIa, there are large costs, probably reduced equity and the intervention is probably not feasible.

The concern about metastases that would not give symptoms in the life of a patient increases as breast cancer stages become lower.

Subgroup considerations

The GDG agreed that for stage IIb there are more scenarios (clinical presentations) that would lead the clinician/patient to opt for doing a PET-CT (tumour grade, age).

Implementation considerations

None were considered by the GDG.

Monitoring and evaluation

None were considered by the GDG.

Research priorities

The GDG suggested the following:

- More knowledge on determining the probability of metastases that would not give symptoms in the life of a patient would improve describing the conditions for which PET-CT testing is indicated.
- Better characterisation of clinical tumour stages (stage IIa and stage IIb).

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