



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 followed by 18F-FDG PET-CT staging vs. conventional staging exams be used for patients with clinical stage III breast cancer without symptoms suggestive of metastases?

POPULATION:	patients with clinical stage III breast cancer without symptoms suggestive of metastases
INTERVENTION:	conventional staging exams followed by 18F-FDG PET-CT staging
COMPARISON:	conventional staging exams
MAIN OUTCOMES:	Additional Detection rate (negative to conventional staging exams); 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 distant 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 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>
CONFLICT OF INTEREST:	<p>Col's 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 CoI 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> <p>For more information please visit: http://ecibc.jrc.ec.europa.eu/gdg-documents</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 due to 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
<ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know 	Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	<p>61 fewer false positives (difference between false positives in PET and conventional) if all all women will undergo PET-CT</p> <p>The subgroup analysis did not find difference in the rate of distant metastases (per 1000 examined patients) at clinical stage III, between women with triple negative breast cancer (TNBC) (DR: 255.9; 95% CI: 170.8 - 350.9) to general breast cancer population (DR 338.3; 95% CI: 247.4 - 435.3) (Test heterogeneity: <i>p value</i> = 0.20)</p> <p>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 (<i>p value</i>=1.0).</p> <p>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. One 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 (<i>p</i> =0.42).</p> <p>The clinical impact of detecting distant metastasis (in practice moving the patient to Stage IV) can be considered</p>
	<p>Additional Detection rate (negative to conventional staging exams)</p>	<p>Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382</p>	<p>(7 RCTs)^{1,2,3,4,5,6,7}</p>	<p>⊕⊕⊕○ MODERATE^{a,b}</p>	
	<p>Detection rate</p>	<p>*18F-FDG PET/CT: 301 per 1,000 examinations (95% CI: 225 - 382); n/N = 180/627. *Combined conventional test: 157 per 1,000 examinations (95% CI 125 - 192); n/N = 74/465.</p>	<p>(8 RCTs)^{10,11,12,13,14,4,8,9,c}</p>	<p>⊕○○○ VERY LOW^{a,b,d}</p>	
	<ol style="list-style-type: none"> Reddy Akepati NK, Abubakar ZA,Bikkina P.. Role of 18F-Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography Scan in Primary Staging of Breast Cancer Compared to Conventional Staging.. Indian J Nucl Med.; 2018. Krammer J, Schnitzer A,Kaiser CG,Buesing KA,Sperk E,Brade J,Wasgindt S,Suetterlin M,Schoenberg SO,Sutton EJ,Wasser K.. (18) F-FDG PET/CT for initial staging in breast cancer patients - Is there a relevant impact on treatment planning compared to conventional staging modalities?. Eur Radiol. ; 2015. Ng SP, David S,Alamgeer M,Ganju V.. Impact of Pretreatment Combined (18)F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging on Radiation Therapy Treatment Decisions in Locally Advanced Breast Cancer.. Int J Radiat Oncol Biol Phys.; 2015. 				

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(1)(8)F-FDG PET/CT provides powerful prognostic stratification in the primary staging of large breast cancer when compared with conventional explorations. Eur J Nucl Med Mol Imaging; Mar 2014. 8. Groheux, D., Hindie, E., Delord, M., Giacchetti, S., Hamy, A. S., de Bazelaire, C., de Roquancourt, A., Vercellino, L., Toubert, M. E., Merlet, P., Espie, M.. Prognostic impact of (18)FDG-PET-CT findings in clinical stage III and IIB breast cancer. J Natl Cancer Inst; Dec 19 2012. 9. 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. 10. 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. 11. 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. 12. 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. 13. Carkaci S, Macapinlac HA, Cristofanilli M, Mawlawi O, Rohren E, Gonzalez Angulo AM, Dawood S, Resetskova E, Le-Petross HT, Yang WT.. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data.. J Nucl Med; 2009. 14. 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. <ol style="list-style-type: none"> a. Different reference standards were used accross 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 a retrospective design which preclude them from implementing standard procediments and quality of data. c. Seven studies included in the pooled analysis for 18F-FDG PET/CT, and 5 studies for conventional tests (see ref in the technical report for conventional tests). d. Event rates to assess 18F-FDG PET/CT and conventional tests were inderectly compared. Studies differ in the number of patients, level of health care and time of follow-up. 	<p>on two domains:</p> <p><u>Survival</u></p> <p>The 5-year relative survival rate for women with breast cancer by stage is approximately:</p> <ul style="list-style-type: none"> -Stage III breast cancer is about 72% -Metastatic, or stage IV breast cancers survival rate of about 22%. <p><u>Quality of life</u> This domain is influenced by the change of treatment plans in each clinical stage according to the presence of distant metastases:</p> <ul style="list-style-type: none"> -Clinical stage III: 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 HER2+ possibly addition of Pertuzumab to the anti-HER2 therapy. <p>PET/CT impact after Conventional Tests (Cochet 2013)</p> <p>The PET/CT results were believed to have high impact on 16 patients (11%). This group included four patients (3 %) for whom only palliative therapy was initially considered and then received curative treatment after PET/CT suggested absence of distant lesions</p> <p>Glycolytic activity with 18F-FDG PET/CT, tumor biology, and prognosis (Aroztegui 2017, 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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Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
False positive	*18F-FDG PET/CT (pooled FP): 7 per 1,000 examinations (95% CI: 0 - 24); n/N = 3/328. *Combined conventional tests: 68 per 1,000 examinations (95%CI 13 – 156) n/N= 88/792. ^a	(4 RCTs) ^{1,2,3,4,b}	⊕○○○ VERY LOW ^{c,d,e,f,g}

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.
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- a. Two studies reported false positives rates for patients in stage II/III as overall, from 7.6 (Groheux 2012) to 11.8 (Groheux 2011) per 1000 examined women.
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 - e. Event rates to assess 18F-FDG PET/CT and conventional tests were indirectly compared. Studies differ in the number of patients, level of health care and time of follow-up.
 - f. Judgement of imprecision depends on the panel decision about the detection rate threshold which lead to change decision.
 - g. Overall studies included small sample sizes, therefore confidence interval are widen.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE				ADDITIONAL CONSIDERATIONS
<div>○ Large</div> <div>○ Moderate</div> <div>○ Small</div> <div>● Trivial</div> <div>○ Varies</div> <div>○ Don't know</div>	Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)	<div>The proportion of metastases that would not give symptoms in the life of a patient will likely be very small although it cannot be estimated exactly considered less important given the limited impact on treatment & management decisions.</div> <div>Radiation is a possible adverse effect and radionuclide exposure.</div> <div>Carrying two tests (conventional staging and PET) compared to one (only conventional staging) can be considered an undesirable effect (extra examinations and additional radiation).</div>
	Additional Detection rate (negative to conventional staging exams)	Pooled additional detection rate: 205 per 1,000 examinations (95% CI 154 - 261) n/N = 19/382	(7 RCTs) ^{1,2,3,4,5,6,7}	⊕⊕⊕○ MODERATE ^{a,b}	
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- 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.
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False positive	*18F-FDG PET/CT (pooled FP): 7 per 1,000 examinations (95% CI: 0 - 24); n/N = 3/328. *Combined conventional tests: 68 per 1,000 examinations (95%CI 13 – 156) n/N= 88/792. ^a	(4 RCTs) ^{1,2,3,4,b}	⊕○○○ VERY LOW ^{c,d,e,f,g}

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	<p>(see ref in the technical report for conventional tests).</p> <ul style="list-style-type: none"> c. Different reference standards were used accross 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. d. Some studies collected its data from medical registries on a retrospective design which preclude them from implementing standard procediments and quality of data. e. Event rates to assess 18F-FDG PET/CT and conventional tests were inderectly compared. Studies differ in the number of patients, level of health care and time of follow-up. f. Judgement of imprecision depends on the panel decision about the detection rate threshold which lead to change decision. g. Overall studies included small sample sizes, therefore confidence interval are widen. 	
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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 evidence for correct diagnosis was considered moderate applying a testing framework.</p> <p>The GDG had moderate 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 low.</p>

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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<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 		
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>PET/CT</p> <p>One study performed in the Netherlands ((1)) 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: 199 €</p> <p>FES-PET: 1.505 €</p> <p>FDG-PET: 1.505 €</p> <p>The unit prices of the tests based on tariffs of The Dutch Healthcare Authority.</p> <p>Costs informed by the GDG</p>	<p>The cost per patient with Stage II breast cancer receiving PET- CT is about EUR 1500.</p> <p>The cost per patient receiving conventional testing is about EUR 300 to 500, but women in both intervention and comparison arm receive conventional testing.</p> <p>Total cost difference is the additional PET in the intervention arm which is EUR 1500.</p> <p>Savings might result from more appropriate treatment.</p> <p>As there was disagreement among GDG members regarding whether the costs were large or moderate, voting took place among GDG members without conflict of interest:</p> <p>11 members voted for "moderate costs" and six members voted for "large costs".</p>

Cost PET-CT

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

* including all the cost for machine, radionuclide and the work of doctors and technicians

Resources required PET-CT

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

Conventional tests

Direct evidence: Mean cost and utilization

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.

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)

¹Prices were reported in 2011 Euros value.

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
		III
Chest radiograph	80 £	4,021 £
Ultrasound liver	176 £	
Bone scan	184 £	
CT (chest, abdomen, and pelvis)	271 £	2,405 £

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 	Have direct information from hospitals in Europe.	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
<ul style="list-style-type: none">○ Reduced● Probably reduced○ Probably no impact○ Probably increased○ Increased○ Varies○ 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.

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	No systematic review was carried out.	The GDG agreed it was probably acceptable. The main concern for acceptability would be payers.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none">○ No○ Probably no○ Probably yes○ Yes	No systematic review was carried out.	The GDG agreed the feasibility would vary.

<ul style="list-style-type: none"> ● Varies ○ Don't know 		
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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 III breast cancer without symptoms suggestive of metastases, the ECIBC's Guidelines Development Group (GDG) suggests using conventional staging followed by positron emission tomography-computed tomography (PET-CT) over conventional staging alone (conditional recommendation, low certainty of the evidence).

Justification

The conditional recommendation is a result of a balance of effects that probably favours the intervention (conventional staging followed by PET-CT) but has moderate costs and probably reduces equity.

Subgroup considerations

None were considered by the GDG.

Implementation considerations

None were considered by the GDG.

Monitoring and evaluation

None were considered by the GDG.

Research priorities

None were considered by the GDG.

REFERENCES SUMMARY

1. Koleva-Kolarova RG, Greuter MJ, van Kruchten M, Vermeulen KM, Feenstra T, Buskens E, et al.. The value of PET/CT with FES or FDG tracers in metastatic breast cancer: a computer simulation study in ER-positive patients.. Br J Cancer.; 2015.