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

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QUESTION	
Should contrast-enhanced spectral mammography vs. magnetic resonance imaging be used in assisting surgical treatment planning in women with histologically confirmed invasive breast cancer?	
POPULATION:	women with histologically confirmed invasive breast cancer
INTERVENTION:	contrast-enhanced spectral mammography
COMPARISON:	magnetic resonance imaging
PURPOSE OF THE TEST:	
LINKED TREATMENTS:	
ANTICIPATED OUTCOMES:	CESM triggered treatment change (from breast conservative to mastectomy or from unilateral to bilateral mastectomy rate); Proportion of re-operation after breast conservative surgery (BCS) (re-excision or conversion to mastectomy); Proportion of positive margins after BCS; Mastectomy; Disease-free survival (inferred from loco-regional recurrence); Quality of life (inferred from BCS as initial surgery); Direct adverse events; Test accuracy outcomes.
SETTING:	European Union
PERSPECTIVE:	Population (National Health System)
BACKGROUND:	Breast cancer is the most common cause of death among women. In patients with a biopsy proven invasive breast cancer, additional imaging methods are used in some cases (i. e. defined by tumor type) to decide about the appropriate surgical therapy. At present, two different imaging methods for measuring the extent and also for the proof or exclusion of multicentricity and multifocality are used. Both methods share the underlying principle that tumor tissue has an increased uptake of contrast agent due to hypervascularization. The most widely used method is gadolinium enhanced magnetic resonance imaging (MRI) which does not use ionizing radiation. The contrast agent (gadolinium-containing) is applied during the examination and dynamics of the contrast enhancement are measured in several series to distinguish between benign and malignant findings. Also the shape of the lesion is interpreted. The other technique called contrast enhanced spectral mammography (CESM) uses ionizing radiation and an iodine-containing contrast agent. Two sets of mammography images are taken from each view of each breast after the application of the contrast agent (static examination) a set of low dose images is taken with an energy below the „k-level“ for iodine (k-level means the applied energy dose (kilovolt) when iodine is visible in x-ray images) and a set of high dose images is taken above the k-level of iodine. The low dose image shows the tissue structures without the already applied contrast agent, whereas the high dose image shows the breast tissue and the contrast agent uptaking lesions. These images are then subtracted and a set of images with only the contrast enhancing lesion is calculated and visualized. Afterwards the size of the lesion, multifocality and multicentricity can be assessed. It seems important to compare both methods regarding the possible change of surgical treatment. CESM is regarded as less

	expensive, quicker in examination and reading time. MRI does not use radiation and is at present more commonly available. Both methods use contrast agents with different adverse effects. The objective of this question is, if CESM instead of MRI should be used in women with biopsy proven invasive breast cancer for surgical treatment planning.
CONFLICT OF INTEREST:	Management of Conflicts of Interest (CoI): CoIs for all Guidelines Development Group (GDG) members were assessed and managed by the Joint Research Centre (JRC) following an established procedure in line with European Commission 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 was not allowed to vote due to the established rules for external experts. For more information please visit https://healthcare-quality.jrc.ec.europa.eu/discover-ecibc/governance/ecibc-working-groups

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Breast cancer is the most common cause of death among women. In patients with a biopsy proven invasive breast cancer, additional imaging methods are used in some cases (i. e. defined by tumor type) to decide about the appropriate surgical therapy. At present, two different imaging methods for measuring the extent and also for the proof or exclusion of multicentricity and multifocality are used. Both methods share the underlying principle that tumor tissue has an increased uptake of contrast agent due to hypervascularization. The most widely used method is gadolinium enhanced MRI which does not use ionizing radiation. The contrast agent (gadolinium-containing) is applied during the examination and dynamics of the contrast enhancement are measured in several series to distinguish between benign and malignant findings. Also, the shape of the lesion is interpreted. The other technique called CESM (contrast enhanced spectral mammography) uses ionizing radiation and an iodine-containing contrast agent. Two sets of mammography images are taken from each view of each breast after the application of the contrast agent (static examination) a set of low dose images is taken with an energy below the „k-level“ for iodine (k-level means the applied energy dose (kilovolt) when iodine is visible in x-ray images) and a set of high dose images is taken above the k-level of iodine. The low dose image shows the tissue structures without the already applied contrast agent, whereas the high dose image shows the breast tissue and the contrast agent uptaking lesions. These images are then subtracted and a set of images with only the contrast enhancing lesion is calculated and visualized. Afterwards the size of the lesion, multifocality and multicentricity can be assessed. It seems important to compare both methods regarding the possible change of surgical treatment. CESM is regarded as less expensive, quicker in examination and reading time. MRI does not use radiation and is at present more commonly available. Both methods use contrast agents with different adverse effects.	It seems important to compare both methods regarding the possible change of surgical treatment. CESM is regarded as less expensive, quicker in examination and reading time. MRI does not use radiation and is at present more commonly available. Both methods use contrast agents with different adverse effects. The objective of this question is, if CESM instead of MRI should be used in women with biopsy proven invasive breast cancer for surgical treatment planning.

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ● Accurate ○ Very accurate ○ Varies ○ Don't know	**Index lesions** **Outcomes** / **Impact** / **№ of participants (studies)** / **Certainty of the evidence (GRADE)** Size correlation — Mean absolute difference to pathology: *CESM: 10.1 mm (95%CI 6.95 to 13.23) *MRI: 7.9 mm (95%CI 5.34 to 10.48). — (1 OBS)[1] — ⨁⨁◯◯ LOW[a] 1. Fallenberg EM1, Schmitzberger FF2,Amer H2,Ingold-Heppner B3,Balleyguier C4,Diekmann F5,Engelken F2,Mann RM6,Renz DM7,Bick U2,Hamm B2,Dromain C4.. Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multi-reader evaluation.. Eur Radiol; 2017 . a. This number includes only ipsilateral breast lesions (multicentric or multifocal). b. Only one study informed this outcome included a total of 52 patients, which make the results highly imprecise. **Additional lesions (multicentric or multifocal)** *Accuracy* **Test result** / **Number of results per 1000 patients tested (95% CI)** / **Prevalence 21%** / **Contrast-enhanced spectral mammography** / **MRI** / **№ of participants (studies)** / **Certainty of the evidence (GRADE)** True positives patients with women with histologically confirmed invasive breast cancer — 82 (63 to 101) — 103 (84 to 124) — 149 (1)[a] — ⨁⨁⨁◯ MODERATE[b] 21 fewer TP in Contrast-enhanced spectral mammography	**Digital mamography (additional lesions)** Sensitivity: 17% Specificity: 95% (Fallenberg 2017) **Digital mamography (index size correlation)** Mean absolute diffrence: 12.22 mm (95%CI 8.97 to 15.47). (Fallenberg 2017)

False negatives patients incorrectly classified as not having women with histologically confirmed invasive breast cancer	128 (109 to 147)	107 (86 to 126)		
	21 more FN in Contrast-enhanced spectral mammography			
True negatives patients without women with histologically confirmed invasive breast cancer	743 (624 to 782)	695 (553 to 758)	149 (1)[a]	⨁⨁⨁◯ MODERATE[b]
	48 more TN in Contrast-enhanced spectral mammography			
False positives patients incorrectly classified as having women with histologically confirmed invasive breast cancer	47 (8 to 166)	95 (32 to 237)		
	48 fewer FP in Contrast-enhanced spectral mammography			

a. The numbers represent the number of lesions included in the analysis instead of the number of patients.
b. The results are imprecise due to the low number of lesions/patients included.

Detection rate

Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)
Additional findings (multicentric and multifocal)	Detection rate (over number of patients): *CESM: 17% (95%CI: 8% to 30%) *MRI 29% (95%CI: 17% to 43%)	(1 OBS)[1]	⨁⨁◯◯ LOW[a,b]

1. Jochelson MS, Dershaw DD,Sung JS,Heerdt AS,Thornton C,Moskowitz CS,Ferrara J,Morris EA.. Bilateral contrast-enhanced dual-energy digital mammography: feasibility and comparison with conventional digital mammography and MR imaging in women with known breast carcinoma. Radiology; 2013 .

a. One study (Jochelson) did not included follow-up for patients and then for additional lesions there was a risk of confirmation bias as small resection was provided if no evidence of additional findings.

b. Only one study reported detection rate over a low number of patients (n=52), and did not included a clinical

	follow-up (Jochelson). *False positive* **Outcomes** / **Impact** / **№ of participants (studies)** / **Certainty of the evidence (GRADE)** False positive findings — Number of false positive findings (per patients): *CESM: 4% (95% CI 0% to 13%) *MRI: 15% (95%CI 7% to 28%). [2] — (1 OBS)[1] — ⨁⨁◯◯ LOW[b] 1. Fallenberg EM1, Schmitzberger FF2,Amer H2,Ingold-Heppner B3,Balleyguier C4,Diekmann F5,Engelken F2,Mann RM6,Renz DM7,Bick U2,Hamm B2,Dromain C4.. Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multi-reader evaluation.. Eur Radiol; 2017. a. Only on study informed this outcome with 70 index lesions from 155 patients, the results were imprecise and therefore it was considered asBserious concern on this domain.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	No evidence identified for clinical outcomes.	Considering the less false positive with CESM, GDG agreed that the desirable effects are moderate. **Adverse reactions to contrast material**. Iodinated contrast used in CESM tests is less hazardous than the gadolidium contrast used in MRI. Both, the differences in the frequency of adverse events, as well as the overall frequency, are small (Lewin, 2018).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	No evidence identified for clinical outcomes.	GDG considered as undesirable effects the higher number of false negatives with CESM, the higher radiation dose and possible impact on kidney and thyroid. As consensus was not reached, voting was conducted among the GDG members to judge undesirable effects: 10 members voted “small”, 7 members voted “moderate”.

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		The certainty of the evidence is low.

Certainty of the evidence of test's effects

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence was identified	

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High	No research evidence was identified	A systematic review about the role of preoperative MRI versus no-MRI in all breast cancer histology suggested an unfavourable harm-benefit ratio for routine use of preoperative MRI in the management of breast cancer

● No included studies		(MRI significantly increased mastectomy rates - adjusted OR, 1.51, P < 0.001-) (Houssami 2013). [see recommendation on peri-operative MRI]

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence was identified	

Certainty of effects

What is the overall certainty of the evidence of effects of the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		Overall certainty not determined, the GDG focused on certainty of the evidence about test accuracy. This is true for both the index and the comparison test.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	No research evidence was identified	The GDG judged that there may be possibly important uncertainty or variability in how much women would value the main outcomes. Better mastectomy and reconstructive surgery may change the values placed on it, but conservative surgery will be preferred by others. As consensus was not reached, voting was conducted among the GDG members to judge values: 12 members voted “possibly important”, 5 members voted “probably no important”, 1 member voted “no important uncertainty”.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ 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		As consensus was not reached, voting was conducted among the GDG members to judge the balance of effects: 9 members voted "probably favours the intervention", 8 members voted "does not favour either", 1 member voted "probably favours the comparison".

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	**CESM is less expensive** than MRI due to: 1) Lower equipment cost. The price of an MRI machine is 815,000 USD (including coils, annual maintanence, and injector). The cost of a 2D mammography unit with CESM is 435,000 USD (with annual maintenance and injector) (1). 2) Shorter examination time: CESM acquisition lasts approximately 10 minutes, whereas MRI requires 30–60 minutes. As in MRI, an additional 10–15 minutes is required for contrast injection (1). 3) Sedation is not needed. Potential savings for the 1–15% of patients who need sedation during MRI because of associated claustrophobia (1). 4) Lower reading time. MRI requires 3–10 minutes for interpretation, whereas CESM study can be interpreted in 1–2 minutes (1).	The device for CESM is relatively inexpensive, but it is not available on all devices. MRI machine, its contract agent and breast dedicated coils are more expensive than CESM. More training required for MRI. The GDG judged that there are moderate savings with CESM.

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies	Low certainty of the evidence due to risk of bias and indirectness. The study of Patel et al (1) was a descriptive study that did not consider the consequences of the test. The reported costs were observed in the USA in 2015 only for the Medicare perspective.	

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ 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
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No research evidence was identified	On the basis of availability and the policy of reimbursement. E.g. in Germany a preoperative MRI is not reimbursed; CESM may be cheaper.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes	No research evidence was identified	CESM may be more acceptable because of the invasiveness but others may not want more radiation. In case of an already diagnosed breast cancer the radiation dose on the breast with the cancer is negligible, because

○ Varies ○ Don't know		there will be postsurgical radiation therapy anyway in almost all cases. Direct undesirable consequences of MRI may be less important if the supposed diseases are more severe. CESM is less expensive (policy makers) but more referrals to other centers because of availability but this depends on the availability. Patients have to wait longer for MRI making CESM more acceptable (this may affect all stakeholders). As consensus was not reached, voting was conducted among the GDG members to judge acceptability: 12 members voted “probably yes”, 3 members voted “yes”, 2 members voted “varies”, 1 member voted “probably no”.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified	Many existing mammography units can be upgraded to include CESM capabilities. CESM can be implemented without the space requirements of an MRI magnet. CESM can be used in women with pace makers, MRI not. As consensus was not reached, voting was conducted among the GDG members to judge feasibility: 12 members voted “probably yes”, 4 members voted “yes”, 2 members voted “varies”.

SUMMARY OF JUDGEMENTS

JUDGEMENT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	**Accurate**	Very accurate		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 THE EVIDENCE OF TEST ACCURACY	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF EFFECTS	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
○	○	○	●	○

CONCLUSIONS

Recommendation

In women with histologically confirmed invasive breast cancer, the ECIBC's Guidelines Development Group (GDG) suggests using contrast-enhanced spectral mammography (CESM) over magnetic resonance imaging (MRI) to assist in surgical treatment planning (conditional recommendation, low certainty of the accuracy evidence).

Justification

The differences in health benefits and harms were small but tended to favour CESM, other criteria may be more important such as costs and acceptability and feasibility issues.

Subgroup considerations

E.g. women with Pace Makers who can't have an MRI.

Pre-menopausal women should be informed about the feasibility of carrying out the MRI in the post-ovulation phase of their cycle

Implementation considerations

The GDG discussed MRI being currently the test of choice for certain women and settings. Use of CESM will reduce the bottle neck of MRI availability for these patients (would be urgent MRIs given that they have to be done before surgery).

As for any conditional recommendation values and preferences and shared decision making (possibly decision aids) should be taken into account.

Monitoring and evaluation

Overuse of CESM/MRI should be monitored (increase in referral because of easy of conduct of test).

Research priorities

Better research on accuracy and patient impact.

Subtypes of breast cancer with CESM especially regarding the likelihood of multicentricity or multifocality.

REFERENCES SUMMARY

1. Patel BK, Gray RJ,Pockaj BA.. Potential Cost Savings of Contrast-Enhanced Digital Mammography.. AJR Am J Roentgenol; 2017.

Evidence profile

Healthcare question	Should contrast-enhanced spectral mammography vs. magnetic resonance imaging be used as additional imaging method in assisting surgical treatment planning in women with histologically confirmed invasive breast cancer?
Date	July 2018
Authors	Guidelines Development Group (GDG): Mariangela Autelitano, Bettina Borisch, Mireille Broeders, Xavier Castells, Edoardo Colzani, Jan Daneš, Stephen Duffy, Patricia Fitzpatrick, Markus Follmann, Livia Giordano, Paolo Giorgi Rossi, Axel Gräwingholt, Solveig Hofvind, Lydia Ioannidou-Mouzaka, Susan Knox, Miranda Langendam, Annette Lebeau, Helen Mcgarrigle, Lennarth Nyström, Elsa Pérez Gómez, Cecily Quinn, Holger Schünemann, Alberto Torresin, Ruben Van Engen, Cary Van Landsveld-Verhoeven, Sue Warman, Kenneth Young. Systematic Review team: Carlos Canelo-Aybar, Margarita Posso, David Rigau, Ivan Solá, Pablo Alonso-Coello. JRC Healthcare Quality team: Elena Parmelli, Zuleika Saz-Parkinson.

Contrast-enhanced spectral mammography		**Magnetic resonance imaging**	
Sensitivity	0.39 (95% CI: 0.30 to 0.48)	Sensitivity	0.49 (95% CI: 0.40 to 0.59)
Specificity	0.94 (95% CI: 0.79 to 0.99)	Specificity	0.88 (95% CI: 0.70 to 0.96)

Prevalence	21%	0%

Outcome	**Nº of studies (Nº of patients)**	**Study design**	**Factors that may decrease certainty of evidence**					**Effect per 1,000 patients tested**				**Test accuracy CoE**
								pre-test probability of 21%		pre-test probability of 0%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Contrast-enhanced spectral mammography	Magnetic resonance imaging	Contrast-enhanced spectral mammography	Magnetic resonance imaging	
True positives (patients with women with histologically confirmed invasive breast cancer)	1 studies 149 patients [a]	cross-sectional (cohort type accuracy study) [1]	not serious	not serious	not serious	serious [b]	none	82 (63 to 101)	103 (84 to 124)	0 (0 to 0)	0 (0 to 0)	⨁⨁⨁◯ MODERATE
								21 fewer TP in contrast-enhanced spectral mammography		**0 fewer TP in contrast-enhanced spectral mammography**		
False negatives (patients incorrectly								128 (109 to 147)	107 (86 to 126)	0 (0 to 0)	0 (0 to 0)	
								21 more FN in contrast-enhanced spectral		**0 fewer FN in contrast-enhanced spectral mammography**		

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested				Test accuracy CoE
								pre-test probability of 21%		pre-test probability of 0%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Contrast-enhanced spectral mammography	Magnetic resonance imaging	Contrast-enhanced spectral mammography	Magnetic resonance imaging	
classified as not having women with histologically confirmed invasive breast cancer)								**mammography**				
True negatives (patients without women with histologically confirmed invasive breast cancer)	1 studies 149 patients [a]	cross-sectional (cohort type accuracy study) [1]	not serious	not serious	not serious	serious [b]	none	743 (624 to 782)	695 (553 to 758)	940 (790 to 990)	880 (700 to 960)	⨁⨁⨁◯ MODERATE
								48 more TN in contrast-enhanced spectral mammography		**60 more TN in contrast-enhanced spectral mammography**		
False positives (patients incorrectly classified as having women with histologically confirmed invasive breast cancer)								47 (8 to 166)	95 (32 to 237)	60 (10 to 210)	120 (40 to 300)	
								48 fewer FP in contrast-enhanced spectral mammography		**60 fewer FP in contrast-enhanced spectral mammography**		

Explanations

a. The numbers represent the number of lesions included in the analysis instead of the number of patients.

b. The results are imprecise due to the low number of lesions/patients included.

References

1. Fallenberg EM1, Schmitzberger FF2,Amer H2,Ingold-Heppner B3,Balleyguier C4,Diekmann F5,Engelken F2,Mann RM6,Renz DM7,Bick U2,Hamm B2,Dromain C4.. Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multi-reader evaluation.. Eur Radiol; 2017.

Bibliography

Evidence of effects

Fallenberg EM, Schmitzberger FF, Amer H,Ingold-Heppner B,Balleyguier C,Diekmann F et al. Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multi-reader evaluation. Eur Radiol. 2017 Jul;27(7):2752-2764.

Jochelson MS, Dershaw DD,Sung JS,Heerdt AS,Thornton C,Moskowitz CS et al. Bilateral contrast-enhanced dual-energy digital mammography: feasibility and comparison with conventional digital mammography and MR imaging in women with known breast carcinoma Radiology. 2013 Mar;266(3):743-51.

Economic evidence

Patel BK, Gray RJ,Pockaj BA.. Potential Cost Savings of Contrast-Enhanced Digital Mammography. AJR Am J Roentgenol; 2017.