



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 10% or more of cells showing oestrogen receptor positivity vs. 1% or more be used for a threshold to provide endocrine therapy in women with invasive breast cancer?

POPULATION:	women with invasive breast cancer
INTERVENTION:	10% or more of cells showing oestrogen receptor positivity
COMPARISON:	1% or more
MAIN OUTCOMES:	Overall survival; disease free survival; direct response to endocrine therapy (defined, according to the World Health Organization criteria, as complete response, partial response, no change, or progressive disease); adverse effects of endocrine therapy, and; health-related quality of life.
SETTING:	
PERSPECTIVE:	
BACKGROUND:	<p>The hormone receptor status (oestrogen receptor (ER) and/or progesterone receptor (PR) status) of an invasive breast carcinoma is a strong predictive marker of likely tumour response to endocrine therapy (1, 2). Approximately 80% of invasive breast carcinomas are hormone receptor positive (3). The majority of hormone receptor positive breast tumours are ER positive. A small percentage of ER negative tumours are PR positive and may benefit from endocrine therapy but there is uncertainty about the benefits of endocrine therapy in these patients and if this response depends on the level of PR positivity.</p> <p>All invasive breast carcinomas are tested for ER status as standard of care. Many centres/countries also test tumours for PR status as a routine. Some centres test ER negative tumours only for PR status.</p> <p>The optimal method tumour testing for hormone receptor status is by immunohistochemistry on formalin- fixed, paraffin-embedded tissue using monoclonal antibodies (4, 5, 6, 7) . ER and PR testing is usually performed on the core biopsy specimen which facilitates early treatment planning, in particular identification of patients who may be candidates for neoadjuvant therapy. ER and PR studies may be repeated on the operative excision specimen and there is a strong correlation with the results obtained on core biopsy.</p> <p>It is recommended that ER and PR testing is carried out according to a quality assured testing protocol that complies with recommended test validation and internal and external quality assurance procedures (8).</p> <p>Historically different methods of scoring ER and PR status were used including assessment of strength and percentage of tumour cell positivity on IHC staining.</p> <p>Cut off levels of IHC staining, applied for categorising a tumour as hormone receptor positive, have changed from 10% to 5% to 1% at the present time (8). As such, patients with breast tumours that show positive IHC staining for ER and/or PR in at least 1% of tumour cells are considered likely to benefit from endocrine therapy. However, immunohistochemistry has evolved in the last decades. The</p>

	established retrieval methods, antibodies and detection systems have increased the sensitivity of immunohistochemistry.
CONFLICT OF INTEREST:	Management of Conflicts of Interests (Col): Cols of 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 Col disclosure. Consequently, for this particular question, no GDG members were recused from voting except for Miranda Langendam, as external expert, who was 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 	Endocrine therapy may be associated with side effects depending on the drug administered and menopausal status of the patient. Accuracy in predicting likely response to endocrine therapy is clearly important in designing the appropriate treatment regime for individual patients.	The GDG prioritised this question for the ECIBC.

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>In addition Yi 2014 (9) observed that:</p> <p>a) patients with tumours at 1%–9% ER positivity had worse recurrence-free survival than did patients with tumours at ≥10% positivity when both groups received treatment (p=0.0005), and when neither received treatment (p=0.0003), and;</p> <p>b)-patients with tumours at 1%–9% ER positivity had worse overall survival than did patients with tumours at ≥10% positive when both groups received treatment (p<0.0001), and when neither received treatment (p=0.002).</p> <p>The GDG notes that a trivial difference between receptor status and endocrine treatment between 1% and 10% thresholds was observed in the Honma 2014 study(10). Due to the measurement of cumulative threshold in the Honma study, the GDG notes that interpretation of the hazard ratio between 1 and 10% is limited.</p>
	Recurrence free survival (Honma 2014)	(Honma 2014): tamoxifen vs no endocrine treatment on 5 years recurrence-free survival in ER positive cases according to different thresholds. The following adjusted HR (95%CI) were observed: • At >0% threshold: 0.633 (0.426; 0.934) • At 1% threshold:	(1 observational study) ^{1,a}	⊕○○○ VERY LOW ^{b,c,d}	

	0.649 (0.431; 0.973) • At 10% threshold: 0.671 (0.434; 1.039) • At 33% threshold: 0.555 (0.342; 0.898) • At 67% threshold: 0.472 (0.272; 0.816).			The GDG also considered that a small number of patients were included in the Honma 2014 study that had ER positivity values >0% and ≤67%(10). The GDG judged by consensus that there are no desirable effects of the intervention.
Recurrence free survival (Yi 2014)	(Yi 2014): patients with ER-positive tumours at 1-9% receiving endocrine treatment vs patients with ER-negative tumours (i.e. <1%) who did not receive treatment; no difference was observed (p=0.7) – see Figure 1 below. ^e	(1 observational study) ^{2,a}	⊕○○○ VERY LOW ^{f,g}	
Overall survival (Yi 2014) (OS)	(Yi 2014): patients with 1-9% ER-positive tumours receiving endocrine treatment had worse survival rates than patients with ER-negative tumours (i.e. <1%) who did not receive treatment (p=0.04) - see Figure 2 below. ^h	(1 observational study) ^{2,a}	⊕○○○ VERY LOW ^{f,g}	
Direct response to endocrine therapy (defined according to World Health Organization criteria as complete response, partial response, no change, or progressive disease) (Direct response to endocrine therapy)	No studies identified	(0 studies)	-	
Adverse effects of endocrine therapy (Adverse effects)	No studies identified	(0 studies)	-	

Health-related quality of life	No studies identified	(0 studies)	-
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1. Honma, N., Horii, R., Iwase, T., Saji, S., Younes, M., Ito, Y., Akiyama, F.. Proportion of estrogen or progesterone receptor expressing cells in breast cancers and response to endocrine therapy. Breast; Dec 2014.
2. Yi, M., Huo, L., Koenig, K. B., Mittendorf, E. A., Meric-Bernstam, F., Kuerer, H. M., Bedrosian, I., Buzdar, A. U., Symmans, W. F., Crow, J. R., Bender, M., Shah, R. R., Hortobagyi, G. N., Hunt, K. K.. Which threshold for ER positivity? a retrospective study based on 9639 patients. Ann Oncol; May 2014.
 - a. Retrospective cohort study
 - b. Honma 2014 presented serious risk of bias due to the nature of the study design (retrospective cohort study), which resulted in increased risk of bias in terms of the selection of participants to the study and in terms of the classification of interventions.
 - c. Wide confidence intervals. Number of events not reported.
 - d. Honma 2014 did not report direct comparisons of thresholds $\geq 1\%$ vs $\geq 10\%$, but rather conducted subgroup analyses according to different thresholds of the comparison treatment vs no treatment. Treatment effect according to the different subgroups (1-9%; 10-33%; 33-67%) was not reported either. In addition available evidence is exclusively based on a single drug (tamoxifen). The expert group should agree on whether these issues result or not in serious indirectness.
 - e. In addition Yi 2014 observed that patients with tumours at 1%–9% ER positivity had worse recurrence-free survival than patients with tumours at $\geq 10\%$ positivity, when both groups received treatment ($p=0.0005$), and when neither received treatment ($p=0.0003$).
 - f. Yi 2014 presented serious risk of bias due to confounding: There are important differences between patients with 1-9% positivity (with a more advanced disease, more likely to receive neoadjuvant chemotherapy, and more likely to have HER-2 positive and grade III disease). The Kaplan-Meier curves used to provide the relevant information for this PICO did not adjust for these differences.
 - g. Indirect comparison: Yi 2014 did not provide results for patients with 1-9% ER+ on tamoxifen versus no endocrine treatment. Instead, they compared 1-9% ER+ patients who received endocrine treatment vs ER negative patients who did not receive treatment, and also compared 1-9% vs $\geq 10\%$ ER+ in subgroups of patients receiving and not receiving endocrine treatment.
 - h. In addition Yi 2014 observed that patients with tumours at 1%–9% ER positivity had worse overall survival than patients with tumours at $\geq 10\%$ positive when both groups received treatment ($p<0.0001$), and when neither received treatment ($p=0.002$).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE				ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know 	Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)	<p>The GDG notes that the Honma study data demonstrates that the group between 0 and 10% positivity benefits from treatment, however, that there is significant uncertainty in the evidence⁽¹⁰⁾. As agreement was not reached by consensus, voting was conducted by members of the GDG without COL: 11 members voted 'moderate undesirable effects', 5 members voted 'large undesirable effects', 3 members voted 'don't know', 2 members voted 'small undesirable effects and 1 member abstained from voting.</p>
	Recurrence free survival (Honma 2014)	(Honma 2014): tamoxifen vs no endocrine treatment on 5 years recurrence-free survival in ER positive cases according to different thresholds. The following adjusted HR (95%CI) were observed: • At >0% threshold: 0.633 (0.426; 0.934) • At 1% threshold: 0.649 (0.431; 0.973) • At 10% threshold: 0.671 (0.434; 1.039) • At 33% threshold: 0.555 (0.342; 0.898) • At 67% threshold: 0.472 (0.272; 0.816).	(1 observational study) ^{1,a}	⊕○○○ VERY LOW ^{b,c,d}	
	Recurrence free survival (Yi 2014)	(Yi 2014): patients with ER-positive tumours at 1-9% receiving endocrine treatment vs patients with ER-negative tumours (i.e. <1%) who did not receive treatment; no difference was observed (p=0.7) – see Figure 1 below. ^e	(1 observational study) ^{2,a}	⊕○○○ VERY LOW ^{f,g}	
	Overall survival (Yi 2014) (OS)	(Yi 2014): patients with 1-9% ER-positive tumours receiving endocrine treatment had worse survival rates than patients with ER-negative tumours (i.e. <1%) who did not receive treatment (p=0.04) - see Figure 2 below. ^h	(1 observational study) ^{2,a}	⊕○○○ VERY LOW ^{f,g}	
	Direct response to endocrine therapy (defined according to World Health Organization criteria as complete response, partial response, no change, or progressive disease)	No studies identified	(0 studies)	-	

(Direct response to endocrine therapy)			
Adverse effects of endocrine therapy (Adverse effects)	No studies identified	(0 studies)	-
Health-related quality of life	No studies identified	(0 studies)	-

1. Honma, N., Horii, R., Iwase, T., Saji, S., Younes, M., Ito, Y., Akiyama, F.. Proportion of estrogen or progesterone receptor expressing cells in breast cancers and response to endocrine therapy. Breast; Dec 2014.
2. Yi, M., Huo, L., Koenig, K. B., Mittendorf, E. A., Meric-Bernstam, F., Kuerer, H. M., Bedrosian, I., Buzdar, A. U., Symmans, W. F., Crow, J. R., Bender, M., Shah, R. R., Hortobagyi, G. N., Hunt, K. K.. Which threshold for ER positivity? a retrospective study based on 9639 patients. Ann Oncol; May 2014.
 - a. Retrospective cohort study
 - b. Honma 2014 presented serious risk of bias due to the nature of the study design (retrospective cohort study), which resulted in increased risk of bias in terms of the selection of participants to the study and in terms of the classification of interventions.
 - c. Wide confidence intervals. Number of events not reported.
 - d. Honma 2014 did not report direct comparisons of thresholds $\geq 1\%$ vs $\geq 10\%$, but rather conducted subgroup analyses according to different thresholds of the comparison treatment vs no treatment. Treatment effect according to the different subgroups (1-9%; 10-33%; 33-67%) was not reported either. In addition available evidence is exclusively based on a single drug (tamoxifen). The expert group should agree on whether these issues result or not in serious indirectness.
 - e. In addition Yi 2014 observed that patients with tumours at 1%–9% ER positivity had worse recurrence-free survival than patients with tumours at $\geq 10\%$ positivity, when both groups received treatment ($p=0.0005$), and when neither received treatment ($p=0.0003$).
 - f. Yi 2014 presented serious risk of bias due to confounding: There are important differences between patients with 1-9% positivity (with a more advanced disease, more likely to receive neoadjuvant chemotherapy, and more likely to have HER-2 positive and grade III disease). The Kaplan-Meier curves used to provide the relevant information for this PICO did not adjust for these differences.
 - g. Indirect comparison: Yi 2014 did not provide results for patients with 1-9% ER+ on tamoxifen versus no endocrine treatment. Instead, they compared 1-9% ER+ patients who received endocrine treatment vs ER negative patients who did not receive treatment, and also compared 1-9% vs $>10\%$ ER+ in subgroups of patients receiving and not receiving endocrine treatment.
 - h. In addition Yi 2014 observed that patients with tumours at 1%–9% ER positivity had worse overall survival than patients with tumours at $\geq 10\%$ positive when both groups received treatment ($p<0.0001$), and when neither received treatment ($p=0.002$).

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 data included was very low quality and very indirect. Furthermore, it notes that interpretation of ER positivity thresholds based on data from the Honma study is limited due to the method of statistical analysis, involving cumulative percentages at different thresholds, not a separate hazard ratio at each level of positivity. It was also mentioned that some extend of indirectness might be caused by possible technical weaknesses of the study. Since the included patients had surgery between the early 80s and 90s fixation might have been not optimal for immunohistochemistry. Nowadays 6-72 h fixation in 10% buffered formalin is recommended. It is not described in the publication how fixation was performed or if immunohistochemistry was performed on tissue primarily used for frozen section analysis that was fixed in a second step at least in some patients. Fixation is crucial for the immunoreactivity of the tissue. Furthermore the description of the immunohistochemistry technique lacks relevant information (pre-treatment, detection systems) needed to assess if the used technique is as sensitive as current protocols. Additionally, the GDG noted additional indirectness due to technical weaknesses of the study.</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 notes that there is uncertainty on whether treatment is effective through each threshold. The GDG notes that the side effects of endocrine therapy are significant and there may therefore be variability in the way women value this outcome. The GDG agreed by consensus that there is 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 	No studies identified comparing the impact on adverse effects of using a threshold of 1% or more vs. 10% or more of cells showing oestrogen receptor positivity for the provision of endocrine therapy in women with invasive breast cancer	The GDG notes that due to the very low certainty in the evidence, the balance probably favours the comparison. The GDG agreed by consensus that the balance probably favours the comparison.

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 		

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 		

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 	A specific bibliographic search on cost-effectiveness was undertaken, however, no relevant studies 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 		The GDG agreed by consensus that there would probably be no impact on health equity.

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 		The GDG agreed by consensus that the intervention would be acceptable to key stakeholders.

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 		The GDG agreed by consensus that the intervention would be feasible to implement.

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

In women with invasive breast cancer, the ECIBC Guidelines Development Group suggests administration of adjuvant endocrine therapy if 1% or greater of tumour cells show oestrogen receptor positivity rather than applying a threshold of 10% tumour cell oestrogen receptor positivity (conditional recommendation, very low certainty in the evidence).

Justification

Overall justification

The GDG agreed by consensus that the limited very low quality evidence reviewed favours the current practice, using an ER threshold of 1% positivity.

Detailed justification

Desirable Effects

The GDG judged that the desirable anticipated effects of a change in ER positivity threshold from current practice of 1% to 10% were trivial.

Undesirable Effects

The GDG judged that there were moderate undesirable effects due to uncertainty in the data regarding thresholds, and the potential that patients with ER positivity between 1 and 10% would not be treated with the endocrine therapy.

Certainty of evidence

The GDG notes that the data included was very indirect and very low quality. Furthermore, it notes that interpretation of ER positivity thresholds based on data from the Honma study is limited due to the method of statistical analysis, involving cumulative hazard ratios at different thresholds, not a separate hazard ratio at each level of positivity.

Subgroup considerations

None considered.

Implementation considerations

The comparison is already current practice, therefore no implementation considerations were identified.

Monitoring and evaluation

The GDG suggests monitoring low (1-9%) and high (10% and above) ER positivity in relation to patient outcomes to better assess ER thresholds for treatment.

Research priorities

1. New research using ideally modern ER immunohistochemical techniques on tumor tissue primarily fixed in 10% neutral buffered formalin.
2. The GDG suggests additional observational studies to provide evidence on the current threshold used in practice, ideally using modern immunohistochemical techniques.

REFERENCES SUMMARY

1. Fitzgibbons, PL. Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med; 2000.
2. Gown, AM. Current issues in ER and HER2 testing by IHC in breast cancer. Mod Pathol; 2008.
3. Rhodes, A. Frequency of oestrogen and progesterone receptor positivity by immunohistochemical analysis in 7016 breast carcinomas: correlation with patient age, assay sensitivity, threshold value, and mammographic screening. J Clin Pathol; 2000.
4. Harvey, J. M., Clark, G. M., Osborne, C. K., & Allred, D. C.. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol; 1999.
5. Mohsin, SK. Progesterone receptor by immunohistochemistry and clinical outcome in breast cancer: a validation study. Mod Pathol; 2004.
6. Nofech-Mozes, S. Systematic review on hormone receptor testing in breast cancer.. Appl Immunohistochem Mol Morphol; 2012.
7. Ellis, IO. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer. Cancer datasets and tissue pathways. Royal College of Pathologists UK.; 2016.
8. Hammond, M. E. et al.. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol; 2010.
9. Yi, M., Huo, L., Koenig, K. B., Mittendorf, E. A., Meric-Bernstam, F., Kuerer, H. M., Bedrosian, I., Buzdar, A. U., Symmans, W. F., Crow, J. R., Bender, M., Shah, R. R., Hortobagyi, G. N., Hunt, K. K.. Which threshold for ER positivity? a retrospective study based on 9639 patients. Ann Oncol; May 2014.
10. Honma, N., Horii, R., Iwase, T., Saji, S., Younes, M., Ito, Y., Akiyama, F.. Proportion of estrogen or progesterone receptor expressing cells in breast cancers and response to endocrine therapy. Breast; Dec 2014.