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

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 progesterone receptor positivity rather than applying a threshold of 10% tumour cell progesterone receptor positivity (conditional recommendation, very low certainty in the evidence).

ASSESSMENT

POPULATION	women with invasive breast cancer
INTERVENTION	a threshold of 10% or more
COMPARISON	1% or more of cells showing progesterone receptor positivity
MAIN OUTCOMES	Overall survival; disease free survival; direct response to endocrine therapy (defined according to 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	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 (Fitzgibbons, 2000, Gown, 2008). Approximately 80% of invasive breast carcinomas are hormone receptor positive (Rhodes, 2000). 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. 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. The optimal method tumour testing for hormone receptor status is by immunohistochemistry on formalin- fixed, paraffin-embedded tissue using monoclonal antibodies (Harvey, 1999, Mohsin, 2004, Nofech-Mozes, 2012, Ellis, 2016) . 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. 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 (Hammond, 2010).
Historically different methods of scoring ER and PR status were used including assessment of strength and percentage of tumour cell positivity on IHC staining.
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 (Hammond, 2010) . 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 established retrieval methods, antibodies and detection systems have increased the sensitivity of immunohistochemistry.

JUDGEMENTS

Is the problem a priority?

- ◯ 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 the design of an appropriate treatment regime for individual patients.

Additional considerations

The GDG prioritised this question for the ECIBC.

How substantial are the desirable anticipated effects?

- ⊗ Trivial
- ◯ Small
- ◯ Moderate
- ◯ Large
- ◯ Varies
- ◯ Don't know

Outcomes	Impact	? of participants (studies)	Certainty of the evidence (GRADE)
Recurrence free survival	(Honma 2014): tamoxifen vs no endocrine treatment on 5 years recurrence-free survival in PR positive cases according to different thresholds. The following results (reported in terms of HR (95%CI)) were observed: • At >0% threshold: 0.603 (0.390; 0.927) • At 1% threshold: 0.604 (0.366; 0.986) • At 10% threshold: 0.625 (0.351; 1.103) • At 33% threshold: 0.420 (0.194; 0.869) • At 67% threshold: 0.320 (0.272; 0.816)	(1 observational study)[1,a]	???? VERY LOW[b,c,d]
Overall survival	No studies identified	(0 studies)	-
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)	-

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.

1. Retrospective cohort study
2. Honma 2014 presented serious risk of bias due to the nature of the study design (retrospective cohort study), which resulted in an increased risk of bias in terms of the

selection of participants to the study and in terms of the classification of interventions.

3. Wide confidence intervals. Number of events not reported.
4. Honma 2014 did not report direct comparisons of thresholds >=1% vs >=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.

How substantial are the undesirable anticipated effects?

- ◯ Large
- ⊗ Moderate
- ◯ Small
- ◯ Trivial
- ◯ Varies
- ◯ Don't know

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Additional considerations

The GDG notes that the population of women who fall between the 1% and 10% thresholds in the Honma 2014 study was 16.8% of the total study population. These patients would not be offered endocrine therapy with a PR positivity threshold of 10%. As agreement was not reached by consensus, voting was conducted by members of the GDG without COI: 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.

What is the overall certainty of the evidence of effects?

- ⊗ Very low
- ○ Low
- ○ Moderate
- ○ High
- ○ No included studies

Additional considerations

The GDG notes that the data included was of very low quality and very indirect. Furthermore, it notes that interpretation of PR 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 as a separate hazard ratio at each positivity level. It was also mentioned that, to 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 not been 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 then 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 the current protocols. Additionally, the GDG noted additional indirectness due to technical weaknesses of the study.

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

- ◯ Important uncertainty or variability
- ⊗ Possibly important uncertainty or variability
- ◯ Probably no important uncertainty or variability
- ◯ No important uncertainty or variability
- ◯ No known undesirable outcomes

Additional considerations

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.

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

- ◯ 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 progesterone receptor positivity for the provision of endocrine therapy in women with invasive breast cancer

Additional considerations

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.

How large are the resource requirements (costs)?

- ◯ Large costs
- ◯ Moderate costs
- ◯ Negligible costs and savings
- ◯ Moderate savings
- ◯ Large savings
- ◯ Varies
- ⊗ Don't know

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

- ◯ Very low
- ◯ Low
- ◯ Moderate
- ◯ High
- ⊗ No included studies

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

- ◯ 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

Although a specific bibliographic search on cost-effectiveness has been undertaken, no relevant studies were identified.

What would be the impact on health equity?

- ◯ Reduced
- ◯ Probably reduced
- ⊗ Probably no impact
- ◯ Probably increased
- ◯ Increased
- ◯ Varies
- ◯ Don't know

Additional considerations

The GDG agreed by consensus that there would probably be no impact on health equity.

Is the intervention acceptable to key stakeholders?

- ◯ No
- ◯ Probably no
- ◯ Probably yes
- ⊗ Yes
- ◯ Varies
- ◯ Don't know

Additional considerations

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

Is the intervention feasible to implement?

- ◯ No
- ◯ Probably no
- ◯ Probably yes
- ⊗ Yes
- ◯ Varies
- ◯ Don't know

Additional considerations

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

CONCLUSIONS

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

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
	○	⊗	○	○	○

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 progesterone receptor positivity rather than applying a threshold of 10% tumour cell progesterone 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, of using a progesterone (PR) threshold of 1% positivity.

Detailed justification

Desirable Effects:

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

Undesirable Effects:

The GDG judged that there were moderate undesirable effects due to uncertainty in the data regarding the thresholds, and that, potentially, patients with PR 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 of very low quality. Furthermore, it notes that interpretation of PR positivity thresholds based on data from the Honma study is limited due to the statistical method analysis, involving cumulative hazard ratios at different thresholds, not a separate hazard ratio at each positivity level.

SUBGROUP CONSIDERATIONS

None considered.

IMPLEMENTATION CONSIDERATIONS

The comparison, using a threshold of 1%, 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) PR positivity in relation to patient outcomes to better assess PR thresholds for treatment.

RESEARCH PRIORITIES

1. New research using ideally modern PR 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.