



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 Evidence profile

Healthcare question	Should a threshold of 10% or more vs. 1% or more of cells showing oestrogen receptor positivity be used as a threshold to provide endocrine therapy in women with invasive breast cancer?
Date	March 2017
Authors	ECIBC Guidelines Development Group (GDG): Mariangela Autelitano, Bettina Borisch, Mireille Broeders, Xavier Castells, Roberto D'Amico, Edoardo Colzani, Jan Daneš, Stephen Duffy, Patricia Fitzpatrick, Markus Follmann, Livia Giordano, Paolo Giorgi Rossi, Axel Gräwingholt, Solveig Hofvind, Lydia Ioannidou-Mouzaka, Susan Knox, Annette Lebeau, Helen McGarrigle, Lennarth Nyström, Elsa Pérez Gómez, Cecily Quinn, Peter Rabe, Holger Schünemann, Alberto Torresin, Ruben Van Engen, Cary Van Landsveld-Verhoeven, Sue Warman, Kenneth Young. Systematic Review team: Ignacio Ricci Cabello, David Rigau, Pablo Alonso-Coello. JRC Healthcare Quality team: Asli Uluturk, Donata Lerda
Abbreviations	CI: Confidence interval

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrence free survival (Honma 2014)									
1 ¹	observational studies ^a	serious ^b	not serious	serious ^c	serious ^d	none	(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).	⊕○○○ VERY LOW	

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Recurrence free survival (Yi 2014)									
1 ²	observational studies ^a	serious ^e	not serious	very serious ^f	not serious	none	(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. ^g	⊕○○○ VERY LOW	
Overall survival (Yi 2014)									
1 ²	observational studies ^a	serious ^e	not serious	very serious ^f	not serious	none	(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	⊕○○○ VERY LOW	
Direct response to endocrine therapy (defined according to World Health Organization criteria as complete response, partial response, no change, or progressive disease)									
0							No studies identified	-	
Adverse effects of endocrine therapy									
0							No studies identified	-	
Health-related quality of life									
0							No studies identified	-	

Explanations

- Retrospective cohort study
- 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.
- 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.
- Wide confidence intervals. Number of events not reported.
- 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.
- 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.
- 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).
- 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).

References

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.