



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 21 gene recurrence score compared to no testing be used for patients who have hormone receptor positive, HER2-negative, lymph node negative or up to 3 lymph nodes positive invasive breast cancer to guide the use of chemotherapy
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Abbreviations	CI: Confidence interval HR: Hazard ratio

TABLE 1/3: subgroup: lymph node negative

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endocrine therapy plus chemotherapy	Endocrine therapy	Relative (95% CI)	Absolute (95% CI)		
Freedom from distant recurrence - low genomic risk ^a												
1 ¹	randomised trials	serious _{b,c}	not serious	serious ^d	serious ^e	none	6/135 (4.4%)	11/353 (3.1%)	HR 1.31 (0.46 to 3.78)	9 more per 1,000 (from 17 fewer to 82 more)	⊕○○○ VERY LOW	CRITICAL

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endocrine therapy plus chemotherapy	Endocrine therapy	Relative (95% CI)	Absolute (95% CI)		
Freedom from distant recurrence - intermediate genomic risk ^a												
1 ¹	randomised trials	serious _{b,c}	not serious	serious ^d	serious ^e	none	5/45 (11.1%)	12/134 (9.0%)	HR 0.61 (0.24 to 1.59)	34 fewer per 1,000 (from 67 fewer to 49 more)	⊕○○○ VERY LOW	CRITICAL
Freedom from distant recurrence - high genomic risk ^a												
1 ¹	randomised trials	serious _{b,c}	not serious	serious ^d	not serious	none	6/47 (12.8%)	65/164 (39.6%)	HR 0.26 (0.13 to 0.53)	273 fewer per 1,000 (from 333 fewer to 162 fewer)	⊕⊕○○ LOW	CRITICAL

Explanations

- Contralateral disease, other second primary cancers, and deaths before distant recurrence were considered censoring events.
- The original trial (B-20) did not provide information about the HER-2 status among the included patients. Given that the positivity of HER-2 is a strong predictive marker and is included in the 21-gene recurrence test, it can bias the results
- Part of the sample was previously used to validate (although a previous version) the gene markers test which might lead to over fitting in subsequent analysis.
- The study enrolled patients that were treated more than ten years ago. The chemotherapy regime is very different now which precludes the applicability of the results. The study design used did not provide the relevant clinical information of interest (i.e. number of chemotherapies avoided, direct comparison between use or not of the test) thus, extrapolation of those events from the study's results is required.
- There were a low number of events in each genomic risk group. The effect size estimates were imprecise which led to a low power to test interaction.

References

- Paik. Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor-Positive Breast Cancer. J Clin Oncol; 2006.

TABLE 2/3: subgroup: lymph node positive

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endocrine therapy plus chemotherapy	Endocrine therapy	Relative (95% CI)	Absolute (95% CI)		
Disease free survival - stratified by genomic risk groups ^a												
1 ¹	randomised trials	not serious	not serious	very serious _{b,c,d}	serious ^e	none	The trend of recurrence over time as reported graphically showed a difference by the genomic risk groups although there was overlapping in the confidence intervals of the trend lines. ^f			⊕○○○ VERY LOW	CRITICAL	
Overall survival - low genomic risk group												
1 ¹	randomised trials	not serious	not serious	very serious _{b,c,d,g}	serious ^e	none	0/91 (0.0%)	24.0%	HR 1.18 (0.55 to 2.54)	37 more per 1,000 (from 100 fewer to 262 more)	⊕○○○ VERY LOW	CRITICAL
Overall survival - intermediate genomic risk group												
1 ¹	randomised trials	not serious	not serious	very serious _{b,c,d,g}	serious ^e	none	0/57 (0.0%)	35.0%	HR 0.84 (0.40 to 1.78)	46 fewer per 1,000 (from 192 fewer to 185 more)	⊕○○○ VERY LOW	CRITICAL
Overall survival - high genomic risk group												
1 ¹	randomised trials	not serious	not serious	very serious _{b,c,d,g}	serious ^e	none	0/71 (0.0%)	49.0%	HR 0.56 (0.31 to 1.02)	176 fewer per 1,000 (from 302 fewer to 7 more)	⊕○○○ VERY LOW	CRITICAL

Explanations

- a. Time elapsed from the enrolment to the first breast cancer relapse (local or distant), new primary breast cancer, or death due to any cause.
- b. The post-hoc analysis compared the sequential use of chemotherapy (CAF-T) versus tamoxifen; the arm of concomitant chemotherapy plus tamoxifen was not included in this sub-study due to less effectiveness in the parent trial.
- c. A 12% of the included subjects in the analysis were HER2-positive based on the 21-gene assay.
- d. The study enrolled patients that were treated more than ten years ago. The chemotherapy regime is very different now which precludes the applicability of the results. The study design used did not provide the relevant clinical information of interest (i.e. number of chemotherapies avoided, direct comparison between use or not of the test) thus extrapolation of those events from the study's results is required.
- e. There were a low number of events in each genomic risk group. The effect size estimates were imprecise.
- f. Interaction of test of linear RS, adjusting for number of positive nodes. Over the entire time period, the significance of the RS-treatment interaction is $p=0.053$ for DFS. However, the effect of the RS on treatment is not constant over time.
- g. Results were not provided by strata of the number of positive lymph nodes (ie.1 to 3 vs 4 or more), instead as adjusted estimations by number of nodes. Adjustment might be inappropriate if there is interaction between the outcome and the number positive lymph node, which were not assessed in the analysis.

References

1. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, Ravdin P, Bugarini R, Baehner FL, Davidson NE, Sledge GW, Winer EP, Hudis C, Ingle JN, Perez EA, Pritchard KI, Shepherd L, Gralow JR, Yoshizawa C, Allred DC, Osborne CK, Hayes DF, American Society of Clinical Oncology. Prognostic and Predictive Value of the 21-Gene Recurrence Score Assay in a Randomized Trial of Chemotherapy for Postmenopausal, Node-Positive, Estrogen Receptor-Positive Breast Cancer. *Lancet Oncol*; 2010.

TABLE 3/3: subgroup: lymph node negative & intermediate genomic risk

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endocrine therapy	Endocrine therapy plus chemotherapy	Relative (95% CI)	Absolute (95% CI)		
Invasive disease-free survival												
1 ¹	randomised trials ^{ab}	serious ^{cd}	not serious	serious ^e	not serious ^f	none	574/3399 (16.9%)	507/3313 (15.3%)	HR 1.14 (0.99 to 1.31)	19 more per 1,000 (from 1 fewer to 43 more)	⊕⊕○○ LOW	
Freedom from recurrence at a distant site												
1 ¹	randomised trials ^{ab}	serious ^{cd}	not serious	serious ^e	not serious ^f	none	265/3399 (7.8%)	235/3313 (7.1%)	HR 1.03 (0.80 to 1.33)	2 more per 1,000 (from 14 fewer to 22 more)	⊕⊕○○ LOW	
Freedom from recurrence at a distant or local-regional site												
1 ¹	randomised trials ^{ab}	serious ^{cd}	not serious	serious ^e	not serious ^f	none	187/3399 (5.5%)	166/3313 (5.0%)	HR 1.12 (0.91 to 1.38)	6 more per 1,000 (from 4 fewer to 18 more)	⊕⊕○○ LOW	
Overall survival												
1 ¹	randomised trials ^{ab}	serious ^{cd}	not serious	serious ^e	not serious ^f	none	211/3399 (6.2%)	205/3313 (6.2%)	HR 0.97 (0.78 to 1.21)	2 fewer per 1,000 (from 13 fewer to 12 more)	⊕⊕○○ LOW	

Explanations

- A different threshold was used for interpreting the test's results. Thus, the intermediate range was defined as those with a score from 11 to 25, which is not consistent with previous studies assessing the same test.
- Clinical risk was defined as in the MINDACT trial (i.e., with low risk defined as low histologic grade and tumour size ≤3 cm, intermediate histologic grade and tumour size ≤2 cm, or high histologic grade and tumour size ≤1 cm; and with high risk defined as all other cases with known values for grade and tumour size). Among the randomised patients, 75% were of low clinical risk, and 25% were of high clinical risk.
- There was an important imbalance in the proportions of patients that broke the protocol (not received the intended intervention), which was larger in the chemotherapy plus endocrine therapy group
- The study did not use an appropriate non-inferiority design. Instead they tested difference between arms based in a 32% increase or risk. Additionally, the high rate of non-adherence lead to an increase of the sample size non-initially planned.
- The study enrolled patients that were treated more than ten years ago. The chemotherapy regime is very different now which precludes the applicability of the results. The study design used did not provide the relevant clinical information of interest (i.e. number of chemotherapies avoided, direct comparison between use or not use the test across genomic risk groups) thus extrapolation of those events from the study's results is required.

- f. The confidence interval of the effect sizes were as wide, indicating a potential harmful effect for endocrine therapy alone for the upper limit. However, in absolute terms the difference was less evident.

References

1. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med.; 2018.

DEFINITIONS OF OUTCOMES (ACCORDING TO THE STUDIES)		
Paik 2006	Freedom from distant recurrence	Contralateral disease, other second primary cancers, and deaths before distant recurrence were considered censoring events. Ipsilateral breast recurrence, local chest wall recurrence, and regional recurrences were not considered either as events or as censoring events.
Albain 2010	Disease-free survival	Time from registration to breast cancer relapse (local or distant), new primary breast cancer, or death due to any cause, whichever came first
	Overall survival	Time from registration to death due to any cause. Patients without an event were censored at the last follow-up visit
Sparano 2018	Invasive disease-free survival	Time from registration to first event, where the first event is any of ipsilateral breast tumor recurrence, local recurrence, regional recurrence, distant recurrence, contralateral second primary invasive cancer, second primary non-breast invasive cancer (excluding non-melanoma skin cancers), or death without evidence of recurrence
	Freedom from recurrence at a distant site	Time from registration to date of distant recurrence of breast cancer, or of death with distant recurrence, if death is the first manifestation of distant recurrence
	Freedom from recurrence at a distant or local-regional site	Time from registration to first recurrence of breast cancer (ipsilateral breast, local-regional, or distant), or to the date of death with recurrence, if death is the first manifestation of recurrence
	Overall survival	Time from registration to death due to any cause