original article

Clinical outcome of adjuvant endocrine treatment according to PR and HER-2 status in early breast cancer

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Patients with estrogen receptor (ER)+/progesterone receptor (PR)− and/or HER-2 overexpressing breast carcinomas may derive lower benefit from endocrine treatment. We examined retrospectively data from 972 breast cancer patients who received tamoxifen (725), tamoxifen + Gn-RH analogs (127) and aromatase inhibitors (120) as adjuvant treatments. ER+/PR− versus ER+/PR+ tumours were characterised by larger size ($P = 0.001$), higher tumour grade ($P = 0.001$), higher Ki-67 expression ($P = 0.001$) and lower mean ER ($P = 0.000$) and HER-2 expression ($P = 0.000$). At univariate analysis, tumour grading [hazard ratio (HR) = 4.0; 95% confidence interval (CI) = 1.4–11.1; $P = 0.007$], nodal status (HR = 3.4; 95% CI 1.2–5.7; $P = 0.000$), tumour diameter (HR = 2.9; 95% CI 1.7–4.7; $P = 0.000$) lack of PR expression (HR = 2.1; 95% CI 1.3–3.4; $P = 0.002$) and HER-2 overexpression (HR = 1.9; 95% CI 1.0–3.5; $P = 0.03$), as well as Ki 67 expression (HR = 1.7; 95% CI 1.0–2.7; $P = 0.04$) were associated with shorter disease-free survival (DFS). At the multivariate analysis, nodal status (HR = 3.6; 95% CI 1.9–6.8; $P = 0.0001$), lack of PR expression (HR = 2.3; 95% CI 1.3–4.0; $P = 0.003$) and tumour diameter (HR = 2.1; 95% CI 1.1–3.8; $P = 0.018$) retained their prognostic significance, whereas HER-2 overexpression was associated with a trend towards shorter DFS that was of borderline statistical significance (HR = 2.0; 95 % CI 1.0–3.9; $P = 0.05$). Our data suggest that lack of PR expression and HER-2 overexpression are both associated with aggressive tumour features, but the prognostic information of PR status on the risk of recurrence in endocrine-treated breast cancer patients is stronger.

Key words: adjuvant, breast neoplasm, endocrine therapy, estrogen receptor, HER-2, progesterone receptor

introduction

New molecular technologies have provided the experimental basis to confirm that the variability of breast cancer outcome largely depends on its intrinsic biologic heterogeneity. Therefore, breast cancer is currently considered as not a single, but instead a spectrum of diseases characterised by their own molecular features, aggressiveness and response to treatments [1].

Endocrine sensitivity, assessed by the expression of the estrogen receptor (ER) and/or progesterone receptor (PR), has long been the only recognised and validated predictive factor to guide therapeutic decisions. The Oxford overview on adjuvant therapies for breast cancer clearly shows that the benefit of endocrine treatment is limited to patients with tumours expressing the ER and/or PR [2]. The degree of endocrine sensitivity is currently quantified by immunohistochemistry (IHC), and may be expressed as the percentage of cells stained after treatment with anti-ER/PR antibodies. According to the conclusions reached at the Consensus Conference held by the

National Cancer Institute in the year 2000, all tumours with at least 1% of cells expressing the ER/PR are considered as potentially endocrine sensitive [3].

More recently, also the overexpression of the HER-2 (c-erbB-2/neu) oncogene has been recognised as a significant variable for the assessment of breast cancer prognosis and response to treatments in the metastatic and adjuvant settings [4, 5]. Therefore, a different clinical management is now reserved to HER-2 overexpressing (HER-2+) versus HER-2 nonoverexpressing (HER-2−), as it is for ER positive (ER+) and/or PR positive (PR+) versus ER negative (ER−) and PR negative (PR−) tumours [6].

Several retrospective studies suggest that HER-2+ tumours may be less sensitive to endocrine treatments and, namely, to tamoxifen. This finding has been attributed to the existence of a cross talk between the ER and HER-2 metabolic pathways [7] and to the detection of lower absolute levels of ER when HER-2 is amplified/overexpressed [8]. In postmenopausal women, third generation aromatase inhibitors (AIs) have successfully challenged the prominent role of tamoxifen as treatment of choice both in the adjuvant and metastatic settings [9]. According to preliminary data, the advantage of AIs over

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tamoxifen could be more relevant in the subgroups of ER+/PR− and HER-2+ tumours [10–13].

The aim of our study is to verify the influence of PR and HER-2 status on the clinical and pathological characteristics of a consecutive series of largely ER+ breast cancer patients and to assess whether these two variables are associated with the outcome of patients receiving adjuvant endocrine treatment.

subjects and methods

study population

Cases were selected by an institutional database containing all patients treated for primary breast cancer at the Academic Division of Gynaecological Oncology, University of Turin. Out of 2259 treated since January 1988 to January 2005, 972 consecutive patients who received adjuvant endocrine treatment, and for whom clinical–pathological data and updated follow-up information were available, were included in the study.

Microscopic tumour size, tumour grading according to Elston and Ellis [14] and nodal involvement were assessed on sections stained with conventional hematoxylin and eosin. IHC was used to measure ER and PR expression (>1% of the cell staining was coded as positive) and cell proliferation by Ki-67 (<20% was coded as low; ≥20% as high). HER-2 overexpression was assessed as the percentage of cell stained by two Food and Drug Administration approved tests (CB 11, Ventana Medical System Inc., Tucson, AZ, until 2000 and Herceptest, DAKO, Corp., Carpinteria, CA, thereafter). The cut-off for HER-2 overexpression was set at ≥40% cells stained because it allowed the best discrimination between relapsing and nonrelapsing patients.

Surgical treatment consisted in wide local excision plus axillary dissection followed by whole breast radiotherapy plus a boost on the tumour bed, or modified radical mastectomy when breast-conserving surgery was not indicated. After mastectomy, only selected high-risk patients received radiotherapy to the chest wall and supraclavicular nodes. In our institution, sentinel node biopsy became standard treatment of clinically node negative patients in 1999; since then, completion axillary dissection was carried out only in case of micro- and macrometastatic sentinel node.

Adjuvant treatments of patients not enrolled in clinical-controlled studies were prescribed on the basis of international guidelines and consensus conferences (Table 1). In general, all patients with ER and/or PR expression >1% were prescribed endocrine treatment with tamoxifen 20 mg/day for 5 years. Premenopausal women also received ovarian inhibition by Gn-RH analogs for 2 years. Since 2001, postmenopausal patients with contraindication or intolerance to tamoxifen received an AI for 5 years. Most of the patients with axillary nodal involvement, <70 years of age and no significant morbidity, received adjuvant chemotherapy before the commencement of endocrine treatment. Node-negative patients underwent chemotherapy if classified as at intermediate/high risk on the basis of tumour size, grading and age. Most common cytotoxic therapies were represented by non-antracyclin-containing combinations [combination

chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF) q1:8:28 × six cycles], antracyclin-containing combinations [adriamycin, clycophosphamide (AC) q1:21 × four cycles; fluorouracil, epirubicin/adriamycin, cyclophosphamide (FEC/FAC) q1:21 × six cycles; epirubicin q21 × four cycles followed by CMF q1:8:28 × four cycles) (E-CMF)] and antracyclin–taxane combinations [AC q1:21 × four cycles followed by paclitaxel (Taxol) q1:21 × four cycles].

All patients signed a written informed consent stating that their clinical data and biological material could be used for research purposes and the study received institutional board approval.

statistical analysis

The clinical and pathologic characteristics of women in study are reported as frequencies, means and ranges. Quantitative variables were compared by the Pearson's chi-square test or with the Fisher's exact test when required. Qualitative variables were compared by the analysis of variance. Normality of the variables' distribution was tested by the Kolmogorov–Smirnov test. For non-normally distributed variables, a nonparametric analysis was carried out with the Mann–Whitney U test.

The primary outcome was disease-free survival (DFS) defined as the length of time from the date of surgery to first local or distant recurrences (contralateral cancers not included) for relapsing patients, while the others were censored at the time of last follow-up or death. Median follow-up was 35 months (range 1–205). Overall survival was not calculated as too few events (deaths) were recorded. DFS curves were estimated using the Kaplan–Meier method and were compared by the log-rank test. A univariate Cox regression model was used to determine the association of variables with DFS. Hazard ratios (HRs) are presented with their 95% confidence intervals (CIs). The assumption that regression coefficients are constant over time was verified by testing the variables for the lack of proportionality and by examining the smoothed plots of the rescaled Schoenfeld residuals and pointwise 95% confidence bands for each variable as described by Hilsenbeck et al. [15]. The independent value of these variables was assessed in multivariable Cox regression model, including the potential interaction between ER/PR status and HER-2 status. Statistical analyses were carried out using the SPSS software, version No. 9. All statistical tests were two-sided, and a P value <0.05 was deemed statistically significant.

results

Table 2 shows the mean distribution of clinical and pathological variables in the whole series of 972 patients. Due to the criteria

Table 1. Adjuvant endocrine and cytotoxic treatments

Type of treatment	n	%
Endocrine therapy (±chemotherapy)	972	100
Tamoxifen	725	74.6
Tamoxifen + Gn-RH analogs	127	13.0
Aromatase inhibitors	120	12.3
Chemotherapy (+endocrine therapy)	382	39.3

Table 2. Mean distribution of clinical and pathological characteristics

Variable	No. tested	Mean	Median	Range
Age (years)	962	60.0	60.5	20–90
Tumour diameter (mm)	945	20.9	18	0.1–10
No. involved axillary nodes	839	2.5	0	0–45
Grading	848	2.0	2	1–3
ER (per cent positive cells at IHC)	942	67.2	70.5	0–100
PR (per cent positive cells at IHC)	936	41.3	50	0–100
HER-2 (per cent positive cells at IHC)	877	11.9	0	0–100
Ki 67 (per cent positive cells at IHC)	810	15.7	12	0–85

ER, estrogen receptor; IHC, immunohistochemistry; PR, progesterone receptor.

used for patients' selection, the mean percentage of cells expressing ER was high. Also the low percentage of HER-2 expressing cells, as well as the low proliferative index measured by Ki-67 are in line with the selection criteria which favoured endocrine sensitive and slowly growing tumours.

tumour characterisation according to PR and HER 2 status

Older patients had lower PR expression, while patients with HER-2+ tumours were slightly younger, although not significantly. PR− tumours were characterised by larger size as compared to PR+ tumours, as well as HER-2+ versus HER-2− tumours, but again this difference did not reach statistical significance. PR− and HER-2+ tumours showed higher proliferative activity measured by Ki-67 and higher tumour grade as compared with PR+ and HER-2− tumours, respectively. Conversely, nodal involvement was not influenced by both PR and HER-2 status (Table 3).

correlation between ER, PR and HER-2 status

Overall, 76% of the tumours showed both ER and PR expression (ER+/PR+), 18% ER expression only (ER+/PR−), 3.5% PR expression only (ER−/PR+), while none of the two receptors was expressed in 3.5% of the patients (ER−/PR−).

The levels of both ER and PR were inversely correlated with HER-2 overexpression (Table 4). In particular, HER-2+ tumours were more represented in ER+/PR− versus ER+/PR+ tumours (39.0% versus 17.7%; P = 0.000); accordingly, the

mean percentage of HER-2+ cells was significantly higher in ER+/PR− versus ER+/PR+ tumours (21.4% versus 9.2%; P = 0.000).

clinical outcome according to clinical–pathological variables

At the univariate analysis of survival, lack of PR expression (Figure 1) and HER-2 overexpression (Figure 2) as well as nodal status, tumour diameter, tumour grading and Ki-67 expression showed a significant association with shorter DFS (Table 5), even after controlling for continuous levels of ER expression (data not shown). All the other variables, including the administration of adjuvant chemotherapy, did not influence DFS.

In the multivariate Cox model including all variables, nodal status (HR = 3.6; 95% CI 1.9–6.8; P = 0.0001), lack of PR expression (HR = 2.3; 95% CI 1.3–4.0; P = 0.003) and tumour diameter (HR = 2.1; 95% CI 1.1–3.8; P = 0.018) retained their prognostic significance. HER-2 overexpression was associated with a trend towards worse DFS that resulted of borderline statistical significance (HR = 2.0; 95 % CI 1.0–3.9; P = 0.05).

We then conducted a subset analysis to evaluate whether the prognostic value of HER-2 overexpression differed in the subgroups of ER+/PR+ and ER+/PR− tumours. Indeed, it appeared that the prognostic significance of HER-2 overexpression was restricted to the latter group of patients (HR = 2.4; 95% CI 1.1–5.3; P = 0.04), whereas no significant effect of HER-2 status was evident for ER+/PR+ patients (HR = 0.8; 95% CI 0.3–2.8; P not significant).

Table 3. Clinical–pathological characteristics according to PR and HER-2 status

Variable	PR+[a]	PR−	P value	HER 2−	HER 2+[b]	P value
Age						
No. tested	735	190		749	117	
Mean (range)	59.4 (29–90)	62.7 (33–87)	0.001	60.2 (29–90)	58.7 (30–84)	NS
<50 years (%)	25.0	12.6		22.3	26.5	
≥50 years (%)	75.0	87.4	0.000	77.7	73.5	NS
Tumour size						
No. tested	727	189		745	115	
<2 cm (%)	57.4	42.9		55.2	47.0	
≥2 cm (%)	42.6	57.1	0.001	44.8	53.0	NS
Nodal status						
No. tested	636	171		645	112	
Negative (%)	55.0	48.0		54.1	51.8	
Positive (%)	45.0	52.0	NS	45.9	48.2	NS
Tumour grading						
No. tested	658	168		676	106	
G1 (%)	23.9	14.9		23.7	7.7	
G2 (%)	46.5	40.5		46.2	34.6	
G3 (%)	29.6	44.6	0.001	30.1	57.7	0.000
Ki 67 expression						
No. tested	651	154		671	99	
Low (<20%)	71.3	57.1		72.0	47.5	
High (≥20%)	28.7	42.9	0.001	28.0	52.5	0.000

PR, progesterone receptor; NS, not significant.
[a]PR+, ≥1% stained cells.
[b]HER-2+, ≥40% stained cells.

Table 4. Correlation between HER-2 status and levels of ER and PR expression

Variable	HER-2 status		P
	Negative (0–1+)	Positive (2–3+)	
ER expression			
No. tested	755	120	
Mean levels[a]	69.7%	53.3%	0.000
PR expression			
No. tested	752	121	
Mean levels[a]	43.3%	29.5%	0.000

ER, estrogen receptor; PR, progesterone receptor.
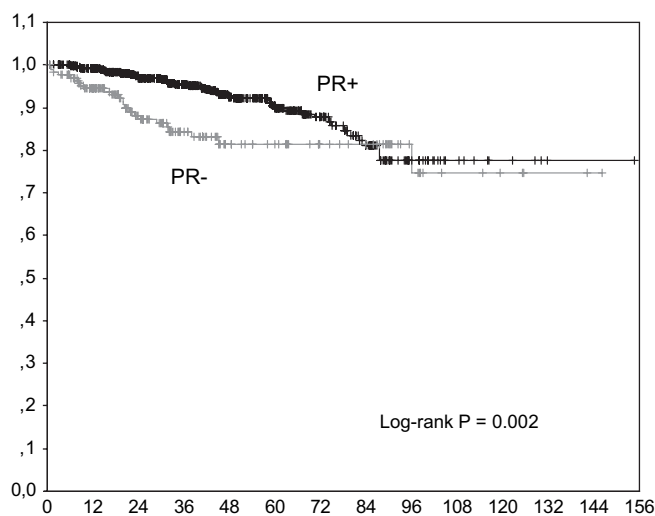[a]Expressed as the mean percentage of cells stained at immunohistochemistry.

Figure 2. Kaplan–Meier curves for disease-free survival according to HER-2 status (<40% negative; ≥40% positive).

Cox model, but since we did not obtain significant variations of the results, this violation was ignored in the final model.

discussion

Our study confirms that lack of PR expression and HER-2 overexpression are both associated with aggressive tumour features in predominantly ER+ breast carcinomas. PR expression is generally considered a marker of integrity of the estrogenic metabolic pathway as it requires the activation of the ER. The lower mean percentage of ER-stained cells in PR– as compared to PR+ tumours found in our study is in line with this hypothesis and with the literature data.

Lower mean levels of ER and PR were also found in HER-2+ versus HER-2– tumours. It has been hypothesised that HER-2 overexpression may interact with some of the metabolic pathways triggered by the activation of the ER [16]. A possible explanation for the lower PR concentration in the presence of HER-2 overexpression is the activation of the P13K–Akt–mTor pathway by an increased growth factor activity. It has been reported that this pathway can actually reduce the expression of PR at the transcriptional level by activating the AP-1 site in the PR gene promoter [17].

Biological and clinical data suggest that lack of PR expression and HER-2 overexpression may predict lower endocrine sensitivity in ER+ tumours. In particular, the predictive value of HER-2 status is highly debated: a subgroup analysis of the Cancer and Leukemia Group B 8541 study [18] showed a lack of interaction of tamoxifen use and HER-2 expression, whereas in the large study by Arpino et al. [19], both PR and HER-2 independently predicted DFS; furthermore, in a recent retrospective analysis of the National Atlantic Treaty Organisation and Cancer Research Campaign adjuvant trials, HER2-positive patients failed to benefit from tamoxifen treatment [20].

In our series, both PR and HER-2 status as well as other established prognostic markers like nodal involvement, tumour

Figure 1. Kaplan–Meier curves for disease-free survival according to progesterone receptor status (0%: negative; ≥1%: positive).

analysis of PR and HER-2 status as time-dependent variables

Although a significant difference in DFS was found according to PR status, the survival curves cross at 96 months of follow-up. The time-dependent nature of the prognostic information provided by PR was confirmed by the violation of the proportional hazard assumption in the Cox regression model ($P = 0.001$), with the time-varying curve crossing the null line (crossover effect). As depicted in Figure 3, PR expression is protective for early relapse, but changes at ∼3.5 years of follow-up indicating a switch to poor prognosis. A formal test for lack of proportionality suggests that also the HR of HER-2 status is not constant, but it decreases with time ($P = 0.027$). Nevertheless, the time-varying curve never dips below the null value indicating that HER-2 overexpression continues to carry unfavourable prognostic value with longer follow-up (Figure 4). Similarly, none of the other significant variables at the univariate analysis of survival showed a crossover effect like that of PR. Crossover violations of the proportional hazard assumption are more important to detect and model explicitly; therefore, we tried to add PR as time-dependent covariate in the
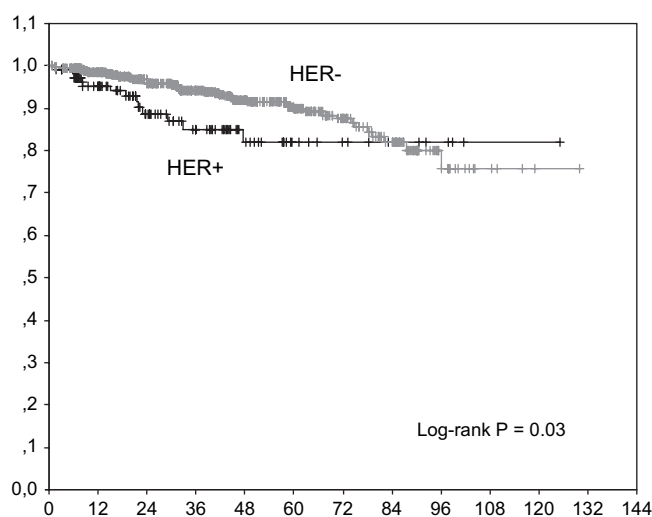
Table 5. Univariate analysis of disease-free survival

Variable	HR	95% CI	*P*
Tumour diameter			
≥2 cm versus <2 cm	2.9	1.7–4.7	0.000
Nodal status			
Positive versus negative	3.4	1.2–5.7	0.000
Tumour grading			
G2–G3 versus G1	4.0	1.4–11.1	0.007
Ki 67 expression			
≥20% versus <20%	1.7	1.0–2.7	0.04
PR status			
0% versus ≥1%	2.1	1.3–3.4	0.002
HER-2 expression			
≥40% versus <40%	1.9	1.0–3.5	0.03

HR, hazard ratio; CI, confidence interval; PR, progesterone receptor.

Figure 4. Time-dependent hazard ratio for HER-2 ≥40% versus HER-2 <40% (solid line) and the corresponding pointwise 95% confidence bands (vertical solid lanes). The dashed line represents the null value.
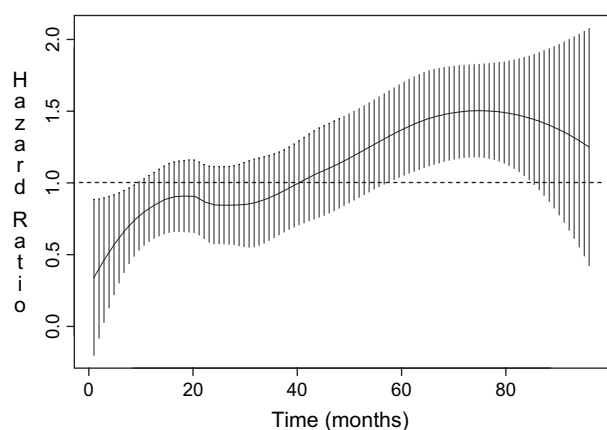

Figure 3. Time-dependent hazard ratio for progesterone receptor (PR) ≥1 versus PR = 0 (solid line) and the corresponding pointwise 95% confidence bands (vertical solid lanes). The dashed line represents the null value.

diameter, grading and Ki-67 expression were associated with reduced DFS in patients who underwent endocrine therapy. Nevertheless, at the multivariate analysis of survival, PR status showed a much stronger association with DFS as compared to HER-2; furthermore, the unfavourable prognostic value of HER-2 overexpression was restricted to ER+/PR− and not to ER+/PR+ patients, as suggested also by others [19].

The absence of PR expression has been interpreted as a surrogate marker for HER-2 activation. This hypothesis has been questioned by a recent study [21] showing that ER+/PR− tumours and HER-2+ tumours represent distinct patient subgroups and concluding that alternative mechanisms must underpin tamoxifen resistance in PR− tumours. Both this study and ours do not include a no-treatment arm which would be required in order to ascertain the existence of a true endocrine resistance in HER-2+ and/or ER+/PR− tumours, yet they suggest caution before concluding that PR loss simply represents an epiphenomenon of HER-2 overexpression or that these markers provide comparable predictive information.

The borderline significance of HER-2 overexpression as an independent predictor of DFS could be due to the smaller
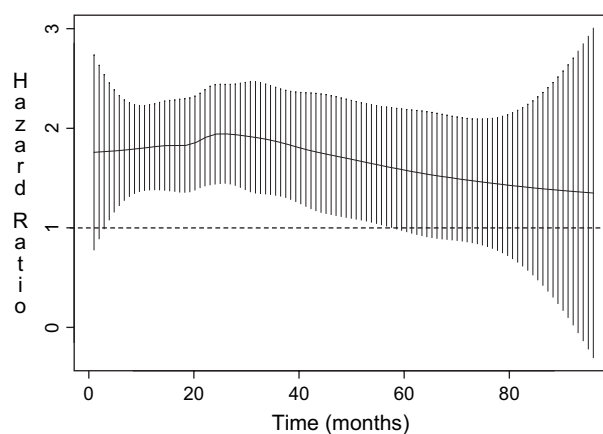
sample size of our study as compared to the study of Arpino et al. [19], but their patient population also differed in two important aspects. First, 25% of our patients received other hormonal drugs in addition (Gn-RH) or instead of (AIs) tamoxifen, whereas in their study tamoxifen was the only adjuvant treatment of all patients. The inclusion of patients who received different treatments might have obscured the selective influence of HER-2 status on tamoxifen efficacy. Furthermore, as our selection criteria included all patients who received endocrine treatment, a small percentage of tumours displayed ER−/PR+ (3.5%) and also ER−/PR− (2.4%) phenotypes, which were not represented in their study. Unfortunately, by restricting the analysis to ER+ patients who received tamoxifen as the sole endocrine treatment, both PR and HER-2 status would loose their association with DFS in our series. Since the study was not designed to test tamoxifen resistance, but instead to assess the prognostic/predictive value of PR and HER-2 status, we decided to include all patients who received some form of endocrine treatment.

The time dependence of the prognostic value of ER status has been repeatedly reported in the literature [15, 22]; our data on PR are consistent with a real change in the relative effect of hormone receptors as a function of time. A retrospective analysis of the arimidex, tamoxifen, alone and in combination (ATAC) trial [10] suggests that the advantage of initial treatment with anastrozole versus tamoxifen is greater for ER+/PR− as compared to ER+/PR+ patients. In addition, >15% of ER+/PR− patients on tamoxifen in this trial recurred throughout the first 3 years. Interestingly, similar conclusions were drawn by Tovey et al. [21], who showed that also HER-2 overexpression, as well as PR negativity, is a marker of tamoxifen resistance in the first 3 years after primary treatment. These studies suggest that PR and HER-2 expression identify patients who exhibit *de novo* tamoxifen resistance since both variables behave as time-dependent predictors of risk of relapse, with a sharp decline of the risk after 3 years of tamoxifen treatment. Therefore, the lack of significance of PR status when patients switch to AIs after 2–3 years of tamoxifen reported by

two large studies [23, 24] could be due to the fact that most of the recurrences in PR— tumours actually occur before the switch. This finding was confirmed in our series where the majority of the events in the PR-negative subset occurred within the fourth year of follow-up. Conversely, the time-dependent nature of the prognostic information of HER-2 overexpression was less clear, although the small sample size of our study could have hindered this specific effect.

In conclusion, our study confirms that PR status defines a subset of tumours with distinctive pathological characteristics and may help select those patients who derive the greatest benefit from endocrine adjuvant treatment, particularly within the first few years of follow-up. HER-2 status carries a prognostic information of borderline significance at the multivariate analysis, although HER-2 overexpression is associated with aggressive clinical and pathological features. Larger and prospective studies are warranted to clarify this issue, given the recent trend towards a widespread introduction of AIs and trastuzumab in the adjuvant setting as first choice treatments of ER+/PR— and HER-2 positive tumours, respectively.

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