IJC
International Journal of Cancer

Tumor size, node status, grading, HER2 and estrogen receptor status still retain a strong value in patients with operable breast cancer diagnosed in recent years

Laura Cortesi[1], Luigi Marcheselli[1], Valentina Guarneri[1], Claudia Cirilli[1], Barbara Braghiroli[1], Angela Toss[1], Milena Sant[2], Guido Ficarra[3], Pier Franco Conte[1] and Massimo Federico[1]

[1] Department of Oncology and Haematology, University of Modena and Reggio Emilia, Modena, Italy
[2] Department of Preventive and Predictive Medicine, Analytical Epidemiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
[3] Department of Laboratory, Pathological Anatomy and Forensic Medicine, University of Modena and Reggio Emilia, Modena, Italy

Breast cancer prognosis has improved greatly in recent years. Consequently, a thorough search for sensitive prognostic factors, able to help clinicians offer appropriate therapy, has become a priority in this area. In this study, we considered all new cases of invasive breast cancer diagnosed in the Province of Modena, Italy, between 1997 and 2007, registered by the Modena Cancer Registry. The principal endpoint of this study was relapse-free survival (RFS). A set of 11 clinic and pathological parameters was investigated. After a median follow-up of 73 months, 494 relapses were recorded. Tumor size, node status, grading, HER2 and estrogen receptor status were retained as independent factors in a multivariate analysis. Using these variables, a prognostic model was devised to identify three groups at different risk. In the training sample, the 5-year RFS rates resulted 96.0%, 82.9% and 63.7% in patients at low, intermediate and high risk, respectively ($p < 0.0001$). In the validation sample, the 5-year RFS was 96.2%, 85.4% and 66.9%, respectively. To conclude our study demonstrates that a very simple prognostic index based on easily available clinical data may represent a useful tool for the identification of patients at different risk of relapse and may be a notable device to predict who truly benefits from medical treatment.

The adoption of wide-scale mammographic screening for the detection of breast cancer at an earlier phase of development has resulted in an increasing number of cases being diagnosed at a very early stage, together with a reduction in breast cancer morbidity and mortality.[1–3] However, the risk that screen-detected cancer can lead to overdiagnosis in up to 24% of the cases, has been recently suggested.[4,5] Moreover, the introduction of the sentinel node procedure[6–8] has led to an increase in the detection rate of small lymph node metastases, due to more accurate pathological assessment that include step sectioning[9,10] and immunohistochemistry.[11] Finally, the new drugs and an enhanced tuning of already existing therapeutic approaches have contributed to a better disease control.

Consequently, a thorough search for more sensitive prognostic factors, able to help clinicians offer appropriate adjuvant therapy after surgery, balancing the benefits of the prevention of recurrence and the risks related with unnecessary treatment, has become a priority in this area.

In the past, the recognition of prognostic factors was based on the retrospective analysis of archive data and results were limited by patient selection criteria, missing data, no inclusion of more recently reported parameters and outdated adjuvant therapies. Finally, although overall survival (OS) should be the optimal endpoint, in a disease with an increasing scarcity of events, it appears unrealistic and requires a very long follow-up period.

For all these reasons, we collected an exhaustive set of clinical, laboratory, pathological and therapeutic information for all cases of breast cancer diagnosed in the Province of Modena, Northern Italy, with the aim of identifying appropriate factors able to better define the disease prognosis in terms of relapse-free survival (RFS).

Here we present the results of this study, which involved 4,970 new cases of operable breast cancer, registered between 1997 and 2007 and followed up to the year 2009.

Material and Methods

The Modena Cancer Registry collects data concerning incident cases of all malignant tumors in the province of Modena (Italy). In this study, we considered all new cases of invasive breast cancer (ICD03 site code C50.0–C50.9 and behavior code/3)[12] diagnosed between 1997 and 2007 with the last follow-up updated to December 31, 2009. We excluded patients with metastatic disease and those treated with neo-adjuvant therapy.

Key words: prognostic index, breast cancer, mammographic screening
Grant sponsor: Istituto Superiore di Sanità; **Grant number:** ACC2/R4.2; **Grant sponsor:** Associazione Angela Serra per la Ricerca sul Cancro
DOI: 10.1002/ijc.27795
History: Received 8 May 2012; Accepted 13 Aug 2012; Online 23 Aug 2012
Correspondence to: Laura Cortesi, Department of Oncology and Haematology, University of Modena and Reggio Emilia, Via del Pozzo 71, 41100 Modena, Italy, Tel.: +39-059-4224334, Fax: +39-059-4224152, E-mail: hbc@unimore.it

What's new?
Mammography helps catch breast tumors while they are still treatable. Identifying more sensitive prognostic factors that could be used during the course of treatment would help clinicians prevent recurrence and avoid unnecessary therapies. In this paper, the authors collected clinical, laboratory, pathological, and therapeutic information on almost 5,000 cases of operable breast cancer to find out which factors predicted successful recovery. They developed a prognostic index based on five variables that can help clinicians determine whether a patient's disease is likely to be helped by a particular drug, making it worth the toxic side effects.

Statistical analysis

The principal endpoint of this study was RFS, defined as the time from the date of diagnosis to date of relapse of the primary breast cancer, or date of last follow-up for uncensored cases. Local and distant relapses were considered as recurrences. RFS was estimated using the Kaplan–Meier method.[13] Relative survival was calculated according to Ederer method.[14] We investigated 11 parameters dichotomized as follows: age <70 *vs.* ≥ 70 years, tumor size ≤ 20 *vs.* >20 mm, nodal status (defined by the ratio of the percentage of positive nodes to total analyzed nodes) <10 *vs.* $\geq 10\%$, Ki67 proliferative activity <20 *vs.* $\geq 20\%$, expression of estrogen receptors (ER) ≥ 70 *vs.* $<70\%$, expression of progesterone receptors (PgR) ≥ 40 *vs.* $<40\%$, presence or absence of associated ductal carcinoma *in situ* (DCIS), tumor grading (3 *vs.* 1–2), presence of angioinvasion, presence of multifocality, and positivity to the human epidermal growth factor receptor 2 (HER2). The cut-off values for age, tumor size, nodal status, Ki67, ER and PgR were chosen subdividing the patients distribution in quartiles for explorative analysis and then and identifying upper or lower quartiles or merging two neighbors quartiles according to covariates. The age was dichotomized at 70-year old for considering the elderly patients in the upper quartile. The cut-off <20 mm in tumor size corresponded to status T1 and represented the lower quartile whereas the proliferative activity cut-off was predefined at Ki67 proliferation index of $\geq 20\%$ (since the third upper quartile corresponding to a high positively stained tumor cells, 25%, falls close the cut-point reported in literature). The covariate nodal status was grouped for any increased of the ratio of 5% and the ratio $>10\%$ represented the upper quartile. Estrogen receptor expression $<70\%$ represented the lower quartile cut-off. The PgR expression cut-off corresponded to the lower merged quartiles or median ($<40\%$). Grading III represented the upper quartile for grading score compared to grading I-II put together.

Angioinvasion, DCIS associated, multifocality and HER2 overexpression were considered in a categorical way.

Angioinvasion was considered as little cluster of neoplastic cells (≥ 5) inside the vessels by hematoxylin–eosin. Angioinvasion in peritumoral tissue was confirmed by CD31 immunostaining. The scoring of HER-2 by IHC was evaluated semiquantitatively according to the following categories: 0, no membrane staining; 1+, partial membrane staining in $>10\%$ of tumor cells; 2+, weak complete staining in $>10\%$ of tumor cells; 3+, complete staining of the membrane in $>10\%$ of tumor cells. The *HER2/neu* gene status was scored as the ratio between *HER-2* red signals and *CEP17* green signals. A *HER-2/CEP17* ratio >2 was interpreted as positive for gene amplification.[15]

The database was split into a training sample and a test sample by residence in the health districts of the province of Modena (training sample: district of Modena, Carpi and Pavullo, $N = 2{,}296$, 68%; test sample: districts of Mirandola, Castelfranco Emilia and Vignola, $N = 1{,}099$, 32%). The training sample was used to develop and validate the model, identifying the most appropriate score and the test sample was excluded from the original database, "frozen" and used for external validation. Univariate and multivariate analysis were performed by means of Cox proportional hazard (PH) regression.[16]

The Stata 8.2/SE package (StataCorp, College Station, TX) was used for all statistical analysis. All P values were two sided.

Results

Patient characteristics

Between 1997 and 2007, there were 6,131 new cases of invasive breast cancer in the province of Modena. Excluding 781 patients because of lacking of status, metastatic disease or neoadjuvant treatment before surgery, 5,350 cases were considered eligible for the purposes of the study. Finally, after further exclusion of 377 cases, mainly due to lack of data, the cohort considered for the analysis was composed of 4,970 women initially treated with radical tumor resection.

The main characteristics of the 4,970 eligible cases included in the analysis are summarized in Table 1. As regards the diagnostic modality, 1,641 tumors (33%) were screen-detected. Mean age at diagnosis was 61 years (range, 26–95 years). Median tumor size was 15 mm (range, 1–46 mm), with most cases (2,164, 44%) falling in the T1c category. Nodal status was available in 4,723 cases. In 247 cases, axillary dissection or sentinel node biopsy was spared because of the advanced age of the patients (72% of them were ≥ 70 years). Among 97 patients aged less than 70 years, 45 had a tumor size ≤ 1 cm, whereas for 52 cases there was no clear reason for lacking of nodal status information.

After a median follow-up of 73 months (range, 1–155), and follow-up completeness of 88% (19), 494 relapses (9.9%) were recorded, including 126 local (26%) and 368 distant (74%) relapses. The average relapse rate was 16.4 (95% CI, 15.0–17.9) per 1,000 person-years; peak recurrence (21.6,

Table 1. Characteristics of the patients recorded in Modena Cancer registry between 1997 and 2007

Variable	*N*	Mean	Median	Range
Age (year)	4,970	61	61	22–96
Tumor size (mm)	4,895	17	15	1–90
Estrogen receptor (%)	4,605	68	85	0–100
Progesterone receptor (%)	4,593	41	35	0–100
Proliferative activity (%)	4,517	18	13	0–100
Nodal status (%)	4,930	8	0	0–100
	N	%		
Grading	4,646			
1	736	16		
2	2,060	44		
3	1,850	40		
N	4,970			
NX	247	5		
N0	3,126	63		
N1	1,067	21		
N2	304	6		
N3	226	5		
T	4,950			
T1mic-T1b	1,497	30		
T1c	2,164	44		
T2	1,289	26		
DCIS associated	4,970			
No	2,321	47		
Yes	2,649	53		
Sentinel node	4,970			
No	3,187	64		
Yes	1,783	36		
Axillary node dissection	4,970			
No	1,472	30		
Yes	3,498	70		
Multifocality	4,970			
No	4,356	88		
Yes	614	12		
Angioinvasion	4,970			
No	4,338	87		
Yes	632	13		
HER2	3,610			
Negative	3,131	87		
Positive	479	13		
Year of diagnosis				
1997–2001	2,178	44		
2002–2004	1,442	29		
2005–2007	1,350	27		

N, nodes; T, tumor; DCIS, ductal carcinoma *in situ*; HER2: epidermal growth factor receptor 2.

95% CI, 17.6–26.5 per 1,000 person-years) was observed between the second and third year after diagnosis of primary breast cancer.

The 5- and 10-year RFS rates were 91.3% (95% CI, 90.4–92.1%) and 85.4% (95% CI, 83.9–86.7%), respectively. The outcome improved through the study period, with the 4-year RFS 92% for cases diagnosed in the period 1997–2001 and 95% for those diagnosed in the years 2005–2007 ($p = 0.005$).

At the same intervals, 5- and 10-year OS rates were 88.2 (95% CI, 87.2–89.1%) and 75.5% (95% CI, 73.7–77.1%), respectively. Indeed the relative survival of the general population after 5 and 10 years were 95.5% (95% CI, 94.4–96.5%) and 91.5% (95% CI, 89.8–93.2%), respectively.

Prognostic model development

In univariate analysis, all 11 investigated variables had a statistically significant impact; thus further analyses were performed in the group of 3,395 cases (68%) with a complete set of data. The final study sample of 3,395 cases was then split into one training and one test sample. In the training sample, a total of 206 events were observed, corresponding to an event/variable ratio of 19:1, which represents a satisfactory ratio for carrying out the multivariate analysis and avoiding the problem of overfitting the model.[17]

As far as adjuvant therapy is concerned, 2,878 patients (85%) were treated with systemic approach (chemotherapy and/or hormone therapy plus or minus radiotherapy) whereas 517 (15%) received solely surgical treatment with or without radiotherapy. Details on adjuvant therapy are given in Table 2.

The model was built by means of a bootstrap screening with a backward elimination over the training sample. These procedures were performed by means of a multivariate Cox proportional hazard model with a selection guide of $p = 0.10$. The performance of the selected model was assessed by the error rate (1-c Harrell) in an out-of bootstrap sample that was used like a test data set. The procedure was repeated 1,000 times.[18] Since the model gave the lowest error with five or six covariates, we choose the five covariates more frequently included, *i.e.*, tumor size (100%), node status (99%), grading (97%), HER2 status (85%) and estrogen receptor status (64%). The subsequent covariates, angioinvasion (38%), association with DCIS (37%), proliferative activity (31%), progesterone receptor (30%), multifocality (13%) and age (8%) were excluded from the multivariate analysis since had a low frequency and high rate of error. At the end of this process, a simple risk score was obtained using the five variables retained in the final model (Table 3). A score was attributed to each variable according to its relative weight, derived from the *z*-Wald values found in the Cox PH model, which attributed nodal status and tumor size a weight double that of tumor grading, estrogen receptor status and HER2 status. The score ranged from 0 to 7 and the patients were stratified according to the following three risk groups: score 0–2 (72.4%), low risk; score 3 and 4 (19.0%), intermediate risk and score 5–7 (8.6%), high risk.

Table 2. Distribution of therapies in the 3,395 patients included in the building and validation model recorded in the Modena Cancer Registry between 1997 and 2007 and modality of diagnosis

Therapy	*N*	%
Chemotherapy	1,275	
CPM	493	39
ANTHRA	660	51
ANTHRA ± TAX	117	9
Not assessed	5	<1
Radiotherapy	3,395	
No	1,268	37
Yes	2,127	63
Hormone therapy	3,395	
No	840	25
Yes	2,555	75
Therapy combination	3,395	
CHT + RT + HT	678	20
CHT + RT	224	7
CHT + HT	274	8
RT + HT	1,087	32
CHT	99	3
HT	516	15
Surgery ± RT	517	15
Screen detected	3,395	
No	2,183	64
Yes	1,212	36

CPM: regimens containing cyclophosphamide; ANTHRA: regimens containing anthracycline; TAX: regimens containing taxanes; CHT: generic chemotherapy; RT: radiotherapy; HT: hormone therapy. Note: Because of rounding, percentages may not total 100.

In the training sample ($N = 2{,}296$), the 5-year RFS rates were 96.0% (95% CI, 94.8–96.9%), 82.9% (95% CI, 78.6–86.5%) and 63.7% (95% CI, 55.2–70.9%) in patients at low, intermediate and high risk, respectively ($p < 0.0001$, c-Harrell 0.734); and the 10-year RFS rates were 92.1% (95% CI, 88.0–94.9%), 71.5% (95% CI, 60.9–79.6%) and 50.9% (95% CI, 38.7–61.8%) for each risk category, respectively ($p < 0.0001$) (Fig. 1*a*). Furthermore, the hazard ratio between score 3 and 4 and 0/2 was 4.57 (95% CI, 3.28–6.36, $p < 0.001$) and between score 5/7 and 3–4 was 2.36 (95% CI, 1.69–3.30, $p < 0.001$). The 5-year OS rates were 92.5%, 81.0% and 64.8% and the 5-year relative survival rates were 99.1%, 90.0% and 72.5% for patients at low, intermediate and high risk, respectively ($p < 0.0001$).

External validation

Patient characteristics of the test sample were similar to those of the study sample for all variables except high tumor grade (46 *vs.* 40) and large tumor size (35 *vs.* 30). The RFS at 5 and 10 years (90.8% and 84.5%) compared favorably with that observed in the study sample (90.9% and 85.0%) ($p = 0.567$).

Seven hundred and forty patients (67%) had a score of 0–2, 244 (22%), a score of 3–4 and 115 patients (11%) had a score of 5–7. The corresponding RFS at 5 years by score 0–2, 3–4 and 5/7 were 96.2% (95% CI, 94.4–97.5%), 85.4% (95% CI, 79.1–89.8%); and 66.9% (95% CI, 56.1–75.6%), respectively; and RFS at 10 years for scores 0–2, 3–4 and 5–7 were 92.6% (95% CI, 88.2–95.4%), 77.0% (95% CI, 66.3–84.6%) and 40.7% (95% CI, 16.6–63.7%), respectively (Fig. 1*b*).

Patients who only received surgical treatment plus or minus radiotherapy had a median age of 68 years compared to 59 years of patients treated with systemic therapy ($p < 0.001$), were more likely affected with T2 tumor size (36% *vs.* 31%; $p = 0.018$) and had more frequently ER expression <70% (32% *vs.* 24%; $p < 0.001$). On the other hand, patients locally treated had less nodal status ≥10% than those with systemic therapy (14% *vs.* 19%, $p = 0.006$). Finally, no statistically significant difference in frequency distribution for all score levels between patients with and without systemic therapy was seen ($p = 0.200$).

The unstratified hazard ratio of surgery ± RT *vs.* surgery plus systemic therapy on RFS was 1.05 (95% CI, 0.77–1.43, $p = 0.774$). The HR of surgery ± RT *vs.* surgery plus systemic therapy by score 0–2, 3–4 and 5/7 were 1.23 (95% CI, 0.73–2.07; $p = 0.444$), 0.99 (95% CI, 0.58–1.70; $p = 0.986$) and 0.83 (95% CI, 0.47–1.47; $p = 0.529$), respectively (Fig. 2).

Moreover, the difference in *D* statistic between the test and training samples (over 250 bootstrap resample) was −0.02, indicating good reproducibility (Table 4). The hazard ratio between score 3 and 4 and 0–2 was 3.58 (95% CI, 2.18–5.90, $p < 0.001$) and between score 5 and 7 and 3–4, it was 2.92 (95% CI, 1.82–4.68, $p < 0.001$).

Discussion

By using data from a population-based cancer registry, which also allowed us to collect information on treatment modalities and outcome of patients diagnosed with breast cancer in the province of Modena (Italy), we have developed a prognostic index based on the five most appropriate variables such as, tumor size, node status, grading, HER2 status and estrogen receptor status, previously selected according to a bootstrap screening.

Although the adoption of categorical variables in modeling procedures has been heavy criticized by statisticians[19] our results compare favorably with other scores that allow the probability of recurrence from breast cancer to be accurately estimated and include the Nottingham Prognostic Index (NPI),[20] Adjuvant! Online,[21] Mammaprint[22] or Oncotype Dx RSs.[23]

In particular, our study confirms the validity of the NPI, developed in 1982, that divides operable patients with breast cancer into good, moderate and poor prognostic groups with 15-year survival of 80%, 42% and 13%, respectively.[24] In fact, our results, confirmed in the test sample, showed a 10-year RFS rates of 92.1% (95% CI, 88.0–94.9%), 71.5% (95% CI, 60.9–79.6%) and 50.9% (95% CI, 38.7–61.8%) for each risk category, respectively ($p < 0.0001$). The paradox of RFS

Table 3. Association between the patient characteristics at diagnosis and RFS evaluated by means univariate and multivariate Cox proportional hazard analysis in the training sample ($N = 3{,}395$)

Parameter	%	10-years RFS% (SE)	HR (95% CI) Univariate	HR (95% CI) Multivariate	*z*
Nodal status					
<10%	82	89 (1.7)	1.0	1.0	
≥10%	18	64(4.2)	4.33 (3.29–5.71)	2.86 (2.14–3.83)	7.1
Tumor size					
≤20 mm	75	90 (1.7)	1.0	1.0	
>20 mm	25	69 (4.0)	4.00 (3.05–5.27)	2.47 (1.84–3.31)	6.0
Grading					
1–2	60	90 (2.4)	1.0	1.0	
3	40	76 (2.5)	3.55 (2.65–4.75)	2.02 (1.42–2.69)	4.1
HER2					
Negative	87	86 (1.8)	1.0	1.0	
Positive	13	75 (3.5)	2.74 (2.01–3.72)	1.95 (1.42–2.69)	4.1
Estrogen receptor					
≥70%	74	90 (1.2)	1.0	1.0	
<70 %	26	77 (3.0)	2.28 (1.73–3.00)	1.54 (1.16–2.06)	2.9
Angioinvasion					
No	87	87 (1.8)	1.0		
Yes	13	69 (4.0)	3.22 (2.38–4.34)		
DCIS associated					
No	38	80 (3.1)	1.0		
Yes	62	88 (1.4)	0.67 (0.51–0.88)		
Proliferative activity					
<20%	60	87 (2.4)	1.0		
≥20%	40	82 (1.8)	2.53 (1.91–3.35)		
Progesterone receptor					
≥40%	53	86 (3.3)	1.0		
<40%	47	82 (1.8)	1.82 (1.37–2.42)		
Age					
<70	72	88 (1.9)	1.0		
≥70	28	83 (3.0)	1.48 (1.10–1.98)		
Multifocality					
No	87	85 (1.8)	1.0		
Yes	13	84 (2.9)	1.29 (0.89–1.87)		
Slope shrinkage	0.986				
Corrected c-Harrell	0.765				

HR: hazard ratio; CI: confidence intervals; HER2: epidermal growth factor receptor 2; DCIS: ductal carcinoma *in situ*. $z = z$-statistic from Wald test; slope shrinkage and corrected c-Harrell obtained over 250 bootstrap replications.

being better than OS can be attributed to the advanced age of the investigated study population, in which a large proportion of deaths in the general population were unrelated to breast cancer and its treatment.

Recently, the addition of progesteron receptor and HER2 to NPI increases its 5-year prognostic accuracy.[25]

Although no biological material was disposable for comparing our model with a gene expression profiling system, such as OncotypeDX, that uses a candidate-gene approach to generate a quantitative recurrence score (RS) and defines three risk categories of recurrence (low < 18, intermediate between 19 and 31 and high $S > 32$) or MammaPrint,

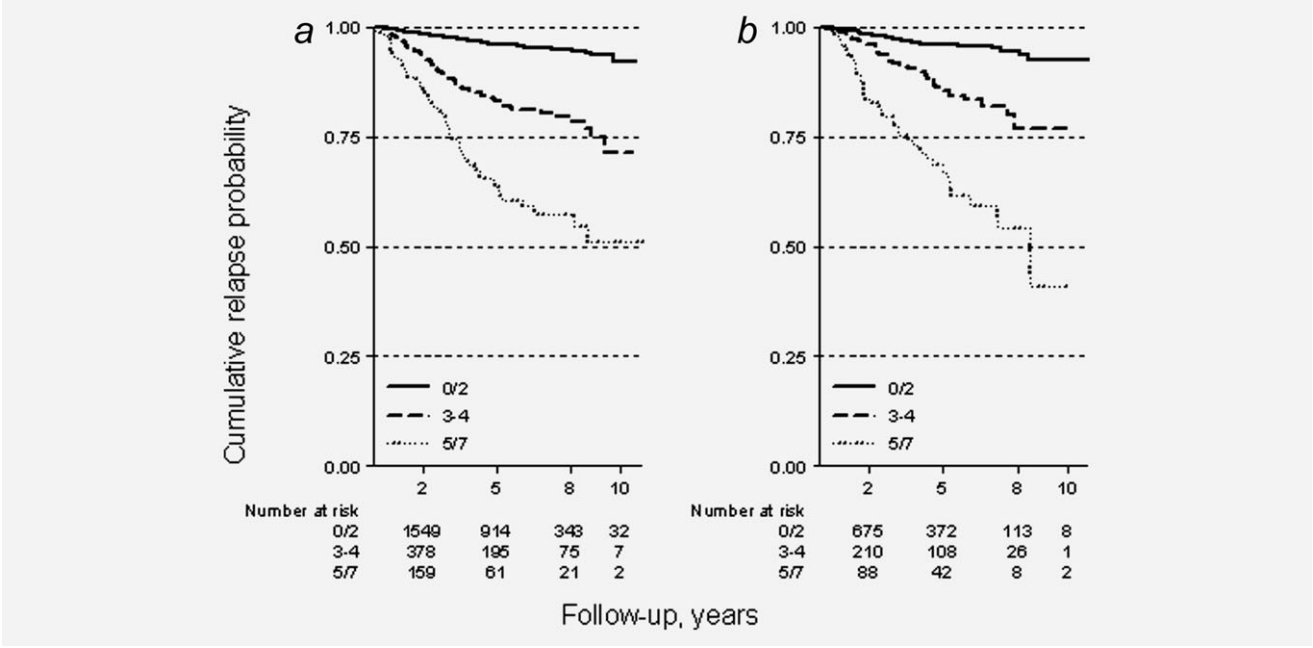

Figure 1. RFS stratified according to prognostic score index in training (*a*) and test sample (*b*). Solid line: low-risk score (0/2); dashed line: intermediate risk score (3–4); dotted line: high-risk score (5/7).

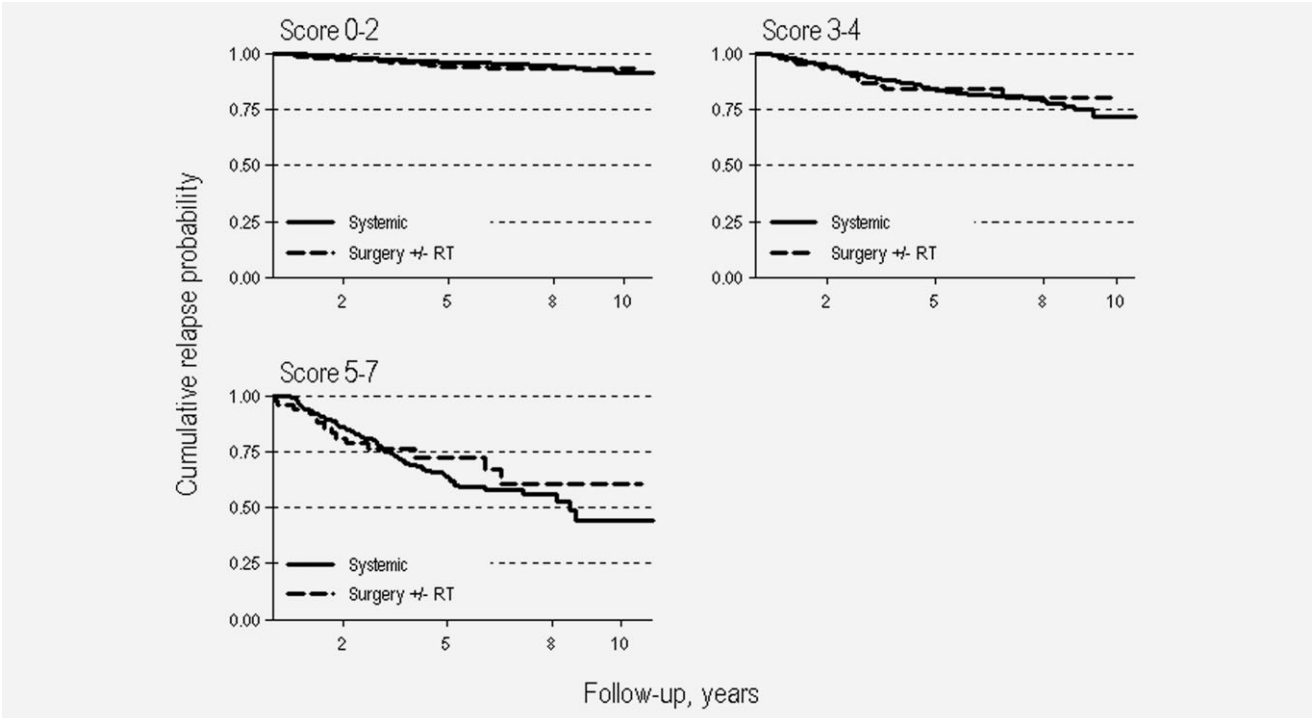

Figure 2. RFS stratified by treatments, according to the proposed prognostic score index, in the 3395 cases with complete data. Solid lines: systemic therapy; dashed lines: surgical treatment ± RT.

developed with a supervised top-down approach, that measures the expression of 70 genes to categorize patients into "good" or "poor" risk groups, we can argue that our results reflect data of a recent breast cancer gene signatures meta-analysis where tumor size and nodal status, still retain an independent predictive value of distant relapse.[26]

An interesting point that emerges from this work is that no differences were observed in RFS between patients who

Table 4. Validation of the prognostic score on the test sample

	Training sample $N = 2,296$			Test sample $N = 1,099$		
	N	%	RFS (%) 10 years	*N*	%	RFS (%) 10 years
Score						
Low (0/2)	1,662	72.4	92	740	67.3	93
Intermediate (3–4)	437	19.0	72	244	22.2	77
High (5/7)	197	8.6	51	115	10.5	41
Score	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Intermediate *vs*. Low	4.57	3.28–6.36	<0.001	3.58	2.18–5.90	<0.001
High *vs*. Intermediate	2.36	1.69–3.30	<0.001	2.92	1.82–4.68	<0.001
High *vs*. Low	10.8	7.67–15.2	<0.001	10.5	6.47–16.9	<0.001
D Royston	1.67 (SE 0.12)			1.65 (SE 0.18)		
D difference				−0.02 (95% CI −0.44 to 0.40)		
Shrinkage				0.982 (SE 0.101)		
c-Harrell	0.734 (95% CI 0.702–0.767)			0.728 (95% CI 0.677–0.778)		

CI: confidence intervals; *D* difference: (*D* test − *D* training) sample. *D* difference and 95% CI of c-Harrell obtained over 250 bootstrap resample.

received only surgery ± radiotherapy compared to patients treated with systemic therapy in the three risk categories. Patients with advanced age were only locally treated probably because of comorbidities. Despite a greater *T* size and lower ER expression of patients treated by surgery plus or minus RT compared to those undergone systemic therapy, no statistically significant differences in score appeared, probably due to the fact that nodal status, which has a double weight in the score assessment, was less frequently evidenced. Our results suggests that elderly patients, although show a greater tumor size than younger ones, probably have less capability to metastasize lymph nodes. So we suggest that elderly people could be spared for such therapies.

Furthermore, screen detected cancers are smaller sized, are more likely to be grading I–II, with low proliferative activity and displays an excellent outcome, thus questioning the need for chemotherapy.[27,28] Our data, derived from an area where a significant proportion of breast cancers were diagnosed with active mammographic screening, indicate that the prognostic categories as defined using classic or genomic methods, can overestimate the risk of recurrence and as a consequence the risk of unnecessary adjuvant treatments is therefore amplified.

Undoubtedly, our model could be improved by reworking the T1 category as a dynamic filing system as suggested by Veronesi *et al.*[29] However, we adopted the T1 cut-off to separate small tumors from large ones, as obtained from our internal analysis on continuous variables.

As far as nodal status is concerned, we incorporated into the model the nodal ratio, a new index that would appear to be more accurate than pN classification in predicting survival after breast cancer and proposed as an alternative to pN staging. In a previous series of 82 patients, a nodal ratio >20% was associated with local recurrence with a 10-year relapse of 28.7%.[30] More recently, Vinh-Hung et al.[8] showed that the lymph node ratio predicts survival after breast cancer more accurately than pN classification and should be considered as an alternative to pN staging, by dividing the patients into low, intermediate and high risk with ≤20%, >20% to ≤65% and >65%, respectively.

Regarding the importance of estrogen receptor status, it is well known that there is a marginally statistically significant relationship between ER level (as a continuous variable) and time to relapse (TTR), with lower levels being associated with a shorter TTR.[31] Estrogen expression dichotomization was chosen according to Collins *et al.*[32] which showed that among 825 cases evaluated for ER expression, 660 (80%) had positivity in 70% or more of the tumor cells. The Ki67 cut-off ≥20%, was found corresponding to the upper quartile in a previous paper published by Ahlin *et al.*[33] before the introduction of 2011 St. Gallen guidelines.

In conclusion, the model proposed here is a simple prognostic index based on readily available clinical data and may represent a promising new tool for the identification of patients with different risks of disease progression at a time when a significant number of cases are diagnosed through active screening procedures. This is particularly relevant considering the increasing availability of new and very expensive drugs that should be offered only if truly able to further improve the chances of cure and thus justify treatment-induced toxicity.

In the future, a comparison with gene expression profiling systems (Mammaprint or Oncotype DX) could be desirable to validate our prognostic model in a prospective study.

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