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ORIGINAL ARTICLE - CLINICAL ONCOLOGY

# Post-operative nomogram for predicting freedom from recurrence after surgery in localised breast cancer receiving adjuvant hormone therapy

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**Abstract**
*Purpose* To develop a prognostic nomogram to predict freedom from recurrence for patients treated with adjuvant hormonal therapy (HT) for localised breast cancer (BC).
*Methods* We performed a retrospective analysis of 142 patients treated with adjuvant HT between 1996 and 2000. Clinical and pathological parameters were analysed.
*Results* A nomogram that predicts the probability of remaining free of recurrence for 5 years after surgery with adjuvant HT was developed using a Cox proportional hazards regression model. The progesterone receptor status ($p < 0.001$), nodal status ($p = 0.008$) and cathepsin-D ($p < 0.001$) were retained to construct the nomogram (C-index 0.734).
*Conclusions* The nomogram we developed may be useful for estimating the probability of successful treatment 5 years after surgery for localised BC.

**Keywords** Breast cancer · Nomograms · Progesterone receptor · Cathepsin-D · Thymidine kinase

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## Introduction

Tumour-derived genomic signatures (Cardoso et al. 2008; Kelly et al. 2010) seem to be future alternative tools for evaluating the prognosis in breast cancer (BC), but other biological tumour factors such as the uPA/PAI-1 system are also promising (Harbeck 2010). In node-negative tumours or even in lesions with low nodal involvement (<3) and thus a better prognosis, adjuvant chemotherapy is discussed, and some patients receive only hormonal therapy (HT) when hormone receptors (HR) are positive. However, a non-negligible 30 % of women relapse after 5 years of adjuvant hormone therapy. An alternative to expensive genomic analyses is the use of mathematical models that include multiple parameters to mimic the biology and natural history of the cancer. Identifying prognostic factors associated with either the metastatic or growth potential of the primary tumour would assist physicians in determining which patients with node-negative disease would benefit from adjuvant therapy.

Predictive nomograms were developed for BC to improve patient management at the individual level. Such nomograms were mainly proposed for the surgical setting to predict the risk of axillary node involvement or to predict response to chemotherapy in the neoadjuvant setting (Van Zee et al. 2003; Houvenaeghel et al. 2009; Rouzier et al. 2005, 2006). Very few models have been proposed to evaluate the prognosis (Hanrahan et al. 2007; Mazouni et al. 2011). One interesting aspect of a nomogram, beyond the user-friendly appearance for both physicians and patients, is that it models the risk on a continuous scale rather than classifying patients into discrete risk groups (Kattan et al. 2001).

The purpose of this study was to develop a nomogram, using clinical and level of evidence (LOEI)-I prognostic

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markers to predict the probability of remaining free of recurrence for 5 years in patients with node-negative BC treated with adjuvant hormonal therapy.

## Patients and methods

A total of 142 patients who had undergone primary surgery to treat their clinically localised BC from 1996 to 2000 were included in this analysis. All patients who had received neoadjuvant therapy or adjuvant chemotherapy were excluded. Patients with evidence of locally advanced (stage IIIB), bilateral, metastatic or inflammatory BC were also excluded. All clinical and histological data were prospectively entered into a computerised research database. The entry of data into the central database was cross-checked by the data verifier and data manager. Follow-up had consisted of a clinical examination thrice yearly and an annual mammography, liver ultrasonography and bone scintigraphy. Women who were hormone receptor (ER) positive had received 5 years of endocrine therapy after radiotherapy had been completed.

In this data set, the ER status and PgR status had been determined through routine pathological assessment using an enzyme immunoassay (EIA). ER and PgR levels had been determined using Abbott kits (Abbott Laboratories, Chicago, USA) according to the manufacturer's instructions. The determination technique has previously been described (Bonnier et al. 1995; Romain et al. 1995). Hormone receptor status had been determined in cytosols prepared according to the recommended EORTC procedure. Tumours were considered ER positive or PgR positive with a cut-off at 15 fmol/mg protein. The nuclear grade had been assessed using the Scarff-Bloom-Richardson system.

Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) (uPA Imubind no 894, PAI-1 Immubind no 821, both from American Diagnostica, Greenwich, USA), had been measured with enzyme immunoassays (Look et al. 2002). uPA and PAI-1 levels had been determined instead of a cut-off because different extraction methods had been used. Thymidine kinase (TK) activity had been determined using a radioenzymatic phosphorylation assay (TK-REA, Sangtec Medical, Bromma, Sweden) optimised to detect the foetal TK1 isoenzyme, as previously described (Romain et al. 2001), (continuous levels of TK activity had been measured). Cathepsin-D levels had been assayed by solid-phase 2-site immunoradiometric methods (Romain et al. 1994) (ELSA-Cath D; CIS Bio-Industries, Gif-sur-Yvette, France). The median level of cathepsin-D had been used as the cut-off. The results were expressed as pmol/mg protein. Quality control had been ensured by frequent testing with internal controls.

The nomogram was developed using a Cox proportional hazards regression model. The predictor variables tested were the patient's age, tumour characteristics and the nodal status. To determine informative covariates required to construct the nomogram, reduced model selection was performed using a backward step-down selection process with Akaike's information criterion (AIC) as a stopping rule. Two validation methods were used. First, discrimination was quantified with the concordance index (C-index) (Harrell et al. 1982), a measure which is similar to the area under the receiver operating characteristic curve but appropriate for censored data (Begg et al. 2000). Second, the calibration was examined by plotting the predictions made by the nomogram against the actual freedom from recurrence, which were measured by the Kaplan–Meier method using the SPSS software package version 21 (SPSS Inc., Chicago, IL). All statistical analyses were performed using the R statistical software. The "Design" package using the R statistical software was used to develop our nomogram for predicting survival. All tests were 2-sided, and $P$ values of 0.05 were considered significant.

## Results

Table 1 summarises the main information concerning the population studied. Patients had undergone a breast-conserving lumpectomy with axillary lymph node dissection ($n = 101$) plus adjuvant radiotherapy ($n = 100$) or a modified radical mastectomy with axillary lymph node dissection ($n = 41$), and 38 of them had received adjuvant radiotherapy. All cases were oestrogen receptor positive. A total

**Table 1** Characteristics of the studied population

| | $n = 142$ |
|---|---|
| Age [median (range)] | 66 (46–89) |
| Tumour size in mm [median (range)] | 18.5 (8–120) |
| *SBR grade (%)* | |
| 1–2 | 118 (83.1) |
| 3 | 23 (16.2) |
| Not assessable | 1 (0.7) |
| *Lymph node status (%)* | |
| Negative | 88 (62) |
| Positive | 54 (38) |
| *Progesterone receptor (%)* | |
| Negative | 23 (16.2) |
| Positive | 119 (83.8) |
| uPA [median (range)] | 0.73 (0–5.38) |
| PAI-1 [median (range)] | 5.2 (0–29.8) |
| Cathepsin-D [median (range)] | 42 (0–167) |
| Thymidine kinase [median (range)] | 47.5 (0–505) |

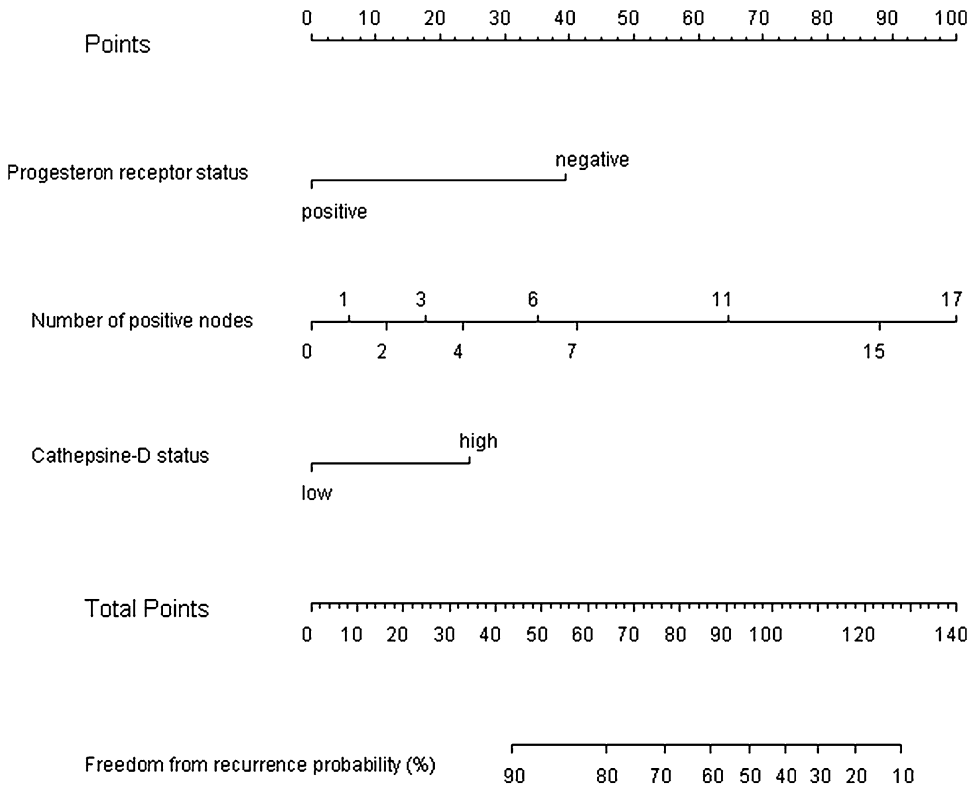


**Fig. 1** Nomogram to predict individual recurrence-free probability. The total score is the sum of the points obtained for each covariate in the nomogram (scale across the *top*). This sum is then referred back to the total points scale and corresponds to a probability obtained on the recurrence-free probability scale

of 16.2 % (23/142) patients had PgR-positive tumours. All patients had received hormonal therapy in accordance with our protocol. For recurrence-free patients, median follow-up was 75 months (range 3–276 months).

At the time of the analysis, 21/142 (14.8 %) patients had relapsed, and six had died. The 3-year OS rate was 99.3 % (95 % CI 97.9–100 %), and the 5-year OS rate was 98.3 % (95 % CI 96.1–100 %). The 3-year RFS rate was 96.2 % (95 % CI 93–99.5 %), and the 5-year RFS rate was 92.5 % (95 % CI 87.9–97.4 %). At 5 years, nine patients had developed a recurrence.

Five-year OS was 98 % for PgR-positive BC and 100 % for PgR-negative BC ($p = 0.19$). Five-year RFS was 93 % for PgR-positive BC and 90.5 % for PgR-negative BC ($p = 0.02$). Five-year OS was 96.8 % for high cathepsin-D BC and 100 % for low cathepsin-D BC ($p = 0.03$). Five-year RFS was 88.4 % for high cathepsin-D BC and 96.9 % for low cathepsin-D BC ($p = 0.03$). Five-year OS was 95.3 % for node-positive BC and 100 % for node-negative BC ($p = 0.006$). Five-year RFS was 83.4 % for node-positive BC and 97.6 % for node-negative BC ($p < 0.001$).

In the univariate analysis, age ($p = 0.04$), PgR ($p = 0.02$), TK ($p = 0.007$) and the nodal status ($p < 0.001$) were independent predictors of freedom from recurrence in the Cox regression model, while the tumour size ($p = 0.06$), grade ($p = 0.21$) and cathepsin-D ($p = 0.11$), uPA ($p = 0.40$) and PAI-1 ($p = 0.40$) levels were not. In the multivariate analysis, we evaluated TK ($p = 0.16$), PgR ($p = 0.001$), cathepsin-D ($p = 0.06$) levels and the nodal status ($p = 0.008$). Using a backward selection procedure and AIC: PgR, the nodal status and cathepsin-D were retained to construct the nomogram. The nomogram derived from this Cox model is shown in Fig. 1.

Using these three variables, the C-index of the nomogram based on the fitted multivariate Cox model was 0.734 before calibration and 0.727 after. The calibration of the nomogram when applied to the validation data sets is shown in Fig. 2. The AIC was 146.5.

The total number of points is obtained by summing the points scored by each variable in the nomogram. This total corresponds to the survival probability reflected by the vertical line drawn between the two axes. Prognostic probabilities were computed as the sum of the points attributed to each level of these three covariates. The points were calculated by rescaling the model-derived beta coefficients to a scale ranging from 0 to 100.

For instance, a women presenting with negative PgR (40 points), 2 positive nodes (10 points) and a high cathepsin-D level (22 points) will score 62 points that convert to an 80 % probability of freedom from recurrence.

We also compared a model that did not include cathepsin-D but two variables (PgR and the nodal status). This comparison showed a lower C-index and a higher AIC model (150.3). The performance of the model was therefore not as satisfactory.

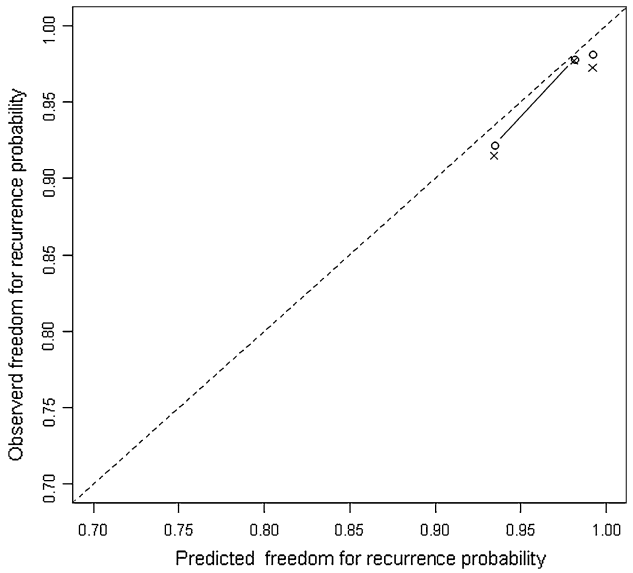


**Fig. 2** Calibration curves for 5-year overall survival. The *dashed line* indicates the ideal reference line where predicted probabilities would match the observed outcome. The 45° reference line shows where perfect predictions would lie. *Open circles* indicate subsets of patients grouped according to their predicted probabilities of remaining free of BC. *Note* patients in the higher-risk groups are well below the reference line

## Discussion

Early recurrence after primary BC is a highly unfavourable event in the natural history of treated BC and is associated with early progression to distant metastases and cancer-specific mortality (Harris et al. 2007). Although it is important to determine recurrence in BC, there are no specific tools capable of predicting the individual probability of early recurrence after primary surgery in low-risk patients. During recent years, several studies have investigated potential biological determinants of tumour progression but few have proven to be of clinical utility (Sturgeon et al. 2008; Schmidt et al. 2009). However, by adding some of these emerging factors to classic prognostic factors, we were able to develop a promising tool to estimate the individual risk of recurrence in patients and to inform them. A combination of several clinicopathological prognostic factors is currently being used for clinical decision-making (Schmitt et al. 2010), and nomograms represent a user-friendly approach.

While developing our nomogram, we assessed several potential biological predictors that had hitherto not been tested in other prognostic nomograms. The uPA and PAI-1 proteases have attained level of evidence (LOE) I (Sturgeon et al. 2008; Schmidt et al. 2009; Silvestrini et al. 1993), while cathepsin-D or the TK proliferation markers are still underevaluation. As reported by several other groups, we found that the PgR status was a good predictor of relapse in patients receiving hormone therapy (Boracchi et al. 2008; Liu et al. 2010; Meijer-van Gelder et al. 2004). In a recent study, Schmidt et al. found that an algorithm comprising PAI-1 was more efficient for predicting the prognosis than St Gallen criteria or the Adjuvant! Online tool (Schmidt et al. 2009). Some authors reported the predictive value of uPA/PAI-1 for deriving a benefit from tamoxifen (Foekens et al. 1999). Previous results regarding cathepsin-D were more controversial, with a few groups finding an independent prognostic value (Ferrandina et al. 1997; Spyratos et al. 1989; Descotes et al. 2008). Interestingly, while the role of uPA and PAI-1 is strong in node-negative patients (Silvestrini et al. 1993; Muss et al. 2007), in our series these factors appeared to be non-contributive for predicting the likelihood of being free of recurrence in our population which included node-positive BC. It is not clear how high levels of protease might influence lymphatic dissemination of BC. Also, a recent study by Harms et al. (2014) confirmed that uPA and PAI-1 are not predictive markers of metastatic lymph node involvement and might explain the absence of an impact of protease markers on recurrence-free survival in node-positive BC.

One of the main limitations of our study is the small sample size of our training set as well as the absence of validation in an independent population. Moreover, the predicted probability of recurrence-free survival within 5 years tended to be overly pessimistic, as depicted in the calibration plot. The practical application of our nomogram consists in identifying individuals at risk of early recurrence after breast surgery and hormone therapy. This tool could facilitate our understanding of the risk of recurrence and shared decision-making between patient and care provider. However, some limitations have been identified in the generalised use of nomograms, such as a difference in treatment between the population which served to develop the nomogram and the validation population (Caras and Sterbis 2014). Nomograms help better determine the wide heterogeneity of BC by combining multiple clinical and biological parameters which reflect the biological behaviour of BC at the individual level. Providing a probability of the risk of recurrence using a cut-off such as that proposed by other algorithms or genomic signatures (mammaprint, Oncotype Dx) might help clinicians decide to pursue hormonotherapy beyond 5 years at a lower cost compared to genomic tools. Boracchi et al. previously developed and validated a nomogram based on the tumour size, nodal involvement, oestrogen and progesterone receptors with a discrimination index of 0.716. This tool is capable of predicting recurrence after hormonotherapy (Boracchi et al. 2008). The clinical application of a nomogram in luminal breast cancer was proposed in a recent series reported by Park et al. They developed a nomogram based on ER and Ki67 to

predict recurrence in receptor-positive BC irrespective of the nodal status. The performance of their nomogram was better than Adjuvant! Online, St. Gallen risk stratification and IHC 4 scores (Park et al. 2014). Patients with luminal breast cancer could therefore be considered for adjuvant therapy (chemotherapy) or as candidates for new drug development.

Our nomogram will be useful for predicting these potentially ominous early failures, by identifying patients who may benefit from adjuvant chemotherapy. Our model could probably be improved by including other biological markers. However, HER-2 as well as Ki-67 previously failed to be good predictors in another series (Kok et al. 2009). The use of molecular signatures predictive of endocrine therapy such as the HOXB13-IL17BR ratio or the 21-gene Recurrence Score were shown to improve the prediction of survival (Habel et al. 2013). During the last decade, various gene signatures have been developed to predict the prognosis of oestrogen-positive BC treated with endocrine therapy. Thus, a recurrence score (Oncotype DX) based on a 21-gene predictor set provided a risk score to determine a prognostic risk and decide upon adjuvant chemotherapy (Paik et al. 2004). In addition, the 70-gene signature MammaPrint (Agendia, Amsterdam, The Netherlands) can be used for node-negative BC irrespective of the ER status (Van de Vijver et al. 2002) and might outperform the Adjuvant! Online web interface (Sotiriou and Pusztai 2009). After evaluation, the genomic grade index, a 97-gene signature, was also found to be better related to outcome than conventional clinical factors (Loi et al. 2007; Desmedt et al. 2009). It is not clear how these signatures would compare with our nomogram which also combines clinical parameters with single biomarkers.

In conclusion, we developed a nomogram based on tumour biology that predicts 5-year patient outcome after primary surgery for localised BC which has a concordance index of 0.734–0.727. It may be a useful tool for physicians and patients as a part of the decision-making process by identifying patients at high risk of failure after adjuvant hormone therapy who may benefit from adjuvant treatment protocols in addition to hormone therapy.

## Summary points

Results

- The levels of PgR ($p = 0.001$), cathepsin-D ($p = 0.06$) biological markers and the nodal status ($p = 0.008$) are predictors of freedom from recurrence.
- A nomogram yielding a per cent risk of recurrence was constructed and shows a good concordance index (0.734).

Prospects

- The nomogram should be a useful additional tool for patient counselling and physician decision-making in node-positive and node-negative BC patient groups.

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**Conflict of interest** Authors do not have conflict of interest to declare.

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