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Original article

Evaluation of a breast cancer nomogram to predict ipsilateral breast relapse after breast-conserving therapy

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ABSTRACT

Background and purpose: A nomogram to predict for the 10-year ipsilateral breast relapse (IBR) after breast-conserving therapy (BCT) for breast cancer (BC) was developed based on the 'boost-no-boost'-trial with a concordance probability estimate (CPE) of 0.68. The aim of our study was to validate that algorithm.

Material and methods: We retrospectively identified 1787 BC cases, treated with BCT and radiotherapy at the University Hospitals Leuven from 2000 to 2007, without missing data of the nomogram variables. Clinicopathologic factors were assessed. Validity of the prediction model was tested in terms of discrimination and calibration.

Results: Median follow-up time was 10.75 years. The validation cohort differed with respect to the administration of a radiation boost, chemo- or hormonal therapy, age, tumour diameter or grade, ductal carcinoma in situ and hormone receptor positivity. On multivariable analysis, the omission of the boost was a significant prognosticator of IBR ($p < 0.01$). The 10-year IBR-rate was 1.4%. The nomogram demonstrated suboptimal discrimination (CPE 0.54) and calibration, with an overestimation of the IBR-risk in general.

Conclusions: The predictive model for IBR in BC is imperfect in this more recent study population.

With the worldwide development of mammographic screening and age-increase, the incidence of early-stage breast cancer has increased. Since randomised controlled trials have shown that local control rates and survival are comparable to those of mastectomy, breast-conserving therapy (BCT) – including breast-conserving surgery (BCS) followed by whole breast irradiation (WBI) and optionally a boost to the tumour bed – is the standard therapeutic option [1,2]. Therapeutic failures leading to local or distant recurrences are a major concern, especially since the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group confirmed the relationship between local control and overall survival. By adding radiotherapy to BCS, the 10-year any first-recurrence rate decreases from 35.0% to 19.3% and breast cancer survival gains 3.8% at 15 years. The prevention of 4 recurrences at 10 years avoids one breast cancer death at 15 years [3].

Although boosting the tumour bed after WBI helps to further increase the local control rates, no consensus on its use has been reached because it increases the risk of fibrosis and might worsen cosmetic outcome [4]. The latest National Comprehensive Cancer Network guidelines recommend a boost in patients at higher risk for recurrence; whereas European guidelines advise a boost in the case of at least one of the following risk factors: age <50 years old, grade 3 tumours, vascular invasion, extensive ductal carcinoma in situ (DCIS) and (focally – otherwise further surgery should be advocated) non-radical tumour excision [5,6]. Several predictive algorithms have been developed to assist with the therapy decision making in breast cancer treatment. The main goal of adjuvant radiotherapy after BCS is to decrease local recurrences and to permit breast conservation with low treatment-induced sequels. Sanghani et al. constructed a nomogram that estimated the 10-year risk of ipsilateral breast relapse (IBR), with and without WBI after BCS [7]. The European Organisation for Research and Treatment of Cancer (EORTC) 22881-10882 (boost versus no boost) trial randomised 5318 patients between no boost and a 16 Gray (Gy) boost dose (or interstitial equivalent) after WBI [8]. Pathology slides from the early years of the accrual period (1989–1996) from

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$$\text{Prob}\{T \geq t\} = S_0(t)^{e^{X\beta}}$$

where

$X\beta = 5.490596 + 0.01184669\text{diameter} - 0.1212663\text{age} + 0.0001316032(\text{age}-36.1)^3_+ - 0.0003111068(\text{age}-49)^3_+ + 0.0001903209(\text{age}-59)^3_+ - 0.00001081729(\text{age}-68)^3_+ - 0.5308367\{\text{tamoxifen Yes}\} - 0.3876239\{\text{chemotherapy Yes}\} - 0.7037333\{\text{16 Gy boost Yes}\} + 0.6720946\{\text{DCIS Yes}\} + 0.1902871\{\text{high grade Yes}\}$

and {Yes}=1, otherwise=0; $(x)_+ = x$ if $x>0$, otherwise=0

t	$S_0(t)$
0	1.000
10	0.937

Fig. 1. Nomogram developed by van Werkhoven et al. [9]

1616 patients were collected and reviewed by a single pathologist. A Cox model was then developed based on the clinical and pathological data of 1603 patients to estimate the 10-year IBR risk after BCT (Fig. 1). The nomogram includes 7 factors: histologic grade, DCIS, tumour diameter, age, tamoxifen, chemotherapy and boost, and was internally validated using the bootstrap procedure with a concordance probability estimate (CPE) of 0.68 [9]. The estimated 10-year IBR risk can be calculated online (http://research.nki.nl/ibr/ibr/index.html).

An objective and thorough validation of any predictive algorithm is of critical importance before its widespread implementation as a useful clinical tool. The aim of our study was to evaluate the nomogram by using a large, external and independent cancer centre database.

Material and methods

Patient selection and data collection

A large database, set up in January 2000 and now containing prospectively obtained data of around 12,200 patient files was used for patient selection. The database includes data of all patients diagnosed with breast cancer and having at least one of the following treatments, i.e. surgery and/or radiotherapy and/or systemic therapy, at the University Hospitals of Leuven (UZL), Belgium.

The patient cohort used for validation of the prediction model included patients diagnosed with a non-metastasised invasive breast cancer between January 1, 2000 and December 31, 2007. All radiation treatments had to be administered at UZL. This study was approved by the Clinical Trial Centre and the Ethics Committee of our institution.

Treatment

Whole breast irradiation was performed with two tangential photon beams with the dose specified at the intersection of the beam axes in the central plane as recommended by the ICRU report 50. The dose given for WBI was 50 Gy in 25 fractions of 2 Gy in all but one patient who received 42.56 Gy in 16 fractions of 2.66 Gy. For the selection of the boost technique, an in-house developed flowchart based on the depth of the tumour bed was used. For a tumour bed lying more than 28 mm beneath the skin, an interstitial or photon boost is chosen over an electron boost because of skin doses and for cosmetic reasons [10]. The standard external boost dose was 16 Gy in 8 fractions. The standard dose with brachytherapy was 15 Gy in low dose rate or pulse dose rate and 8.5 Gy in high dose rate, prescribed at the 85% isodose. Patients in whom no boost was administered, were also included in the analysis. Conform the original article, patients with another boost dose regimen (i.e. lower or higher) were excluded [7,9]. Section margins were considered positive in the case of transection, free if the margin was $\geqslant$2 mm and dubious in other cases. In case of re-excision, section margins thereby were taken into account. Chemotherapy was given according to standard protocol and involved 5 fluorouracil, epirubicin, cyclophosphamide, methotrexate and taxanes.

In patients with bilateral breast cancer, data of both sides were included independently. Validation of the EORTC nomogram was performed only on patients who had no missing data of nomogram variables.

Ipsilateral breast relapse

The event of interest was IBR. Patients without IBR were censored at the time of metastasis, death or end of follow-up. Two definitions of IBR were considered to deal with simultaneous regional or distant recurrence: firstly, patients with simultaneous regional or distant recurrence occurring within 4 months after IBR were censored. This definition is in agreement with the approach in van Werkhoven et al. [7,9]. In the second commonly used definition, patients with simultaneous regional or distant recurrence occurring within 4 months after IBR were considered as local relapse (event).

The prognostic value of patient, tumour and treatment characteristics was evaluated in univariable and multivariable analysis. For binary and categorical variables, the same reference category was chosen as in van Werkhoven et al. [9]. The multivariable model included the same set of variables as the final model [9]. These analyses were based on the first definition of local relapse.

Validation

The validation was performed separately for the two definitions of local relapse. There are two aspects in the evaluation of model performance: discrimination and calibration. Discrimination concerns the relative positioning of patients as the extent to which patients predicted to be at higher risk exhibit higher event rates than those deemed at lower risk. Calibration concerns the absolute risk estimation, or absence of over- or underestimation of the actual risk.

The EORTC nomogram was constructed based on a dataset with patients' age range 27–76 years and tumour size 0–50 mm. When applying the nomogram, no predictions are provided for patients with age or tumour size beyond these ranges. We performed the validation for all data, including patients with values beyond these ranges, and for a restricted dataset, including only patients with values within both ranges.

To assess discrimination, the CPE was determined based on a Cox model with time to IBR as outcome and the EORTC nomogram 10-year IBR-free probability as the only covariate [11,12]. For two patients, one of whom had a local relapse and the other did not by a certain time, the CPE estimates the probability that the model will give higher risk to the one patient compared to the other. A model with a perfect discrimination would have a CPE of 1, whereas a value of 0.5 indicates that a coin toss would provide information as accurate as that given by the model.

A calibration plot was drawn showing predicted 10-year IBR-free probabilities against observed Kaplan–Meier estimates, grouped into five intervals of equal size.

All analyses have been performed using SAS software, version 9.4 of the SAS System for Windows.

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