Development and external validation of nomograms predicting disease-free and cancer-specific survival after radical cystectomy

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Abstract

Purpose—To develop two nomograms predicting disease-free survival (DFS) and cancer-specific survival (CSS) and to externally validate them in multiple series.

Methods—Prospectively collected data from a single-centre series of 818 consecutive patients who underwent RC and PLND were used to build the nomogram. External validation was performed in 3,173 patients from 7 centres worldwide. Time to recurrence and to cancer-specific death were addressed with univariable and multivariable analyses. Nomograms were built to predict 2-, 5- and 8-year DFS and CSS probabilities. Predictive accuracy was quantified using the concordance index.

Results—Age, pathologic T stage, lymph-node density and extent of PLND were independent predictors of DFS and CSS ($p < 0.05$). Discrimination accuracies for DFS and CSS at 2, 5 and 8 years were 0.81, 0.8, 0.79 and 0.82, 0.81, 0.8, respectively, with a slight overestimation at calibration plots beyond 24 months. In the external series, predictive accuracies for DFS and CSS at 2, 5 and 8 years were 0.83, 0.82, 0.82 and 0.85, 0.85, 0.83 for European centres; 0.73, 0.72, 0.71 and 0.80, 0.74, 0.68 for African series; 0.76, 0.74, 0.71 and 0.79, 0.76, 0.73 for American series.

Conclusions—These nomograms developed from a contemporary series are simple clinical tools and provide optimal oncologic outcome prediction in all external cohorts.

Keywords

Nomogram; Prediction; Radical cystectomy; Survival; Urothelial carcinoma

Introduction

The outcome of patients with muscle-invasive urothelial carcinoma of the bladder (UCB) treated with radical cystectomy (RC) and pelvic lymph-node dissection (PLND) mainly depends on pathologic staging. Bochner et al. [1] introduced the first nomogram predicting survival of patients after RC and PLND and demonstrated its superiority over the standard American Joint Committee on Cancer (AJCC) and the tumour-node-metastasis (TNM) staging systems or standard pathologic subgroupings.

In the last decade, clinicians have become more familiar with the use of nomograms in daily clinical practice and nomograms have proven to offer the most accurate prediction of outcomes compared with other prognostic tools [2].

However, today only two nomograms predicting survival after RC are available, and only the one from International Bladder Cancer Nomogram Consortium (IBCNC) was externally validated [1, 3].

The main limitation to the applicability of this nomogram in contemporary settings is the difference between the staging system used (1997 AJCC) and the actual pathologic report (2009 TNM).

Furthermore, none of the nomograms are derived from series with prospective data acquisition.

The goal of this study was to build two nomograms based on a contemporary single-centre series with prospective data acquisition and to perform multiple external validations in series from different continents.

Methods

Study population

Data from 980 consecutive RC carried out at "Regina Elena" National Cancer Institute (Rome, Italy) between January 2000 and December 2009 were collected in a prospectively maintained database. A written informed consent was obtained from all patients before the treatment.

The study was conducted according to the Declaration of Helsinki and was approved by a local ethics committee.

A total of 162 patients were excluded for the following reasons: histology other than pure UCB (54 patients), low grade UCB (six patients), neoadjuvant treatments (18 patients) and RC without curative intent (84 patients); 818 were selected for analysis.

All patients underwent RC; *standard* (six nodal packages: obturator, internal and external iliac, bilaterally) and *extended* PLND (nine nodal packages: obturator, internal, external and common iliac bilaterally, presacral) was performed in 518 and 300 patients, respectively [4].

Pathologic stage and 2004 World Health Organization (WHO) tumour grade was assigned by a single genitourinary pathologist according to the 2002 TNM staging system. Between 2001 and 2007, 92 patients were randomly assigned to adjuvant chemotherapy or observation and treatment on relapse according to a prospective randomized trial [5].

External validation was performed in 3,173 patients who met inclusion criteria from seven centres worldwide, divided as follows: 1,793 treated at University of Southern California (USC), Los Angeles (USA) between 1976 and 2007 (American series); 796 treated between 1996 and 2008 at different European Institutions, 256 from "San Giovanni Bosco", Turin (Italy), 161 from Padua University (Italy), 176 from Humanitas-Gavazzeni, Bergamo (Italy), 245 from Vita-Salute University, San Raffaele, Milan (Italy) and 203 from University Medical Center Hamburg-Eppendorf (Germany); 279 treated between 1995 and 2003 at Mansoura University (Egypt), (African series).

Follow-up regimen

Follow-up was performed according to institutional protocols. Generally, the follow-up schedule included physical examination and routine blood work up, at 3, 6, 12, 18 and 24 months postoperatively, alternatively abdominal ultrasonography and chest X-ray or computed tomography at 6-month intervals for the first 2 years and computed tomography (CT) yearly thereafter.

Urine cytology, urethroscopy, bone scan and positron emission tomography (PET)-CT were performed at the discretion of the treating physician. Any evidence of tumour relapse (pelvic, nodal or visceral, except upper urinary tract) was coded as disease recurrence. Cancer-related death was determined by the treating physicians or by death certificate.

Statistical analysis

Univariable and multivariable Cox regression models addressed time to recurrence and time to cancer-specific death after RC. Predictors included age, gender, pathologic tumour (pT) and pathologic node (pN) stages, lymphovascular invasion (LVI), associated carcinoma in situ, soft tissue surgical margin (STSM) status, lymph-node density (LN-d) and extent of PLND.

Multivariable Cox regression coefficients were then used to generate two nomograms predicting disease-free survival (DFS) and cancer-specific survival (CSS) probabilities, respectively. Predictive accuracy of these nomograms was quantified using Harrell's concordance indexes (CIs), which was used in this analysis. Calibration plots were generated to explore nomogram performance. The Mann–Whitney *U* test and the Chi-square tests were

used to evaluate differences in continuous and categorical variables, respectively. For all tests, the statistical significance was set at 0.05. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) v.19.0 and the R statistical package v.3.1.0.

Results

Internal cohort

Clinical and pathologic characteristics of the internal series are shown in Table 1. All patients had evidence of high-grade muscle-invasive UCB at trans-urethral resection of bladder (TURB) or at final pathology except 26 (3.17 %) who underwent RC after Bacillus Calmette-Guerin (BCG) failure or for unresectable non-muscle-invasive disease. Pelvic lymph-node metastases were found in 208 patients (25.4 %). At a median follow-up of 36 months (IQR 18–65), 270 patients (33 %) died, 211 (25.6 %) of whom died of disease.

At a median time to event of 38 months (IQR 17–61), 290 patients (35.4 %) experienced disease recurrence.

Nomogram development and calibration

DFS and CSS of the internal cohort were reported in Fig. 1. Univariable and multivariable Cox analyses were performed to identify independent predictors of DFS and CSS. At multivariable analysis age, pT stage, LN-d and extent of PLND were independent predictors of DFS (Table 2) and CSS (Table 3).

These variables were included in the nomograms to predict 2-, 5- and 8-year DFS and CSS (Fig. 2a, b, respectively). The discrimination accuracies of the nomograms for DFS and CSS at 2, 5 and 8 year were 0.81, 0.81, 0.79 and 0.82, 0.79, 0.78, respectively. The 2-year calibration plots revealed only a slight overestimation of DFS (Fig. 3) and CSS (Fig. 4) risks.

External cohort and nomogram validation

Distribution of variables included in the nomogram among series is shown in Table 4.

Patients of European series had a higher proportion of organ confined UCB (65.8 vs. 51.4 %, $p < 0.001$) and a significantly lower mean LN-d (3.3 vs. 6.5 %, $p < 0.001$) than those of the internal cohort. Patients of American series had a higher proportion of organ confined UCB (64.1 vs. 51.4 %, $p < 0.001$), a significantly lower LN-d (4 vs. 6.5 %, $p < 0.001$), a significantly longer follow-up (mean follow-up 87.4 vs. 40 months, $p < 0.001$) and were more likely to have undergone extended PLND (78.2 vs. 36.7 %, $p < 0.001$). All these patients had high-grade muscle-invasive UCB, did not undergo neoadjuvant chemotherapy, and had median age comparable with internal series.

Patients of African series were significantly younger (median age 51.7 vs. 66.7, $p < 0.001$) and had a significantly longer follow-up (mean follow-up 57.3 vs. 40 months, $p < 0.001$).

In the external series, predictive accuracies for DFS and CSS at 2, 5 and 8 years were 0.83, 0.82, 0.82 and 0.85, 0.85, 0.83 for European centres; 0.73, 0.72, 0.71 and 0.80, 0.74, 0.68 for African series; 0.76, 0.74, 0.71 and 0.79, 0.76, 0.73 for American series (Table 5).

Discussion

The "ideal" nomogram should combine high discrimination, ease of use and proven efficacy in external validation cohorts. The advantages of nomogram use are not only the individual estimation of prognosis but also a risk-adapted follow-up. Prognosis of patients with muscle-invasive UCB undergoing RC and PLND mainly depends on pT and pN stages. The AJCC staging system, which includes both pT and pN stages, has been considered a standard prognostic tool, however, different nomograms have demonstrated improved survival prediction accuracy [1, 6, 7].

The independent role of pT stage as predictor of CSS was confirmed by several studies, and this variable was integral part of both available nomograms predicting DFS and CSS after RC [1, 3].

In the IBCNC nomogram which was based on 1997 AJCC staging system, patients were further risk stratified for pT0, pTis, pTa and pT1 stages, while in the nomogram by Karakievicz et al. [3] based on 2002 TNM staging system, DFS risk of pT2 patients was not significantly different by that of pT1 patients ($p = 0.087$) In fact, at Kaplan–Meyer analysis, the DFS of 94 pT1 patients was lower than that of 163 pT2 patients, most likely due to the presence of higher stage disease at time of TURB and the small number of patients. In line with these findings, in our development cohort (818 cases), DFS and CSS of patients with pT stage 2a were not significantly different, probably because 96.8 % of patients (792/818) had T2 UC at TURB.

Recently, two studies from an international cohort of 4,431 patients addressed the significant impact of pT substaging into pT2a and pT2b and into pT3a and pT3b, respectively, on oncologic outcomes after RC [8, 9]. With regard to pT substaging, both IBCNC or Karakievicz nomograms grouped patients into four categories (pT1, 2, 3 and 4, respectively), while in our development series, significant differences were observed in terms of DFS and CSS between pT2b, pT3a, pT3b and pT4a compared to the reference category (pT0-a-is-1-2a). Finally, in our series, all patients underwent RC with "intent to cure"; consequently, there was no patient with pT4b UC in the internal series.

Probably, the more significant difference between our nomogram and both the available ones consists of the use of LN-d instead of pN stage. LN-d was first introduced by Herr [10].

Since then, many authors have demonstrated its superiority over pN stage, although with different cut-off points ranging from 4 to 25 % [11–13].

In our nomogram development series, at multivariable analysis, LN-d, together with pT stage, remained the strongest predictor of DFS and CSS, while pN stage was excluded by the model for colinearity. In order to provide the most informative individual risk assessment, LN-d was included in the model as continuous variable, a unique feature of this

nomogram. In the IBCNC nomogram cohort, specific LN data, such as the number of removed and positive nodes, were available only for a limited number of patients. As a consequence, and as acknowledged by authors, LN-d failed to improve the prediction accuracy compared with the simple lymph-node status [1]. Similarly, in the nomogram by Karakiewicz et al. pN stage failed to discriminate prognosis between pN1 and pN2 categories. Potential reasons for such differences with available nomograms cited above could be the prospective data collection in a single centre, with all patients receiving a *standard* or *extended* PLND and all pathologic reports reviewed by a single uropathologist.

Concerning the anatomical boundaries of PLND, in a prospective series by Abol-Enein et al. [14], patients with pathological node metastases who underwent RC and standard PLND (up to iliac bifurcation) were more likely to experience disease recurrence compared with those who underwent RC and *super-extended* PLND (up to inferior mesenteric artery). In a recent study aimed at assessing the therapeutic role of an extended PLND (up to iliac bifurcation) versus a standard PLND in a series of 933 patients, the benefit of an extended PLND was significant across all pT stages but pT < 2 and across all pN stages [4]. However, in a retrospective comparison of two series from USC and from Bern University, super-extended PLND failed to provide any benefit in terms of cancer control outcomes compared with standard PLND [15]. Hopefully, two ongoing prospective randomized trials (the SWOG trial S1011 [16] and the German multicenter study LEA [17]) will answer the question regarding the optimal anatomical template in order to standardize PLND during RC.

This nomogram is the first to include the extent of the PLND as a variable, however, given the lack of difference reported between extended versus super-extended dissections, patients were not further stratified. The last variable included in both nomograms was the age of patients. In a recent paper by Fairey et al. [18], patients older than 80 were more likely to experience disease recurrence after RC (HR 2.06, 95 % CI 1.57–2.70) and had a significant increased risk of cancer-related death compared to the reference group of patients younger than 60 (HR 1.56, 95 % CI 1.09–2.24).

In a series of 1,545 patients who experienced recurrence after RC, Rink et al. [19] found advanced age and female gender significantly associated with CSS. However, in our nomogram development cohort, female gender was not associated with DFS or CSS.

Other pathologic features, such as LVI and positive STSM, were advocated as prognosticators of recurrence after RC and PLND. LVI was defined as the unequivocal presence of tumour cells within an endothelium-lined space with no underlying muscular walls [20, 21]. Effectively, this suggests that each equivocal focus, which is a common finding, should be clarified through immunohistochemistry to distinguish artefacts from involvement of either the lymphatic or vascular lumen, which was not performed in published series "in keeping with the pathologist's practice" [22]. In the internal series, LVI was not an independent predictor of DFS and CSS. Novara et al. [23] provided evidence supporting STSM status as a powerful predictor of DFS and CSS. In a multicentre series of 4,410 patients, positive STSM was an independent predictor of both DFS and CSS (HR 1.52, 1.51; *p* < 0.001, respectively).

In the internal series, the incidence of positive surgical margins was significantly lower than that reported by Novara et al. (1.9 vs. 6.3 %). A possible explanation for this difference can be the exclusion of patients who underwent salvage RC and consequently the lack of patients with pT4b disease at final pathology in the nomogram development cohort. As a consequence, positive STSM was not a predictor of oncologic outcomes in the internal series and was not included in the model.

We recognize that the patients who formed the internal cohort were treated at a tertiary referral centre, and therefore the outcomes outside this setting can be significantly different. In fact, intrinsic limitations of the nomograms built in this study are the need of a standardized PLND, coded as *standard*, *extended* or *super extended*. The accuracy of these nomograms could be significantly impaired in patients undergoing "salvage RC", or cystectomy without PLND, as well as in patients undergoing limited PLND or PLND with a template missing one or more nodal packages among obturator, hypogastric and external iliac nodes. A "separate package" PLND was also supported by a single genitor-urinary pathologist who performed a meticulous lymph-node count, a variable potentially affecting the prognostic powerful of LN-d. In addition, the nomogram development was based on a series of patients with UCB, thus the prediction accuracy for histologies other than pure UC requires further validation.

Another limitation to the use of this nomogram in contemporary settings come from the increasing use of neoadjuvant chemotherapy, based on a level 1 evidence of a 5 % overall survival increase in patients receiving three cycles of methotrexate, vinblastine, doxorubicin and cisplatin.

This survival benefit was evident in a 38 % of patients who had no residual disease at final pathology (pT0) [24]. However, recently, Reardon et al. [25] retrospectively analysed the trend in the use of perioperative chemotherapy in a cohort of 5,692 patients from the National Cancer Database. Interestingly, despite a significant increase in the use of neoadjuvant chemotherapy for muscle-invasive UCB from 10.1 % in 2006 to 20.8 % in 2010 ($p = 0.005$), a lot of variables, including advanced age, increasing comorbidity, lack of insurance, increased travel distance, geographic location outside the north-eastern USA and lower income were negatively associated with perioperative chemotherapy receipt.

With regard to adjuvant chemotherapy, univariable analyses failed to demonstrate any survival benefit in the internal cohort, a finding supported by a previous prospectively randomized trial [5].

Finally, these nomograms were built on a single-centre prospective series of patients treated with RC and "separate package" PLND.

Ease of use, accessibility of variables available in a contemporary pathological report, together with highly accurate discrimination of 2-, 5- and 8-year DFS and CSS on multiple series from different continents and from centres with different case-loads make these nomograms prediction tools widely applicable in daily clinical practice.

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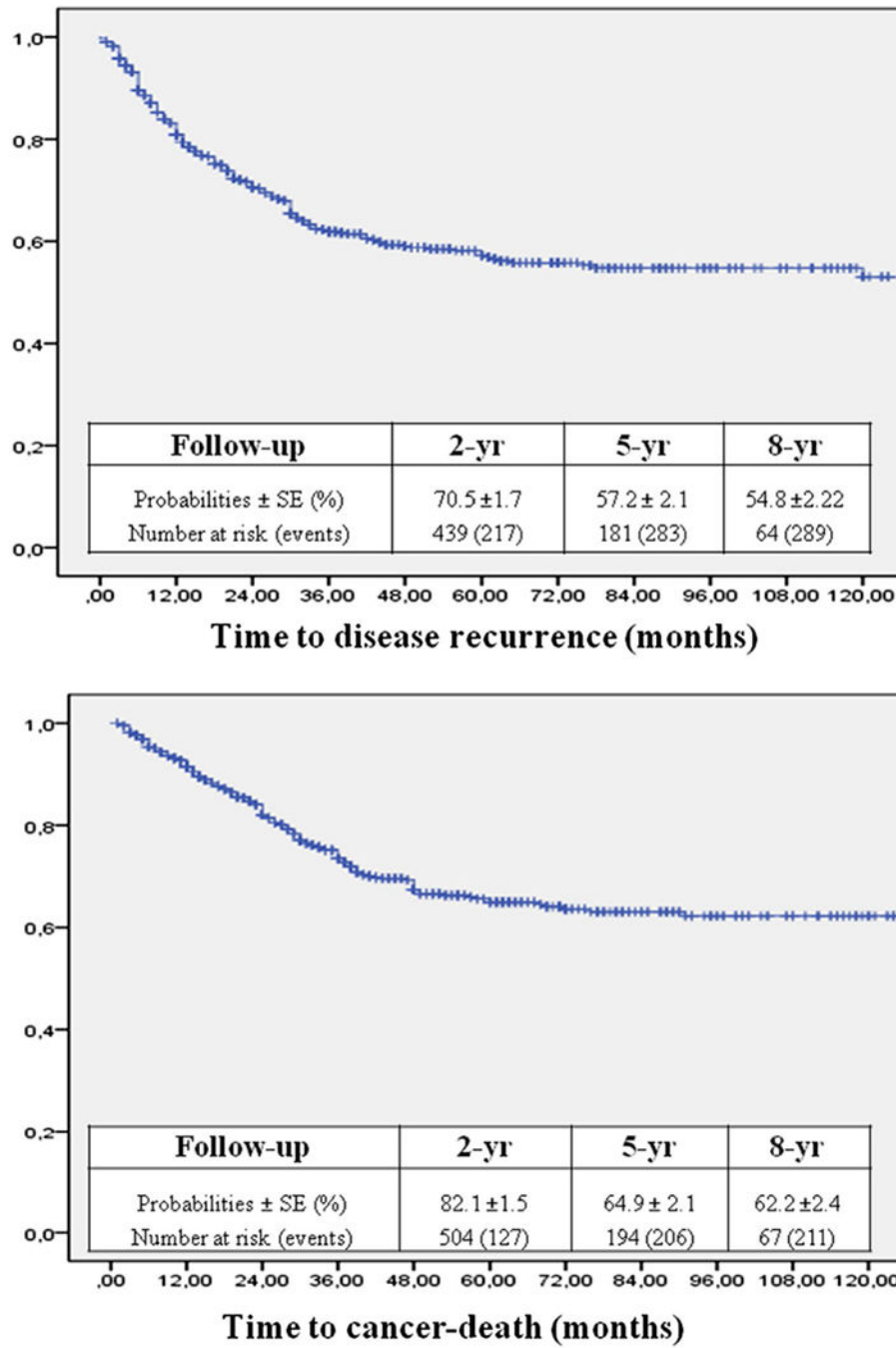
Fig. 1.
Kaplan–Meier estimates of DFS and CSS of the internal series

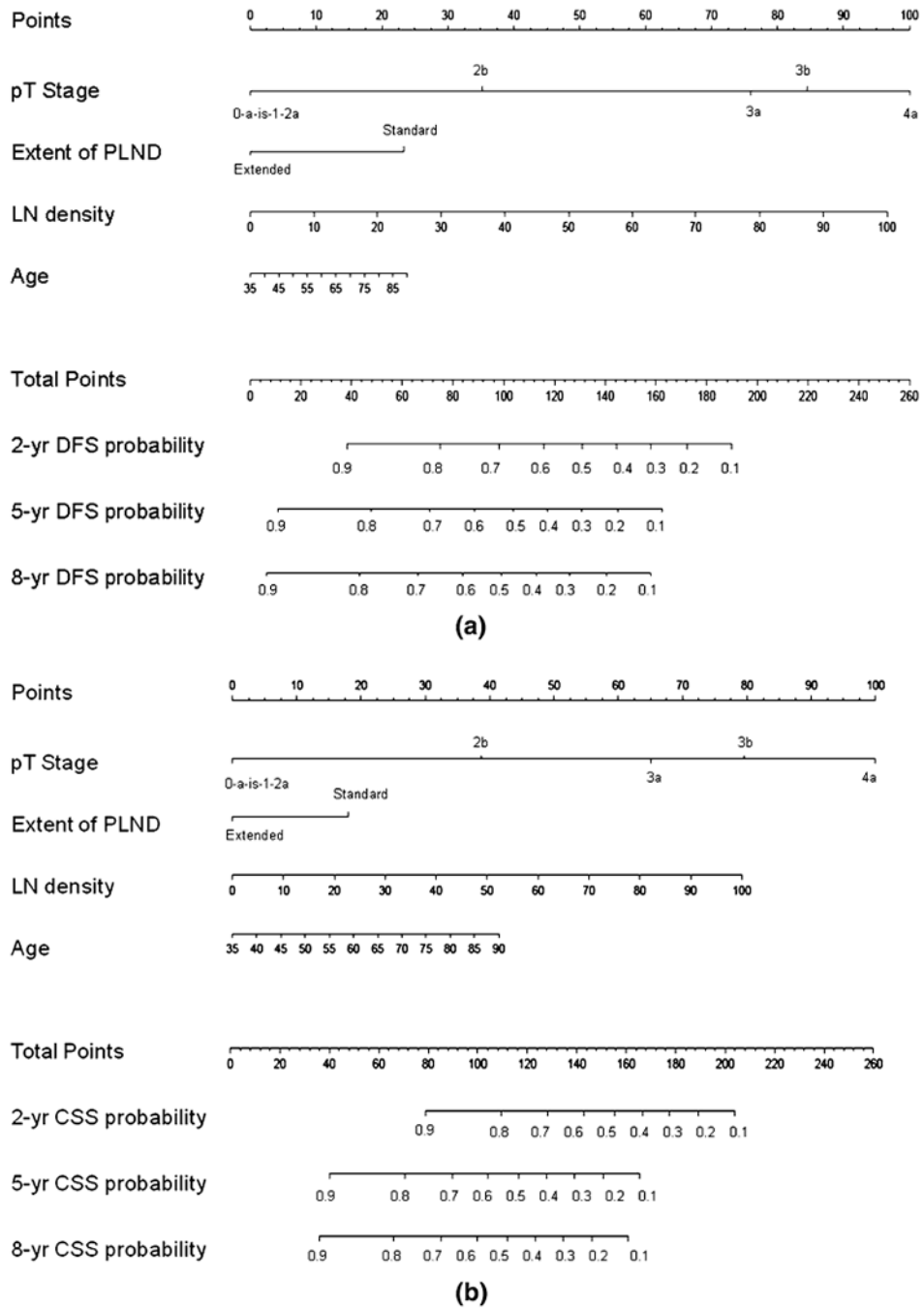Fig. 2.
A nomogram for prediction of DFS. **b** Nomogram for prediction of CSS
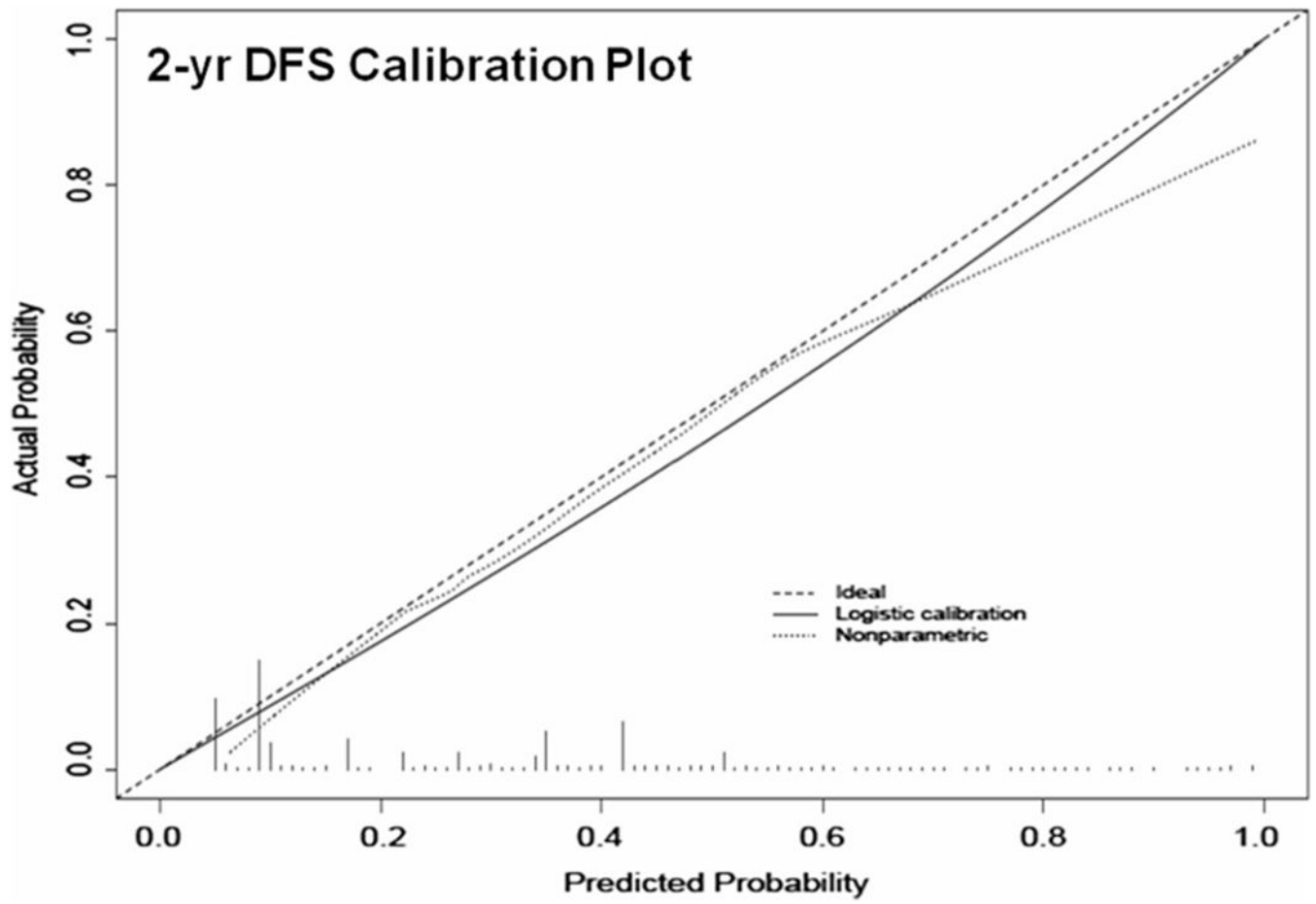
Fig. 3.
Calibration plot for prediction of 2-year disease-free survival
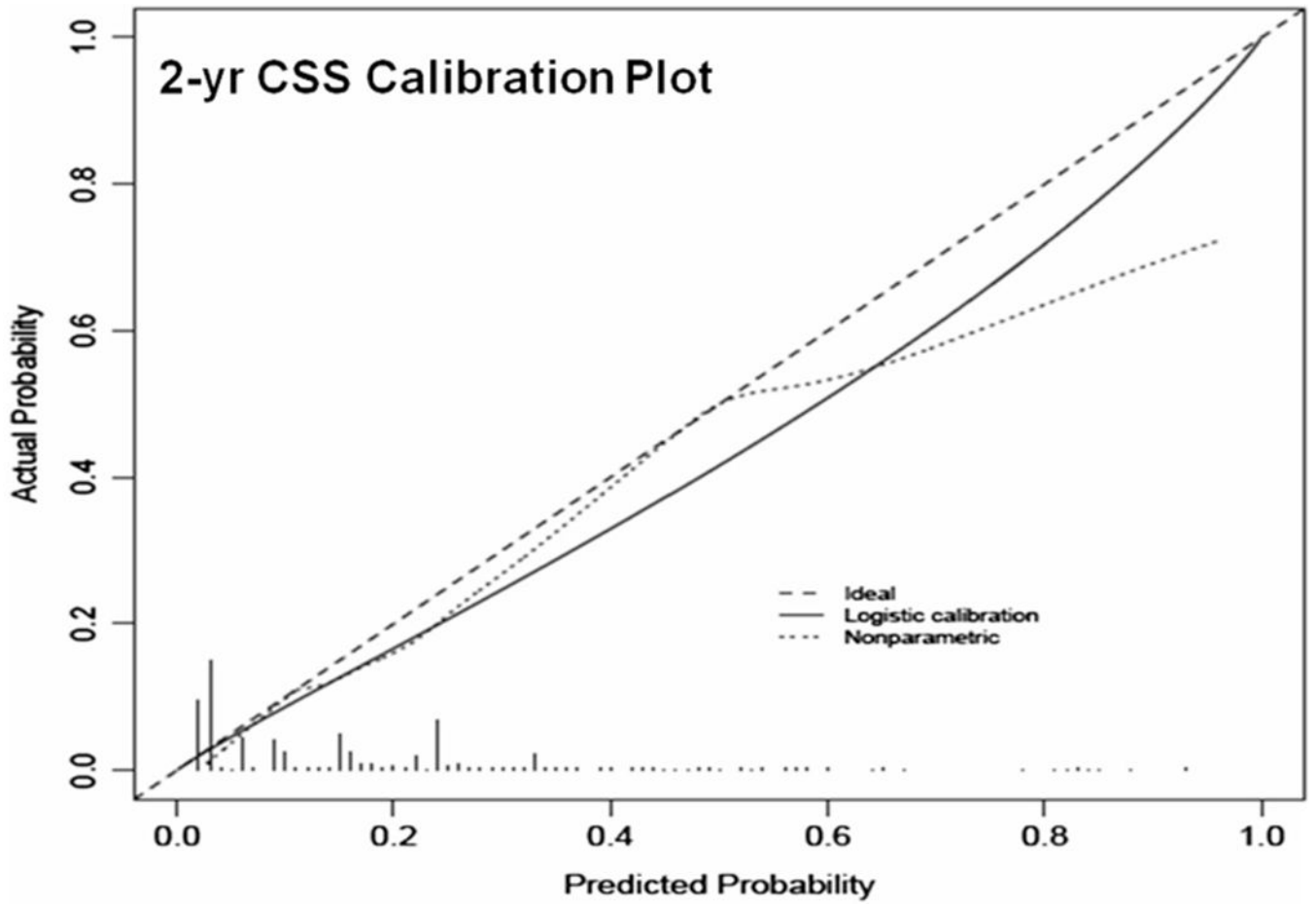
Fig. 4.
Calibration plot for prediction of 2-year cancer-specific survival

Table 1

Clinical and pathologic features of internal cohort

Characteristics	
Age (year)	
Mean ± SD (range)	66.7 ± 9.46 (36–88)
Median (IQR)	67 (60–74)
Gender (%)	
Male	700 (85.6)
Female	118 (14.4)
Follow-up length (month)	
Mean ± SD (range)	40 ± 33 (0–150)
Median (IQR)	31 (14–56)
pT stage (%)	
0-a-is-1-2a	311 (38)
2b	110 (13.4)
3a	123 (15)
3b	183 (22.4)
4a	91 (11.1)
PLND (%)	
Extended	300 (36.7)
Standard	518 (63.3)
pN stage (%)	
0	610 (74.6)
1	52 (6.4)
2	156 (19)
Number of nodes removed	
Mean ± SD (range)	26.4 ± 14 (10–90)
Median (IQR)	22 (16–33)
LN-d	
Mean ± SD	6.5 % ± 17
Median (IQR)	0 (0–2)
LVI (%)	262 (32)
Associated CIS (%)	229 (28)
Positive soft tissue surgical margins (%)	16 (1.9)
Adjuvant chemotherapy (%)	86 (10.5)

Table 2

Univariable and multivariable Cox regression analyses of internal cohort for prediction of disease-free survival

Variable	Univariable analysis			Multivariable analysis		
	HR	95 % CI	p	HR	95 % CI	p
Age (continuous)	1.02	1.01–1.04	<0.001	1.013	1.00–1.03	0.047
Gender						
Male	Reference category			Reference category		
Female	0.9	0.65–1.24	0.521	–		
Pathologic tumour stage						
0-a-is-1-2a	Reference category			Reference category		
2b	1.93	1.19–3.14	0.008	2.11	1.281–3.476	0.003
3a	5.06	3.41–7.51	<0.001	4.823	3.198–7.274	<0.001
3b	6.79	4.7–9.81	<0.001	5.789	3.894–8.606	<0.001
4a	9.29	6.2–13.92	<0.001	7.524	4.848–11.679	<0.001
Pathologic nodal stage (according to 2002 TNM)						
0	Reference category			Reference category		
1	2.47	1.68–3.64	<0.001	Excluded for colinearity with LN-d		
2	4.26	3.26–5.58	<0.001			
3	7.48	4.38–12.77	<0.001			
LN-d (continuous)	1.03	1.02–1.033	<0.001	1.02	1.014–1.024	<0.001
LN-d (categorical)						
0 %	Reference category			Reference category		
1–11 %	2.22	1.56–3.16	<0.001	Included in the model as continuous variable		
12–30 %	3.97	2.86–5.5	<0.001			
31–100 %	9.57	6.83–13.1	<0.001			
Extent of PLND						
Standard	Reference category			Reference category		
Extended	0.52	0.4–0.68	<0.001	0.605	0.45–0.80	0.001
Associated pTis	1.30	1.02–1.67	0.033	0.803	0.753–1.246	0.968
Presence of LVI	1.34	1.05–1.70	0.016	0.857	0.672–1.094	0.215
Positive soft tissue surgical margins	1.50	0.71–3.2	0.288	–		

Variable	Univariable analysis			Multivariable analysis		
	HR	95 % CI	*p*	HR	95 % CI	*p*
Adjuvant chemotherapy	1.1	0.75–1.2	0.9	–		

Table 3

Univariable and multivariable Cox regression analyses of internal cohort for prediction of cancer-specific survival

Variable	Univariable analysis			Multivariable analysis		
	HR	95 % CI	p	HR	95 % CI	p
Age (continuous)	1.04	1.02–1.05	<0.001	1.021	1.01–1.04	0.01
Gender						
Male	Reference category			Reference category		
Female	0.79	0.54–1.13	0.2	–		
Pathologic tumour stage						
0-a-is-1-2a	Reference category			Reference category		
2b	2.601	1.43–4.74	0.002	3.04	1.61–5.71	0.001
3a	5.52	3.31–9.17	<0.001	5.626	3.26–9.72	<0.001
3b	9.31	5.81–14.9	<0.001	8.394	4.98–14.14	<0.001
4a	14.7	8.92–24.2	<0.001	13.04	7.48–22.74	<0.001
Pathologic nodal stage (according to 2002 TNM)						
0	Reference category			Reference category		
1	3.09	2.01–4.75	<0.001	Excluded for colinearity with LN-d		
2	4.88	3.56–6.70	<0.001			
3	7.82	4.38–13.94	<0.001			
LN-d (continuous)	1.03	1.02–1.035	<0.001	1.02	1.014–1.025	<0.001
LN-d (categorical)						
0 %	Reference category			Reference category		
1–11 %	2.9	1.96–4.29	<0.001	Included in the model as continuous variable		
12–30 %	4.3	2.92–6.32	<0.001			
31–100 %	10.6	7.22–15.49	<0.001			
Extent of PLND						
Standard	Reference category			Reference category		
Extended	0.55	0.4–0.75	<0.001	0.656	0.47–0.92	0.014
Associated pTis	1.34	1.01–1.78	0.043	1.016	0.773–1.363	0.916
Presence of LVI	1.30	0.98–1.73	0.066	1.04	0.776–1.385	0.81
Positive soft tissue surgical margins	1.50	0.71–3.2	0.288	–		

Table 4

Distribution of variables included in the model among series

	Internal	European	European versus internal	American	American versus internal	African	African versus internal
Age							
Mean (range)	66.7 (36–88)	65.7 (37–90)	p = 0.027	66.3 (23–93)	p = 0.265	54.3 (20–75)	p < 0.001
pT stage							
pT0-a-is-1-2a	311 (38 %)	438 (55 %)	p < 0.001	921 (51.4 %)	p < 0.001	112 (40.1 %)	p < 0.001
pT2b	110 (13.4 %)	86 (10.8 %)		228 (12.7 %)		95 (34 %)	
pT3a	123 (15 %)	76 (9.3 %)		167 (9.3 %)		34 (12.2 %)	
pT3b	183 (22.4 %)	110 (15.1 %)		315 (17.6 %)		21 (7.5 %)	
pT4a	91 (11.1 %)	78 (9.8 %)		162 (9 %)		17 (6.1 %)	
PLND							
Standard	518 (63.3 %)	485 (60.9 %)	p = 0.32	391 (21.8 %)	p < 0.001	588 (74.7 %)	p < 0.001
Extended	300 (36.7 %)	311 (39.1 %)		1,402 (78.2 %)		199 (25.3 %)	
LN density							
Mean	6.5 %	3.3 %	p < 0.001	4.0 %	p < 0.001	5.3 %	p = 0.141

Table 5

Concordance indexes of both nomograms for each series

	CSS (year)		DFS (year)	
Internal	2	0.83	2	0.81
	5	0.80	5	0.80
	8	0.79	8	0.79
European	2	0.85	2	0.83
	5	0.85	5	0.82
	8	0.83	8	0.82
African	2	0.80	2	0.74
	5	0.72	5	0.73
	8	0.70	8	0.72
American	2	0.79	2	0.76
	5	0.76	5	0.74
	8	0.73	8	0.71