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Original Article: Clinical Investigation

Evaluating the predictive accuracy and the clinical benefit of a nomogram aimed to predict survival in node-positive prostate cancer patients: External validation on a multi-institutional database

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Abbreviations & Acronyms
aADT = adjuvant androgen deprivation therapy
aRT = adjuvant radiotherapy
AUC = area under the curve
BCR = biochemical recurrence
CSM = cancer-specific mortality
DCA = decision curve analysis
IQR = interquartile range
LNM = lymph node metastasis
NPV = negative predictive value
PA = predictive accuracy
PCa = prostate cancer
PLND = pelvic lymph node dissection
pN1 = patients with pathological lymph node metastasis
PPV = positive predictive value
PSA = prostate-specific antigen
ROC = receiver operating characteristic
RP = radical prostatectomy

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Objectives: To assess the predictive accuracy and the clinical value of a recent nomogram predicting cancer-specific mortality-free survival after surgery in pN1 prostate cancer patients through an external validation.

Methods: We evaluated 518 prostate cancer patients treated with radical prostatectomy and pelvic lymph node dissection with evidence of nodal metastases at final pathology, at 10 tertiary centers. External validation was carried out using regression coefficients of the previously published nomogram. The performance characteristics of the model were assessed by quantifying predictive accuracy, according to the area under the curve in the receiver operating characteristic curve and model calibration. Furthermore, we systematically analyzed the specificity, sensitivity, positive predictive value and negative predictive value for each nomogram-derived probability cut-off. Finally, we implemented decision curve analysis, in order to quantify the nomogram's clinical value in routine practice.

Results: External validation showed inferior predictive accuracy as referred to in the internal validation (65.8% *vs* 83.3%, respectively). The discrimination (area under the curve) of the multivariable model was 66.7% (95% CI 60.1–73.0%) by testing with receiver operating characteristic curve analysis. The calibration plot showed an overestimation throughout the range of predicted cancer-specific mortality-free survival rates probabilities. However, in decision curve analysis, the nomogram's use showed a net benefit when compared with the scenarios of treating all patients or none.

Conclusions: In an external setting, the nomogram showed inferior predictive accuracy and suboptimal calibration characteristics as compared to that reported in the original population. However, decision curve analysis showed a clinical net benefit, suggesting a clinical implication to correctly manage pN1 prostate cancer patients after surgery.

Key words: cancer-specific mortality free survival, external validation, lymph node metastases, predictive accuracy, prostate cancer.

Introduction

Despite increasing early detection of clinically localized PCa, nowadays approximately 10% of PCa patients referred to RP and PLND have nodal metastases at final pathology.[1–6] Of note, every PCa patient with LNM is usually considered as affected by systemic disease,[7] and currently classified in a single-risk group.[8] However, recent evidence suggests that men with pN1 PCa represent a heterogeneous population, sharing not invariably poor oncological

outcomes after surgery.[5,9–12] Different prognostic models have been proposed to predict oncological outcomes of patients with LNM according to clinical and pathological parameters.[13–15] More recently, the PSA persistence (namely PSA ≥0.1 ng/mL) at 6 weeks after surgery has been found to be a strong predictor of recurrence and cancer mortality.[16] As a consequence, patients with inadequate surgical debulking, identified by incomplete biochemical response, should receive earlier and more aggressive adjuvant therapies. Despite aADT representing the standard of care in patients with LNM, the optimal management of those individuals is still matter of debate.[17] As approximately 30% of patients do not experience BCR after RP and PLND at long-term follow up,[18] a considerable subset of men with LNM remained free of disease 10 years after surgery without any additional treatment.[19] Considering the conflicting outcomes of pN1 PCa patients, Abdollah *et al.* proposed a nomogram predicting CSM-free survival in 1107 patients with LNM treated with RP and PLND, in order to individualize the postoperative decision-making, patients counseling and follow-up schedule (Table S1).[11] The original nomogram has a PA of 83.3% after internal validation, and actually represents the only available multivariate model predicting survival in pN1 PCa individuals. Despite excellent performance characteristics in the original setting, an external validation is mandatory to confirm the model's potency also in different PCa populations.[11] Hence, we aimed to assess the PA of the nomogram and the clinical benefit of its application in routine practice, through a large multi-institutional series of pN1 PCa patients referred to RP and PLND followed by adjuvant treatments.[11]

Methods

Study population

We reviewed 5538 PCa patients treated with RP and PLND between 1995 and 2015 at 10 tertiary European care centers, different from those included in the population of the original nomogram.[11] In order to evaluate the survival outcomes of pN1 PCa patients, we considered in our analysis 576 individuals (10.4%) with LNM at final pathology. Among these 576 patients, 58 men (10.1%) with incomplete clinical and/or pathological and/or follow-up data, and with <10 lymph nodes retrieved were excluded. There was a final population of 518 patients. All men were preoperatively staged with contrast-enhanced abdominal computed tomography or bone scan or, more recently, with 11C-choline positron-emission tomography scan according to local protocol. During the study period, surgical procedures were carried out with the retropubic, laparoscopic or robotic approach according to the surgeon and center preference. Routine PLND at the time of RP in all the 10 centers was carried out with an extended template[20] in the presence of high-risk and intermediate-risk PCa in men referred to surgery before 2006, whereas an estimated risk for positive lymph nodes >5%[21] by Briganti's nomogram[22] was considered as a threshold to carry out PLND in patients scheduled for RP after its diffusion. However, PLND was carried out in low-risk PCa according to surgeons' attitude. Within all centers, one experienced genitourinary pathologist per each center reviewed all surgical specimens.

Covariates and follow up

All patients had complete data including preoperative PSA, pathological stage and Gleason score, surgical margin status, number of nodes removed, and number of positive nodes. All patients received postoperative therapy including aADT alone or aRT in combination with aADT.

Outcomes

The outcomes of the study were CSM-free survival and the statistical strength of the original nomogram on predicting CSM-free survival rates in our external population.[11]

Statistical analysis

Median and interquartile ranges were reported for continuous variables. Frequencies and proportions were reported for categorical variables. The Mann–Whitney *U*-test and χ^2-tests were used to compare the statistical significance of differences in median and proportions, respectively. Our statistical analyses consisted of several steps. First, Kaplan–Meier analyses were used to assess CSM-free survival rates at 5- and 8-year follow up in the overall population and after stratifying patients according to adjuvant treatments (namely, aRT and aADT *vs* aADT alone). Second, external validation was arranged using regression coefficients of the previously published nomogram.[11] Performance characteristics were derived by quantifying PA and model calibration, in order to graphically investigate the extent of overestimation or underestimation of the model. Third, we evaluated the performance of the nomogram by also drawing a ROC curve and calculating the AUC. Fourth, we systematically analyzed specificity, sensitivity, PPV and NPV for each nomogram-derived CSM-free survival rate probability cut off, after assessing the theoretical nomogram's scores in each patient. Finally, we implemented DCA, in order to quantify the nomogram's clinical benefit in routine clinical practice.[23] DCA investigates the theoretical relationship between the threshold probability of CSM-free survival rates and the relative value of false positive and false negative findings to assess the net benefit of the predictive multivariable model. All statistical tests were carried out using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria) with a two-sided significance level set at $P < 0.05$.

Results

Table 1 shows the baseline characteristics of all patients included in the present study and overall patients' descriptive statistics within the original nomogram, after stratifying patients according to adjuvant treatments (namely, aRT with aADT *vs* aADT alone).[11] In the external cohort, the median number of lymph nodes removed and positive lymph nodes were 15 (IQR 11–21) and two (IQR 1–3), respectively. The external cohort showed pathological features comparable with the original population, except for a higher proportion of Gleason score 8–10 (54.2% *vs* 39.8%) and a higher median number of positive lymph nodes (2 *vs* 1), respectively. Overall, 386 (34.9%) and 300 (57.9%) men were referred to aRT

with aADT in the original population and in our cohort, respectively (Table 1).

The median follow up from RP for survivors was 52 months (IQR 30–84). Overall, the CSM-free survival estimates at 5- and 8-year follow up were 84.3% and 71.2%, respectively (Fig. 1). After stratifying patients according to adjuvant treatments, individuals referred to aADT alone did not experience significantly worse CSM-free survival rates as compared with those scheduled to aRT with aADT (Fig. 2; $P = 0.6$), despite a favorable survival trend within the latter group. In order to externally validate the previously published nomogram, the calibration of the nomogram using the original regression coefficient (including, pathological Gleason score, pathological stage, positive surgical margins and number of positive lymph nodes) was arranged.[11] The PA estimate in our external validation cohort was 0.658. The calibration plot of the nomogram, applied on our multi-institutional dataset, is shown in Figure 3. As compared with the virtually ideal calibration characteristics of the nomogram in the original population, the application of the model in our external cohort pointed out a suboptimal calibration performance with overprediction of the CSM-free survival rate probability.[11] Indeed, the PA of the nomogram's scores was also investigated with the ROC curve (Fig. 4). Accordingly, the discrimination (AUC) of the multivariable model was 66.7% (95% CI 60.1–73.0). Table 2 shows the sensitivity, specificity, PPV, NPV and accuracy for each nomogram-derived CSM-free rate probability cut off, after assessing the theoretical nomogram's scores in each patient. Furthermore, for each nomogram cut off, we recorded the number of individuals who actually experienced CSM-free survival and those who died as a result of PCa. For example, using a nomogram-derived CSM-free survival probability cut-off of 40%, which represents the best accuracy in our population (Table 2), only 0.9% of individuals who actually did not experience CSM would be wrongly counseled against surgery. Conversely, RP and PLND would be correctly discouraged in 6.7% of patients who experienced CSM (Table 2).

Finally, in DCA, the nomogram seemed to be superior to the scenario of treating all individuals with RP, at a probability threshold of ≥60% (Fig. 5). For example, applying a nomogram-derived probability threshold of 80% above which a man would be scheduled to RP, use of the nomogram would result in a net benefit gain of 11. However, this net benefit when compared with the scenario of treating none, assuming that all patients did not experience CSM-free survival, would result in 2.8% fewer false positive results. In other words, use of the prediction model would lead to the equivalent of a net 2.8 true positive results per 100 patients, with no increase in the number of false positive results.[23]

Table 1 Patient characteristics and descriptive statistics of original nomogram population and current cohort of patients

	Original nomogram population[11]				Actual study population			
Variable	Overall	aRT with aADT	aADT alone	*P*-value	Overall	aRT with aADT	aADT alone	*P*-value
No. patients (%)	1107 (100)	386 (34.9)	721 (65.1)	–	518 (100)	300 (57.9)	218 (42.1)	–
Age								
Median	65	65	66	0.4	65	65	67	<0.001
IQR	60–70	60–69.7	60–70		61–70	60–69	61–71	
PSA (ng/mL)								
Median	14	14	14.1	0.2	15	14.9	15.3	0.2
IQR	7.9–28	8–31	7.7–27.1		8.2–29	7.6–27.2	9.0–29.1	
Pathological Gleason score (%)								
≤6	155 (14.0)	32 (8.3)	123 (17.1)	<0.001	34 (6.6)	15 (5.0)	19 (8.7)	0.1
7	518 (46.8)	160 (41.5)	358 (49.7)		203 (39.2)	113 (37.7)	90 (41.3)	
8–10	434 (39.8)	194 (50.3)	240 (33.3)		281 (54.2)	172 (57.3)	109 (50.0)	
Pathological stage (%)								
pT2–pT3a	351 (31.7)	84 (21.8)	267 (37)	<0.001	176 (34.0)	98 (32.7)	78 (35.8)	0.7
pT3b	681 (61.5)	254 (65.8)	427 (59.2)		304 (58.7)	179 (59.7)	125 (57.3)	
pT4	75 (6.8)	48 (12.4)	27 (3.7)		38 (7.3)	23 (7.7)	15 (6.9)	
Surgical margins status (%)								
Negative	450 (40.7)	113 (29.3)	337 (46.7)	<0.001	209 (40.3)	98 (32.7)	111 (50.9)	<0.001
Positive	657 (59.3)	273 (70.7)	384 (53.3)		309 (59.7)	202 (67.3)	107 (49.1)	
No. LNs retrieved								
Median	14	17	13	<0.001	15	15	14	0.08
IQR	10–20	12.–23	9–18		11–21	11–21	10–20	
No. positive LNs								
Median	1	2	1	0.04	2	2	2	0.5
IQR	1–3	1–3	1–2		1–3	1–4	1–3	
Years of surgery	–	–	–	–				
1995–2000					60 (11.6)	19 (6.3)	41 (18.8)	<0.001
2001–2005					106 (20.5)	50 (16.7)	56 (25.7)	
2006–2010					203 (39.2)	127 (42.3)	76 (34.9)	
2011–2014					149 (28.8)	104 (34.7)	45 (20.6)	

Patients are stratified according to the postoperative adjuvant treatments (namely, men referred to aRT with aADT *vs* those submitted to aADT alone).

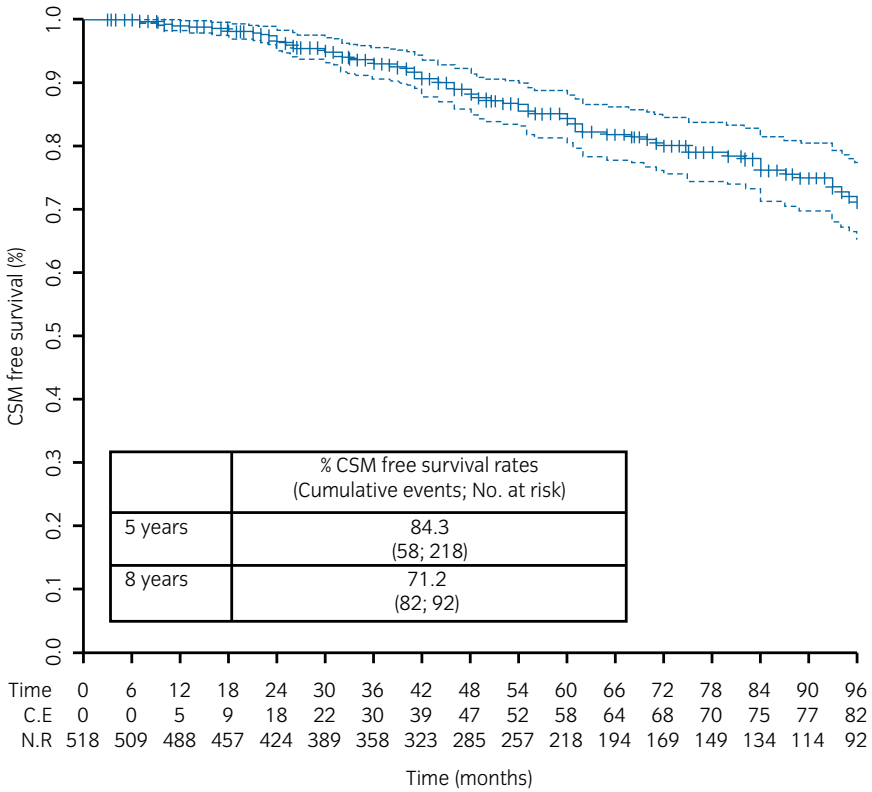

Fig. 1 Kaplan–Meier curve showing CSM-free survival rates in the overall patient population (n = 518).

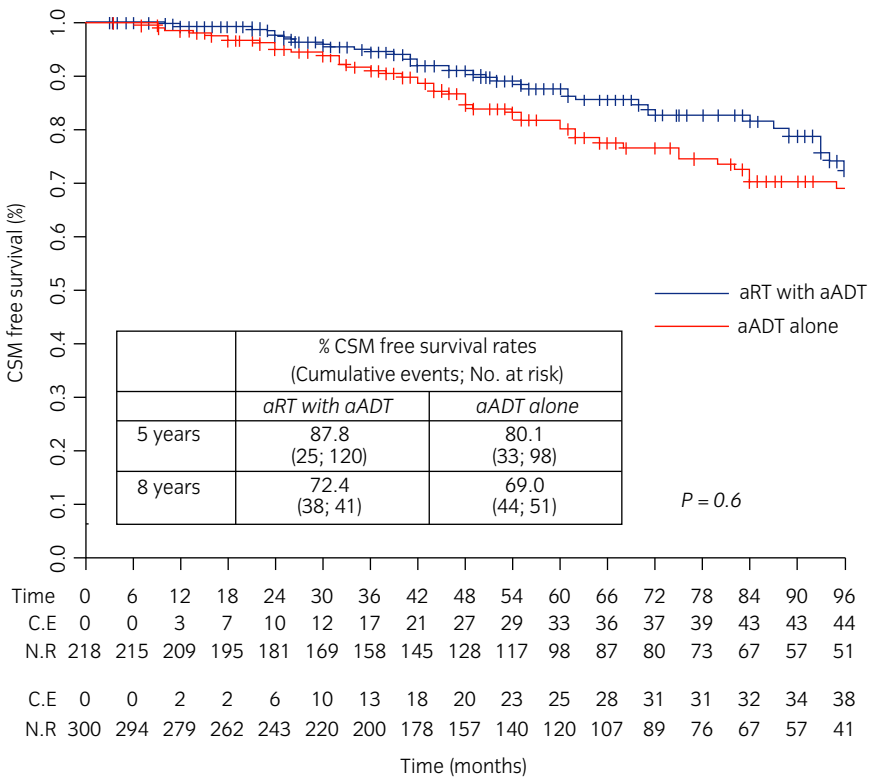

Fig. 2 Kaplan–Meier curve showing CSM-free survival rates in the overall patient population (n = 518) after stratifying according to postoperative adjuvant treatments (namely, aRT with aADT *vs* aADT alone; P = 0.6).

Discussion

Contrary to other tumors, PCa patients with LNM are commonly classified in a single-risk group, with no mention of the number, size or localization of nodal metastases. Of note, nodal metastases are considered as systemic soft tissue disease and pN1 individuals experience worse oncological outcomes, as compared with their counterpart with no evidence

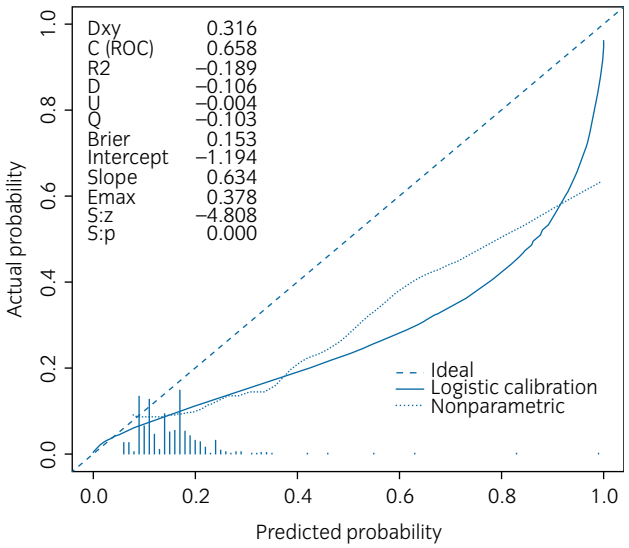

Fig. 3 Calibration plot of the nomogram to predict CSM-free survival in the external validation cohort (n = 518 patients). The predicted probability of the multivariable model is shown on the x-axis, and the observed proportion of men with CSM-free survival is shown on the y-axis. The 45° line indicates perfect agreement between the predicted probability and the observed proportion of men free from cancer-related death.

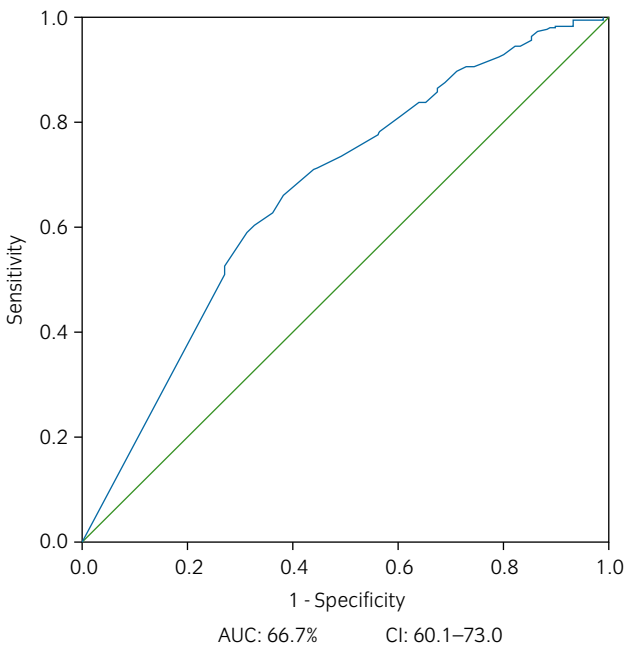

Fig. 4 ROC and AUC of the nomogram after external validation in 518 node-positive PCa patients referred to surgery and subsequent adjuvant treatments.

of LNM.[9,20,24,25] However, pN1 PCa patients represent a highly heterogeneous category,[9–11,25] sharing not invariably poor oncological outcomes after surgery.[5,9–12] In this contest, several long-term data show excellent cancer control outcomes for patients with favorable pathological features,[18,26] suggesting that a considerable subset of men with LNM (approximately 30%) remained free of disease, even without any additional treatments.[19] Of note, the state-of-the-art for metastatic PCa patients consists of hormonal therapy,[27] as it leads to prolonged survival up to 85.8% at 10-year follow up,[25] by turning PCa into a "chronic" disease. Furthermore, approximately one-third of node-positive men who experienced CR after surgery would have the first recurrence in the prostatic bed alone and in the pelvic lymph nodes, suggesting that not all men with LNM will necessarily experience systemic relapse.[28] To confirm this concept, recent retrospective data have supported a potential benefit of aRT on patient survival when combined with aADT, probably related to better local control of disease.[29,30] Some biological characteristics in cancer cells could be related to a higher probability of local rather than nodal skeletal or visceral relapse. Despite such efforts, the best treatment modality for pN1 PCa patients, as well as the correct timing, remain unclear.[30] Taken together, different prognostic models have been proposed to predict oncological outcomes in this population according to clinical and pathological parameters.[13–15] In order to guide physicians on the best individualized postoperative management and follow-up schedules in pN1 PCa men, Abdollah *et al.* developed an internally validated multivariable model to predict the CSM-free survival rate in a series of pN1 PCa patients submitted to RP and PLND followed by adjuvant treatments.[11] The original nomogram, including pathological Gleason score, pathological tumor stage, surgical margins status and the number of positive nodes after stratifying patients according to adjuvant therapies status, showed a PA of 83.3% with ideal calibration characteristics. Such a predictive tool represents the only available nomogram aimed to predict cancer-specific survival in pN1 populations, and supports the need to stratify these subgroups of individuals. However, routine clinical use would be recommended after exploring the predicative value of the nomogram in an external population. To address this issue, we validated the Abdollah *et al.* nomogram by assessing its PA and clinical benefit in daily practice using a multi-institutional series of pN1 PCa patients referred to surgery and adjuvant treatments.[11] Therefore, we investigated the discrimination and the extent of overestimation/underestimation of the model in our external setting. Finally, we implemented DCA in order to assess the real clinical benefit of the nomogram when compared with different scenarios, such as treating all or none.[23]

Several findings of the present study are remarkable. First, our results show that node-positive PCa patients who underwent surgery did not necessary experienced unfavorable prognosis: the 8-year CSM-free survival rate in our population was 71.2% at median follow up of 52 months (Fig. 1). As previously reported by Abdollah *et al.,* individuals referred to aRT and aADT after surgery showed a better CSM-free survival trend as compared with those treated with aADT alone after surgery (72.4% *vs* 69% at 8-year follow up; Fig. 2), despite where not being a statistically significant difference between the two groups.[11] Of note, the beneficial impact of radiotherapy could be underpowered by the relatively short follow-up period and different timing, protocols and indications of radiotherapy between single centers through such a large timespan. Indeed, the effects of aRT with regard to cancer survival could be reduced by the selection of patients

Table 2 Performance characteristics of various nomograms' cut-offs for discriminating between patients who would experience CSM and those who would be alive at 10 years follow up

Nomogram calculated cut-off (%)	Patients in whom RP and PLND would not be recommended according to the cut-off (below cut-off)	Patients below cut-off with CSM†	Patients below cut-off with CSM-free survival	Patients in whom RP and PLND would be recommended according to the cut-off (above cut-off)	Patients above cut-off with CSM	Patients above cut-off with CSM-free survival‡	NPV (%)	PPV (%)	Accuracy (%)
90	276 (53.3)	65 (73.0)	211 (49.2)	242 (46.7)	24 (27.0)	218 (50.8)	23.6	90.0	54.6
80	102 (19.7)	32 (36.0)	70 (16.3)	416 (80.3)	57 (64.0)	359 (83.7)	31.4	86.3	75.5
70	50 (9.7)	18 (20.2)	32 (7.5)	468 (90.3)	71 (79.8)	397 (92.5)	36.0	84.8	80.1
60	24 (4.6)	12 (13.5)	12 (2.8)	494 (95.4)	77 (86.5)	417 (97.2)	50.0	84.4	82.8
50	17 (3.3)	9 (10.1)	8 (1.9)	501 (96.7)	80 (89.9)	421 (98.1)	52.9	84.0	83.0
40	10 (0.2)	6 (6.7)	4 (0.9)	508 (99.8)	83 (93.3)	425 (99.1)	60.0	83.7	83.2
30	6 (0.1)	3 (3.4)	3 (0.7)	512 (99.9)	86 (96.6)	426 (99.3)	50.0	83.2	82.8
20	4 (0.008)	1 (1.1)	3 (0.7)	514 (99.992)	88 (98.9)	426 (99.3)	25.0	82.9	82.4
10	2 (0.004)	1 (1.1)	1 (0.2)	516 (99.996)	88 (98.9)	428 (99.8)	100	82.9	82.8
5	0 (0)	0	0	518 (100)	89 (100)	429 (100)	–	82.8	82.8

†Percentage indicative of specificity. ‡Percentage indicative of sensitivity.

with more aggressive features as compared with individuals referred to hormonal therapy alone. However, the present findings are in line with recent literature that suggests the emerging beneficial role of aRT in patients with LNM, as a result of optimal local control of disease.[28,30] Second, the nomogram's PA to predict CSM-free survival after surgery, once its performance was tested in our independent multi-institutional external validation cohort, was inferior to the internal validation (65.8% *vs* 83.3%, respectively). Accordingly, the discrimination (AUC) of the multivariable model was 66.7% by testing with ROC curve analysis (Fig. 4); this suggests that approximately 35% of patients would be incorrectly classified. Such different accuracy to predict CSM-free survival at the time of surgery, within the external and internal validation cohorts, could be ascribed to significant differences in patient samples (518 *vs* 1107 individuals), median follow-up time (4.3 *vs* 7.1 years) and a different proportion of patients referred to aRT (57.9% *vs* 34.9%), respectively. Hence, despite similar preoperative PSA, pathological stage, positive surgical margins and the median number of lymph nodes retrieved between two cohorts, our population differs from the original in terms of a higher median number of positive lymph nodes (2 *vs* 1), higher proportion of men with pathological Gleason score 8–10 (54.2% *vs* 39.8%) and individuals referred to aRT with aADT (57.9% *vs* 34.9%). Furthermore, in the original population, a significantly higher proportion of patients with pathological Gleason score 8–10 and advanced pathological stage were referred to aRT with aADT rather than aADT alone, whereas in our external cohort we found no significant difference between men referred to aRT with aADT and those scheduled to aADT alone with respect of pathological stage and Gleason score (Table 1). This leads to a substantial suboptimal performance between our external cohort and the initial development. Third, the nomogram's calibration (Fig. 3) showed a not ideal performance after testing in our external cohort, as compared

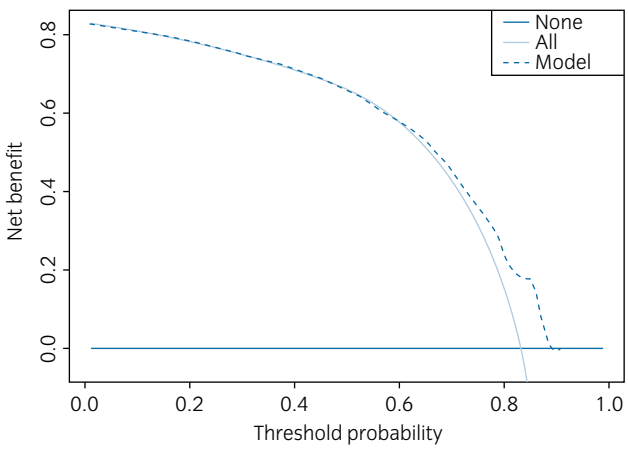

Fig. 5 Decision curve for the nomogram-derived probabilities after validation in the external cohort (*n*: 518)

with the virtually perfect calibration's characteristics within the original population. Precisely, the calibration pointed out an overestimation throughout the range of predicted CSM-free survival rates probabilities. It means that when the probability of CSM-free survival is predicted to be 20%, the actual probability to be alive is approximately 10% (Fig. 3). Hence, the clinicians should consider with attention such overprediction of CSM-free survival when they attempt to use the nomogram in routine patients' counseling process after surgery. Fourth, we systematically tested the performance characteristics of various nomogram's cut-offs for discriminating between patients who actually experienced CSM-free survival and those who died from PCa after surgery, identifying the cut-point with the highest accuracy (83.2%); that is, 40% in our population. Using the latter cut-off, approximately 20% of individuals would be erroneously counseled after surgery and subsequent adjuvant treatments (Table 2). Finally, DCA

showed a net benefit when compared with the scenarios of treating all patients or none. Precisely, the nomogram was found to be superior to the scenario of treating all individuals, at a probability threshold of ≥60% (Fig. 5). In summary, the present findings suggest that the routine use of a previously reported nomogram predicting CSM-free survival in pN1 PCa patients could provide a clinical benefit in post-surgical counseling.[11] However, approximately 35% of patients would be wrongly classified, and the model in our external population tends to overestimate the actual probability to be alive after surgery. However, as it consists of the only available individualized multivariable model to predict survival in pN1 PCa men and it showed good performance at external validation, it represents a useful tool in postoperative patients' counseling and decision-making process. Despite several strengths, the present study was not devoid of limitations. First, our analyses consisted of retrospective assessment. The exact timing of administration of postoperative therapies was left to the clinical decision of each treating physician. Furthermore, even if the multi-institutional dataset adds value to the present results, a central pathology review, that would have influenced our findings, has not been carried out. Second, as the present study covered a long period of time, diagnostic, grading and therapeutic changes that occurred over years might have affected our results. Furthermore, although the extent of the nodal dissection is well standardized in all the treating centers, variability in surgeons' and pathologists' attitudes, as well as interindividual variability, might have limited the accuracy of nodal staging. Third, the inclusion of patients coming from different referral centers could affected our finding, mainly because of possible different surgical approaches and treatment behaviors between single centers. Fourth, almost half of the patients in the overall patient population were referred to aADT with additional aRT, thus our external validation should not be applied to node-positive PCa patients not receiving hormonal treatments after surgery. Finally, our multi-institutional external population, although it represents a large cohort of individuals with LNM, consisted of a smaller sample, as compared with the original cohort.[11] Indeed, further validations based on a larger number of pN1 individuals with different baseline characteristics and a longer follow-up period would assess possible differences in accuracy between different external validation cohorts and the present results. Despite these limitations, the present study represents the first external validation of the unique available multivariable tool for predicting long-term CSM-free survival in the node-positive PCa population.

The present findings confirm the need to change the current management of pN1 PCa patients. As a consequence, prognostication of survival outcomes on an individualized level is essential in order to achieve correct risk stratification, proper counseling and an adequate follow-up schedule. To emphasize this concept, we externally validated the nomogram proposed by Abdollah *et al.,* aimed to predict cancer-specific survival in these individuals.[11] The present results showed inferior PA and suboptimal calibration characteristics as referred to the original cohort, as approximately one-third of patients would be wrongly classified. However, DCA suggested a clinical net benefit of applying this model in a different multi-institutional external cohort.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Nomogram predicting 10-year CSM-free rate in pN1 PCa patients in the original study population.[11] Total point values are calculated and then applied to the desired probability scale at the bottom of the figure.

Editorial Comment

Editorial Comment to Evaluating the predictive accuracy and the clinical benefit of a nomogram aimed to predict survival in node-positive prostate cancer patients: External validation on a multi-institutional database

The paper by Bianchi *et al.* is an interesting study testing, by using a multi-institutional database, the predictive accuracy of a previously published nomogram predicting survival in patients harboring pathological nodes after radical prostatectomy.[1] At the same time, the authors tested the clinical benefit of the above-mentioned nomogram.

Patients with pathological nodes at radical prostatectomy are currently classified as harboring a high-risk disease, regardless of the number, percentage, size or side of nodal metastases. Effectively, a more extensive evaluation of "quantity" of nodal metastases could explain the heterogeneous prognosis of such a high-risk population and why up to a third of patients remain disease-free in the long term without the need of any adjuvant treatment.

As for other predictive tools or nomograms,[2] the original nomogram of Abdollah *et al.*[3] was created by using a well-defined population, within which it received an internal validation. The "success" in terms of acceptance and expendability comes from external validation, which eventually showed that the nomogram can be replicated by uro-oncologists in other samples, times and settings. As its original purpose was to predict cancer-specific mortality-free survival in patients harboring lymph node metastases at radical prostatectomy, its clinical importance in the postoperative decision-making process is pivotal.

The external validation showed that the nomogram revealed inferior predictive accuracy as referred to the original population. As scientists and physicians, this is what we usually experience in real-life practice; that is, certain differences between an ideal setting (such as accurate clinical trials) and current clinical practice, which is usually characterized by different surgical approaches and extension of lymph node dissection, pathology review, timing and type of adjuvant therapy, and follow up. All these factors commonly explain the inferior predictive accuracy in an external validation setting in contrast to an original validation setting, as Bianchi *et al.* correctly suggested. However, the real-life practice is essential to better understand and eventually improve the original, admirable idea of Abdollah *et al*.

Despite this, and confirming the importance of the nomogram, the results coming from the "decision curve analysis" showed a clinical benefit by improving the postoperative management of such complex and heterogeneous patients. It is another step towards a tailored medicine.

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