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Predicting Survival of Patients with Node-positive Prostate Cancer Following Multimodal Treatment

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Abstract

Background: According to the TNM staging system, patients with prostate cancer (PCa) with lymph node invasion (LNI) are considered a single-risk group. However, not all LNI patients share the same cancer control outcomes.
Objective: To develop and internally validate novel nomograms predicting cancer-specific mortality (CSM)–free rate in pN1 patients.
Design, setting, and participants: We evaluated 1107 patients with pN1 PCa treated with radical prostatectomy, pelvic lymph node dissection, and adjuvant therapy at two tertiary care centers between 1988 and 2010.
Outcome measurements and statistical analysis: Univariable and multivariable Cox regression models tested the relationship between CSM and patient clinical and pathologic characteristics, which consisted of prostate-specific antigen (PSA) value, pathologic Gleason score, pathologic tumor stage, status of surgical margins, number of positive lymph nodes, and status of adjuvant therapy. A Cox regression coefficient-based nomogram was developed and internally validated.
Results and limitations: All 1107 patients received adjuvant hormonal therapy (aHT). Additionally, 35% of patients received adjuvant radiotherapy (aRT). The 10-yr CSM-free rate was 84% in the entire cohort and 87% in patients treated with aRT plus aHT versus 82% in patients treated with aHT alone ($p = 0.08$). At multivariable analyses, PSA value, pathologic Gleason score, pathologic tumor stage, surgical margin status, number of positive lymph nodes, and aRT status were statistically significant predictors of CSM (all $p \leq 0.04$). Based on these predictors, nomograms were developed to predict the 10-yr CSM-free rate in the overall patient population and in men with biochemical recurrence. These models showed high discrimination accuracy (79.5–83.3%) and favorable calibration characteristics. These results are limited by their retrospective nature.
Conclusions: Some patients with pN1 PCa have favorable CSM-free rates at 10 yr. We developed and internally validated the first nomograms that allow an accurate prediction of the CSM-free rate in these patients at an individual level.

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1. Introduction

In the last two decades, the widespread use of prostate-specific antigen (PSA) testing in clinical practice has contributed to a downward stage migration in prostate cancer (PCa) [1]. Nevertheless, recent reports show that up to 15% of contemporary patients still harbor lymph node invasion (LNI) at extended pelvic lymph node dissection (ePLND) [2,3]. The presence of LNI in PCa represents an unfavorable pathologic finding with a detrimental impact on cancer control [4–10]. Although patients with other common solid tumors with nodal metastases are further substratified based on different features of LNI [11,12], this is not done in PCa. All men with LNI from PCa are considered a single-risk group, pN1 [13]. Such a one-size-fits-all approach may be misleading and preclude the possibility of optimizing the use of adjuvant therapy as well as patient counseling. Previous reports invariably showed that patients with LNI represent a highly heterogeneous group of individuals who do not share the same cancer control outcomes after treatment [4–6,9]. For example, patients with lower volumes of LNI (one or two positive lymph nodes) have higher survival rates than their counterparts with a higher nodal burden [4–6]. Patients with LNI and locally advanced and/or higher grade tumors have worse cancer outcomes compared with those with less aggressive disease, regardless of the extent of LNI [4–6]. Despite this, there is no available individualized model aimed at predicting cancer-specific survival in patients with LNI. Such a tool would ultimately improve the postoperative clinical decision-making process as well as patient counseling and follow-up schedules after treatment. To address this void, we set out to develop and internally validate novel multivariable tools to predict the cancer-specific mortality (CSM)–free rate in a series of pN1 patients treated with radical prostatectomy (RP), ePLND, and subsequent adjuvant therapy.

2. Materials and methods

We evaluated 1107 consecutive pN1 PCa patients treated with RP and ePLND between 1988 and January 2010 at two tertiary care centers (the Mayo Clinic and San Raffaele Hospital). Inclusion/exclusion criteria are reported in Supplementary Figure 1. All patients were preoperatively staged with abdominal computed tomography and bone scan to exclude the presence of visceral and bone metastases, respectively. During the study period, surgical procedures were performed by 7 surgeons at the Mayo Clinic and by 10 surgeons at San Raffaele Hospital, using a standardized retropubic approach and ePLND. Generally, ePLND consisted of the removal of lymph nodes along the external iliac vessels, obturator

Table 1 – Descriptive statistics for the cohort of 1107 patients with nonmetastatic lymph node–positive prostate cancer

	Entire cohort *n* = 1107 (100%)	Adjuvant hormonal therapy *n* = 721 (65.1%)	Adjuvant hormonal and radiotherapy *n* = 386 (34.9%)	*p* value
Age, yr				0.4
Mean	64.7	64.8	64.5	
Median	65.0	66.0	64.8	
IQR	60.0–70.0	60.0–70.0	60.0–69.7	
Prostate-specific antigen, ng/ml				0.2
Mean	25.8	24.6	27.9	
Median	14.0	14.1	14.0	
IQR	7.9–28	7.7–27.1	8.0–31.0	
Pathologic Gleason score, *n* (%)				<0.001
≤6	155 (14.0)	123 (17.1)	32 (8.3)	
7	518 (46.8)	358 (49.7)	160 (41.5)	
≥8	434 (39.2)	240 (33.3)	194 (50.3)	
Pathologic tumor stage, *n* (%)				<0.001
pT2/pT3a	351 (31.7)	267 (37)	84 (21.8)	
pT3b	681 (61.5)	427 (59.2)	254 (65.8)	
pT4	75 (6.8)	27 (3.7)	48 (12.4)	
Surgical margin status, *n* (%)				<0.001
Negative	450 (40.7)	337 (46.7)	113 (29.3)	
Positive	657 (59.3)	384 (53.3)	273 (70.7)	
No. of positive nodes				0.04
Mean	2.5	2.4	2.8	
Median	1.0	1.0	2.0	
IQR	1.0–3.0	1.0–2.0	1.0–3.0	
No. of removed lymph nodes				<0.001
Mean	15.8	14.1	18.9	
Median	14.0	13.0	17.0	
IQR	10.0–20.0	9.0–18.0	12.0–23.0	
Year of surgery, quartiles, *n* (%)				<0.001
1988–1993	312 (28.2)	272 (37.7)	40 (10.4)	
1994–1999	251 (22.7)	193 (26.8)	58 (15.0)	
2000–2005	298 (26.9)	127 (17.6)	171 (44.3)	
2006–2010	246 (22.2)	129 (17.9)	117 (30.3)	

IQR = interquartile range.
Patients were treated with radical prostatectomy and pelvic lymph node dissection between 1988 and 2010 at two tertiary care centers. Data were stratified according to adjuvant treatment status: adjuvant hormonal therapy versus adjuvant hormonal and radiotherapy.