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Prostate Cancer

Development and Internal Validation of a Novel Model to Identify the Candidates for Extended Pelvic Lymph Node Dissection in Prostate Cancer

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Abstract

Background: Preoperative assessment of the risk of lymph node invasion (LNI) is mandatory to identify prostate cancer (PCa) patients who should receive an extended pelvic lymph node dissection (ePLND).
Objective: To update a nomogram predicting LNI in contemporary PCa patients with detailed biopsy reports.
Design, setting, and participants: Overall, 681 patients with detailed biopsy information, evaluated by a high-volume uropathologist, treated with radical prostatectomy and ePLND between 2011 and 2016 were identified.
Outcome measurements and statistical analysis: A multivariable logistic regression model predicting LNI was fitted and represented the basis for a coefficient-based nomogram. The model was evaluated using the receiver operating characteristic-derived area under the curve (AUC), calibration plot, and decision-curve analyses (DCAs).
Results and limitations: The median number of nodes removed was 16. Overall, 79 (12%) patients had LNI. A multivariable model that included prostate-specific antigen, clinical stage, biopsy Gleason grade group, percentage of cores with highest-grade PCa, and percentage of cores with lower-grade disease represented the basis for the nomogram. After cross validation, the predictive accuracy of these predictors in our cohort was 90.8% and the DCA demonstrated improved risk prediction against threshold probabilities of LNI $\leq$20%. Using a cutoff of 7%, 471 (69%) ePLNDs would be spared and LNI would be missed in seven (1.5%) patients. As compared with the Briganti and Memorial Sloan Kettering Cancer Center nomograms, the novel model showed higher AUC (90.8% vs 89.5% vs 89.5%), better calibration characteristics, and a higher net benefit at DCA.
Conclusions: An ePLND should be avoided in patients with detailed biopsy information and a risk of nodal involvement below 7%, in order to spare approximately 70% ePLNDs at the cost of missing only 1.5% LNIs.
Patient summary: We developed a novel nomogram to predict lymph node invasion (LNI) in patients with clinically localized prostate cancer based on detailed biopsy reports. A lymph node dissection exclusively in men with a risk of LNI $>$ 7% according to this model would significantly reduce the number of unnecessary pelvic nodal dissections with a risk of missing only 1.5% of patients with LNI.

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1. Introduction

Up to 15% of prostate cancer (PCa) patients harbor lymph node invasion (LNI) at radical prostatectomy (RP) [1]. These individuals are at a higher risk of recurrence after primary treatment [2]. Correct nodal staging is crucial to identify patients with poor prognosis who would benefit from additional therapies [3,4]. The implementation of novel imaging modalities such as prostate-specific membrane antigen positron emission tomography /computed tomography scan prior to RP is limited by their poor performance characteristics [5]. Conversely, an anatomically defined extended pelvic lymph node dissection (ePLND) represents the most optimal method for nodal staging [6,7]. Given the prolonged operative time as well as the increased risk of complications associated with an ePLND [8,9], this procedure is indicated only in selected patients at a higher risk of nodal involvement [6,7]. The European Association of Urology (EAU)–European Society for Radiotherapy & Oncology (ESTRO)–International Society of Geriatric Oncology (SIOG) and the National Comprehensive Cancer Network (NCCN) clinical guidelines recommend the use of models based on preoperative characteristics such as the Briganti and Memorial Sloan Kettering Cancer Center (MSKCC) nomograms to estimate the risk of LNI and, in turn, to select men who should be considered for an ePLND [10–13]. However, these tools need to be periodically updated [14]. Moreover, although the Briganti and MSKCC nomograms achieve very good performance characteristics, they can certainly be improved [15]. Indeed, none of them included the precise assessment of cancer involvement within the biopsy cores or accounted for intraprostatic heterogeneity in PCa grade. This might lead to a limited accuracy in estimating the risk of LNI [10,11,13]. Under this light, we sought to develop a novel nomogram predicting LNI in a contemporary cohort of patients treated with RP and ePLND, with detailed biopsy information available after a centralized biopsy specimen review.

2. Patients and methods

2.1. Population source and surgical procedure

After Institutional Review Board approval, clinical and pathologic data were prospectively collected for 2872 patients treated with open or robot-assisted RP and ePLND for localized PCa between January 2011 and July 2016 at a single tertiary referral center. Patients with complete data who underwent centralized biopsy specimens review performed by two high-volume dedicated uropathologists (either R.M. or M.F.) were selected ($n = 681$). No patients received neoadjuvant hormonal therapy. All cases were performed by six surgeons with at least 200 cases at the beginning of data collection who were trained by the same surgeon and applied the same anatomical template for ePLND. The fibrofatty tissue along the external iliac vein was dissected, the lateral limit being the genitofemoralis nerve. Proximally, an ePLND was performed up to and included the crossing between the ureter and common iliac vessels. Lymph nodes along as well as medially and laterally to the internal iliac vessels were removed. All fibrofatty tissue within the obturator fossa was removed, and the Marcille's triangular lumbosacral fossa was dissected free [16]. All specimens were submitted for pathologic evaluation in multiple packages according to their anatomical location and were evaluated by dedicated uropathologists according to a previously described methodology [10,17].

2.2. Covariates and end points

All patients were subjected to a detailed preoperative evaluation that consisted of prostate-specific antigen (PSA), clinical stage obtained according to the digital rectal examination performed by the attending urologist, and transrectal ultrasound-guided prostate biopsy [18]. All patients had complete data, including the percentage of positive cores, biopsy grade group for each positive core, percentage of PCa involvement, and exact tumor length in each core. We calculated the percentage of cores involved by the highest-grade disease by dividing the number of cores with highest-grade PCa by the total number of cores. The percentage of cores involved by lower-grade PCa was abstracted. We calculated tumor length (ie, the sum of tumor length in each single core) overall and stratified according to highest- and lower-grade PCa. Similarly, the percentage of tumor in biopsy cores was abstracted. The modified Gleason scoring system was adopted according to the International Society of Urological Pathology 2005 and 2014 consensus conferences [19,20]. The outcome of our study was LNI, defined as the presence of positive lymph nodes at final pathology.

2.3. Statistical analyses

First, univariable logistic regression analyses assessed predictors of LNI. Given the small number of events in the biopsy grade group 1 and 5 categories, we decided to categorize biopsy grade groups in 1–2 versus 3 versus 4–5. We then developed four different multivariable models predicting LNI including variables that might be considered as a proxy of tumor volume. Preoperative PSA, clinical stage, and biopsy grade group were included in all these models. The discrimination accuracy of multivariable models based on these variables in our cohort was quantified using the receiver operating characteristic-derived area under the curve (AUC). Since the inclusion of information on the maximum percentage of single core involvement and the percentage of tumor in biopsy cores overall and according to the highest- and lower-grade disease did not improve the predictive accuracy, we relied on the most parsimonious model to develop a nomogram predicting LNI. Preoperative PSA, clinical stage, biopsy Gleason grade group, percentage of cores with highest-grade PCa, and percentage of cores with lower-grade disease represented the basis for our coefficient-based nomogram. The extent of over- or underestimation of the histologically confirmed versus nomogram-predicted LNI rates was graphically explored using a calibration plot. A decision-curve analysis (DCA) was used to determine the clinical net benefit associated with the use of the model [21]. The discrimination, calibration, and DCA were corrected for overfit using leave-one-out cross validation. We then compared the predictive accuracy of two existing models (Briganti and MSKCC nomograms) with the novel nomogram using the predetermined regression coefficients [10,11,13]. Calibration plots were used to assess the extent of over- or underestimation associated with their use. Finally, DCAs were used to determine the clinical net benefit associated with the adoption of these models.

All statistical tests were performed using the R statistical package v.3.0.2 (R Project for Statistical Computing, www.r-project.org). All tests were two sided, with a significance level set at $p < 0.05$.

2.4. Sensitivity analyses

We compared baseline and pathologic characteristics of patients included in our cohort and those excluded due to incomplete biopsy information, to investigate whether patients with missing data were different from those included in our analyses. We then repeated our

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