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Pathologic Nodal Staging Scores in Patients Treated with Radical Prostatectomy: A Postoperative Decision Tool

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Abstract

Background: Nodal metastasis is the strongest risk factor of disease recurrence in patients with localized prostate cancer (PCa) treated with radical prostatectomy (RP).
Objective: To develop a model that allows quantification of the likelihood that a pathologically node-negative patient is indeed free of nodal metastasis.
Design, setting, and participants: Data from patients treated with RP and pelvic lymph node dissection (PLND; $n = 7135$) for PCa between 2000 and 2011 were analyzed. For external validation, we used data from patients ($n = 4209$) who underwent an anatomically defined extended PLND.
Intervention: RP and PLND.
Outcome measurements and statistical analysis: We developed a novel pathologic (postoperative) nodal staging score (pNSS) that represents the probability that a patient is correctly staged as node negative based on the number of examined nodes and the patient's characteristics.
Results and limitations: In the development and validation cohorts, the probability of missing a positive node decreases with an increasing number of nodes examined. Whereas in pT2 patients, a 90% pNSS was achieved with one single examined node in both the development and validation cohort, a similar level of nodal staging accuracy was achieved in pT3a patients by examining five and nine nodes, respectively. The pT3b/T4 patients

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achieved a pNSS of 80% and 70% when 17 and 20 nodes in the development and validation cohort were examined, respectively. This study is limited by its retrospective design and multicenter nature. The number of nodes removed was not directly correlated with the extent/template of PLND.

Conclusions: Every patient needs PLND for accurate nodal staging. However, a one-size-fits-all approach is too inaccurate. We developed a tool that indicates a node-negative patient is indeed free of lymph node metastasis by evaluating the number of examined nodes, pT stage, RP Gleason score, surgical margins, and prostate-specific antigen. This tool may help in postoperative decision making.

1. Introduction

Prostate cancer (PCa) is the most common noncutaneous malignancy in men with an estimated 238 590 new cases and 29 720 deaths in 2013 in the United States [1]. Radical prostatectomy (RP) provides good long-term local control and survival when cancer is confined to the prostate [2,3]. In patients with locally advanced disease [4–7], such as extraprostatic extension and lymph node (LN) metastasis [8–10], adjuvant radiation therapy (RT) and androgen-deprivation therapy (ADT) have improved disease-free recurrence and survival rates.

Nodal metastasis is the strongest risk factor for disease recurrence and survival for patients treated with RP [2]. To achieve accurate LN staging, pelvic lymph node dissection (PLND) is necessary in patients undergoing RP [2,11]. However, the rate and extent of PLND over the last decades has been decreasing, leading to a loss of accuracy of true LN status [11,12]. LN dissemination in PCa does not follow a predefined pathway of metastatic spread but rather different lymphatic routes tributary to several primary lymphatic landing sites [13,14]. Many efforts have been made to estimate the number of LNs needed to be removed and examined to achieve an accurate LN staging [15–17]. However, to date, no consensus has been reached on such a number. This issue is key because node-negative patients treated with inadequate extent of nodal dissection may harbor a non-negligible risk of residual or recurrent nodal disease after RP.

We recently developed a methodology that calculates the probability that a pathologic node-negative patient is indeed free of nodal metastasis as a function of the number of examined LNs and tumor stage in colorectal and bladder cancer [18,19]. The aim of this study was to develop a similar pathologic nodal staging score (pNSS) for patients with PCa. We hypothesized that the true nodal status (no false-negative LN status) could be accurately predicted based on the number of LNs examined, pathologic characteristics such as pT stage, RP Gleason score, surgical margin, and preoperative prostate-specific antigen (PSA). Toward this goal, we used a large multicenter cohort of patients treated with RP and a variable extent of PLND to develop the novel nodal staging score (NSS). We subsequently validated the novel model in a large single-center cohort of RP patients who underwent an anatomically defined extended PLND (ePLND).

2. Methods

2.1. Patient selection and data selection

The development cohort included data of 7135 PCa patients with a clinical localized tumor from eight academic centers. All were treated with RP and PLND between 2000 and 2011. In this cohort, the extent of PLND was at the discretion of each treating physician. Although this mainly consisted of an anatomically defined limited PLND, including removal of all lymphatic tissue in the obturator fossa and along the external iliac vessels, ePLND was also performed. The validation cohort included 4209 PCa patients with clinically localized disease who were treated between 1989 and 2012 at a single center with RP and anatomically defined ePLND. The ePLND consisted of excision of fibrofatty tissue along the external iliac vein, with the distal limit the deep circumflex vein and the femoral canal. LNs along the internal iliac artery were also removed. Proximally, ePLND included the bifurcation of the common iliac artery [20]. Preoperative staging was performed with PSA, Gleason score at biopsy, digital rectal examination, and imaging study results. No patient received preoperative RT, hormonal treatment, or chemotherapy. No patient had distant metastatic disease at the time of RP. This study was approved by institutional review boards, with all participating sites providing the necessary institutional data-sharing agreements beforehand.

2.2. Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures as outlined elsewhere [21]. Genitourinary pathologists assigned pathologic stage, which was reassigned according to the 2007 American Joint Committee on Cancer TNM staging system. All lymphoid tissue removed was submitted for histologic examination. In the development cohort, the pathology review was performed by a variety of pathologists from different institutions, whereas in the validation cohort, a central pathology was used.

2.3. Statistical analysis

As in a previously described methodology [18,19], we tested the probability of incorrect nodal staging as a function of the number of examined nodes. Practically, the false-negative rate is not directly estimable from the data because the true nodal status cannot be determined. However, information from node-positive patients can be used to determine if the number of nodes examined and the number of these that are negative are sufficient to classify a patient as node negative. For example, consider a patient with a large number of examined nodes and a small number of positive nodes (called k). If fewer nodes were examined, this patient might be incorrectly deemed node negative. Conversely, for a patient with a small number of examined nodes and large k, it is unlikely that nodal disease would have been missed, even though

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