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Urologic Oncology: Seminars and Original Investigations 35 (2017) 33.e21–33.e26

UROLOGIC ONCOLOGY

Original article

External validation of the pathological nodal staging score in upper tract urothelial carcinoma: A population-based study

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Received 1 May 2016; received in revised form 9 July 2016; accepted 29 July 2016

Abstract

Objectives: To externally validate our previously developed pathological nodal staging model (pNSS) that allows quantification of the likelihood that a patient with pathologic node-negative status has, indeed, no lymph node metastasis (LNM).

Patients and methods: We analyzed data from 2,768 patients treated with radical nephroureterectomy (RNU) and lymph node dissection (LND) using the Surveillance, Epidemiology, and End Results database from 1988 to 2010. We estimated the sensitivity of pathologic nodal staging using a beta-binomial model and developed a new pNSS. Then, we compared these findings with those of the initial cohort.

Results: The mean and median numbers of lymph node (LN) removed were 5 and 2, respectively (interquartile range = 5) in the validation cohort, though 66.5% of the patients ($n = 1814$) were pN0. Similar to the development cohort, the probability of missing a LNM decreased as the number of nodes examined increased in the validation cohort. If only a single node was examined, 35% of patients would be misclassified as pN0 while harboring LNM. Even when 5 nodes were examined, 8% would be misclassified. The probability of having a positive node increased with advancing pathological T stage in both the cohorts. Patients with pT0-Ta-Tis-T1 disease in both cohorts would have more than a 95% chance of a correct pathologic nodal staging with 2 examined nodes. However, if a patient has pT3–T4 disease, more than 12 examined LNs are needed to reach 95% accuracy.

Conclusions: We confirmed that the number of examined nodes needed for adequate staging depends on pT category. We externally validated our previous pNSS in a population-based database, which could help in the clinical decision-making regarding adjuvant chemotherapy administration.

Keywords: Upper tract urothelial carcinoma; Lymphadenectomy; Validation; Pathological nodal staging score; SEER

1. Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare malignancy, accounting for approximately 5% of all urothelial cancers [1]. Up to 30% of patients with muscle-invasive UTUC have metastasis to the regional lymph nodes (LNs) [2,3], which represents a powerful prognostic

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http://dx.doi.org/10.1016/j.urolonc.2016.07.022
1078-1439/

factor of survival [3–5]. Although lymphadenectomy improves tumor staging, its therapeutic benefit remains controversial [3–5]. In addition to LN status, the extent of lymphadenectomy, the number of LNs examined, the number of positive LNs detected, and the LN density are suggested to have both prognostic and potentially therapeutic implications [6]. Knowledge of the true LN status, therefore, is important as it influences patient counseling and, more importantly, clinical decision-making regarding follow-up scheduling and adjuvant chemotherapy [7–10].

We have recently developed a model (i.e., pathological nodal staging score) that allows us to determine the probability that a patient with pathologic node-negative status at radical nephroureterectomy (RNU) truly has no lymph node metastasis (LNM) using the number of examined LNs and established pathological features (such as pathological tumor stage) [11]. The aim of the current study was to externally validate our model in a population-based cohort of patients using the Surveillance, Epidemiology, and End Results (SEER) database.

2. Patients and methods

2.1. Patient selection and data collection

The development cohort comprised 814 patients who underwent RNU and lymphadenectomy for UTUC between 1994 and 2007 at 7 centers worldwide [11]. In this cohort, LN dissections were examined grossly, and all lymphoid tissue was submitted for histological examination. The extent of LN dissection was at the surgeon's discretion. None of patients underwent preoperative chemotherapy or radiotherapy. Adjuvant chemotherapy was administered at clinician's discretion based on tumor stage, LN involvement, and overall health status as well as patients preference.

For the validation cohort, we used the SEER registry data from 1988 to 2010 for our analyses. This period was chosen because SEER did not collect detailed LN data between 1973 and 1987. By the end of the study period, the registry included approximately 28% of the United States population and is considered to be representative of the general population. Patients who underwent RNU for UTUC (codes ICD-0-2 C65.9 and C66.9) were identified. Inclusion criteria consisted of having a diagnosis of UTUC and documentation of the number of LN examined as well as the number of pathologically positive LN. Patients were excluded from analyses if the tumor grade and stage were unknown, there was an evidence of metastatic disease at diagnosis, or patients underwent a partial nephroureterectomy.

2.2. Statistical analysis

2.2.1. Overview

Validation of nodal staging scores cannot be carried out using the standard validation methodology of obtaining predictions in an independent data set and comparing them with the observed outcome. This is because there is no gold standard observation, that is, it is impossible to know if a person with LN categorized as pN0 has indeed no LNM. For this reason, we applied a similar methodology as our previous work to the validation cohort to build a similar pathological nodal staging score (pNSS) [11] and compare the nodal staging scores across the 2 data sets. The primary end point was the probability of incorrect nodal staging of the examined nodes (n). The true nodal status is unascertainable, but we can use the information from patients with LN-positive status to determine if n examined and negative LNs are sufficient to classify a patient with LN-negative status. For example, consider a patient with n large and k small but positive (k = number of positive nodes from patients with node involvement)—if less than n LNs had been examined—there would be a chance that this patient would have been incorrectly deemed as LN negative. Conversely, for a patient with small n and large k, even with fewer examined LNs, it is unlikely that nodal disease would have been missed. Hence, the data from patients with LN-positive status are used to interpret the data for patients with LN-negative status. The probability that a patient with LN-negative status has nodal disease can be computed using the following algorithm: (1) compute the probability of missing a positive node (sensitivity), (2) compute the prevalence, and (3) compute the nodal staging score from sensitivity and prevalence [11–14].

2.3. Probability of missing a positive LN

Probability of missing a positive LN (one minus the sensitivity) is inherent to the process of pathological detection and as such depends on the number of examined LNs but not on patient characteristics [11–14]. We used a beta-binomial model for this purpose, allowing for heterogeneity in the intensity of nodal spread across the patients [11–14]. A total of 3 key assumptions underlie this step: (1) there are no false positives (if the specimen contains a positive LN, it would be correctly identified by the pathologist); (2) all LNs are exchangeable, that is, they all have an equal probability of being involved; and (3) sensitivity is the same for patients with LN-positive and LN-negative status. These assumptions may not be completely tenable, but we find them to be sufficient approximations to our biological understanding of nodal spread and clinical practice of nodal staging [11–14].

2.4. Estimation of prevalence of nodal disease

The observed prevalence (apparent prevalence) is an underestimate and needs to be adjusted for false negatives [11–14]. This was done using 2 steps: first step invokes Assumption 1 and estimates FNk as a function of k, where TPk is the number of true positives for a given k [11–14]. Because prevalence is not a function of k, the second step