

Original article

# Impact of adequate pelvic lymph node dissection on overall survival after radical cystectomy: A stratified analysis by clinical stage and receipt of neoadjuvant chemotherapy

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## Abstract

**Purpose:** An adequate pelvic lymph node dissection (LND) during radical cystectomy (RC) for muscle-invasive bladder cancer (BCa) has been shown to provide a survival benefit. We designed a study to assess the effect of adequate LND on overall survival (OS) according to cT stage and receipt of neoadjuvant chemotherapy (NAC).

**Material and methods:** We identified 16,505 patients with localized BCa who received RC in the National Cancer Database (2004–2012). Inverse probability of treatment weighting (IPTW)-adjusted Kaplan-Meier and Cox regression analyses were used to compare OS between patients who received adequate LND (defined as  $\geq 10$  nodes removed) and those who did not, stratified by cT stage and receipt of NAC.

**Results:** Overall 8,673 (52.55%) patients underwent adequate LND at RC for localized BCa. Median time to last follow-up was 55.49 months (IQR, 34.73–75.96 months). IPTW-adjusted Kaplan-Meier curves showed that median OS was improved in patients who received adequate LND (60.06 vs. 46.88 months). In patients who did not receive NAC, adequate LND was associated with an OS benefit for cT1/a/cis, cT2, and cT3/4 disease ( $P \leq 0.008$ ). Among patients who received NAC, adequate LND was not associated with any OS difference regardless of cT stage.

**Conclusion:** Our data suggest that patients who did not receive NAC benefit from an adequate LND. However, the receipt of an adequate LND was not associated with an OS benefit in patients pretreated with NAC. Our study indicates that the receipt of NAC may eradicate micrometastatic disease, and thus limit the benefit of an adequate LND. © 2018 Elsevier Inc. All rights reserved.

**Keywords:** NCDB; Neoadjuvant chemotherapy; Lymph nodes; Radical cystectomy; Survival

## 1. Introduction

In 2017, approximately 79,030 new bladder cancer (BCa) cases will be diagnosed in the United States (US),

and 16,240 patients will die from BCa [1]. Despite many advances in the management of BCa, including the use of neoadjuvant chemotherapy (NAC) prior to surgery and the advent of immunotherapy, BCa mortality rates remain stable over the past 2 decades. Radical cystectomy (RC) remains the standard of care treatment for localized muscle-invasive BCa [2]. Pelvic lymph node dissection (LND) is

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performed during RC, as it is considered to be a critical component for staging. Moreover, extended LNDs have been shown to improve disease- and recurrence-free survival when compared to a standard LND [3–5]. The adequacy of an LND can be defined anatomically (the European Association of Urology recommends removing LNs to the aortic bifurcation and in the presacral area), or as a minimal threshold of lymph nodes removed (often defined as  $\geq 10$  lymph nodes) [6,7]. Many of the studies showing a benefit to LND rely on institutional data in the pre-NAC era. It is unclear if that benefit is preserved in patients undergoing NAC, which may serve a similar purpose in eliminating micrometastatic disease. [8,9].

Therefore, we designed a study to assess the stage-specific survival benefit of an adequate LND (defined as  $\geq 10$  lymph nodes removed at RC) on the basis of whether a patient received NAC. Given that NAC may perform a similar function to an adequate LND at the time of cystectomy, the benefit of an LND may be lessened in those who received NAC.

## 2. Material and methods

### 2.1. Data source

The National Cancer Database (NCDB), a joint program of the American Cancer Society and the Commission on Cancer, is a nationwide database that contains information on patterns of cancer care and treatment outcomes. The NCDB collects data on newly diagnosed malignancies since 1989 and includes information on more than 29 million unique cancer cases seen in more than 1,500 Commission on Cancer-accredited programs in Puerto Rico and in the US [10]. Approximately 70% of incident neoplasms in the US are reported to the NCDB [11].

### 2.2. Study population and treatment groups

We identified 391,214 men and women with BCa diagnosed between 2004 and 2012 in the NCDB (C670–C679 in ICD-0–3). Of these, we selected 248,288 patients with urothelial tumor and no metastasis to the lymph nodes or other organs at time of bladder biopsy (cT1/a/cis-T4N0M0). We excluded patients ( $n = 228,604$ ) not managed by cystectomy and those with an unknown number of lymph nodes removed ( $n = 563$ ). We then excluded all patients with unknown status of chemotherapy ( $n = 2554$ ) as well as all individuals with missing follow-up data ( $n = 62$ ). Our final cohort consisted of 16,505 patients.

### 2.3. Definition of treatment groups

The eligible population was classified according to inadequate ( $< 10$  lymph nodes removed) vs. adequate ( $\geq 10$  lymph

nodes removed) LND at the time of RC. In the absence of detailed anatomical information on extent of LND, the number of lymph nodes removed has been used as a proxy for extent of LND, with many studies showing a survival benefit when  $\geq 10$  lymph nodes are removed [12–14].

### 2.4. Other variables

We abstracted patient-level variables including age at diagnosis, sex, race, baseline Charlson Comorbidity Index (CCI), and insurance status. Socioeconomic variables were estimated using household income and education level from county of residence. Travel distance as well as hospital type and location were also abstracted. Tumor characteristics included clinical tumor (cT) stage. Furthermore, we assessed for the receipt of NAC, defined as the receipt of systemic chemotherapy within 180 days between BCa diagnosis and RC.

### 2.5. Endpoint

Our primary analytical endpoint was overall survival (OS), computed according to the records of vital status within NCDB and the date of last follow-up.

### 2.6. Statistical analyses

First, we generated interquartile ranges (IQR) and medians for continuous variables and frequencies and proportions for categorical variables. Differences in continuous and categorical variables were examined using the Mann-Whitney test and the chi-square test.

Second, we used the standardized differences approach to compare covariates between patients who received adequate vs. inadequate LND to facilitate assessment for potential confounding [15].

Third, to account for selection bias, observed differences in baseline characteristics between men and women who received adequate vs. inadequate LND were controlled for with a weighted propensity score analysis. The goodness-of-fit statistic of the propensity score model was assessed using the method developed by Lemeshow and Hosmer [16]. Each patient was weighted by the inverse probability of receiving adequate LND, with the aim of balancing out observable properties between the groups; this approach is known as inverse probability of treatment weighting (IPTW) [17,18]. Balance between baseline characteristics in weighted groups was also assessed using the standardized differences approach and by comparing their distribution with unweighted data. In addition, we used Kernel density plots to depict the pre- and post-IPTW adjustment distribution of propensity scores in each treatment groups. If the 2 groups have similar Kernel density plots, then the distribution of confounders likely balance across groups.

Fourth, IPTW-adjusted Kaplan-Meier curves were used to compare OS between patients who received adequate vs.

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