

Original article

Lymph node count at radical cystectomy does not influence long-term survival if surgeons adhere to a standardized template

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Abstract

Introduction: Multiple bladder cancer studies report that the number of removed lymph nodes (lymph node count [LNC]) at radical cystectomy (RC) is positively associated with survival. Although these reports suggest that LNC can be used as a proxy for surgical quality, all studies used variable or inconsistent pelvic lymph node dissection (PLND) templates. We therefore wished to establish whether LNC at RC influences survival if surgeons adhere to a standardized PLND template.

Materials and methods: We included 274 patients who underwent RC from January 2005 until December 2012. All RCs were performed in either one of 2 hospitals (hospital A or B) by the same 4 urologists (all from hospital A) and a standardized PLND template was applied. PLND specimens were processed by 2 independent pathology departments (hospital A and B). We used Cox regression analysis to investigate the prognostic value of LNC adjusted for patient characteristics. We also compared LNC between hospitals and surgeons and investigated the effect of both the variables on overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS).

Results: Median LNC was 17 (interquartile range = 12). At a median follow-up of 64.3 months, there was no association between LNC and OS ($P = 0.328$), CSS ($P = 0.645$), or DFS ($P = 0.450$). Median LNC was higher in hospital B than in hospital A (20.0 vs. 16.0, $P = 0.003$). Median LNC varied significantly among surgeons (12–20, $P < 0.001$). Neither the hospital of surgery nor the surgeon performing PLND influenced OS ($P = 0.771$ and $P = 0.982$, respectively), CSS ($P = 0.310$ and $P = 0.691$, respectively), or DFS ($P = 0.256$ and $P = 0.296$, respectively).

Conclusion: If surgeons adhere to a standardized template, LNC at RC does not affect long-term survival. © 2015 Elsevier Inc. All rights reserved.

Keywords: Cystectomy; Urothelial carcinoma; Lymph nodes; Survival

1. Introduction

Pelvic lymph node dissection (PLND) in bladder cancer (BC) surgery was already described in 1962 [1]. The rationale is based on improved staging and potential higher

survival rates in patients undergoing radical cystectomy (RC) for BC [2]. Multiple studies have reported that an increased LN count (LNC) is associated with improved survival in both node-negative and node-positive disease [3–6]. However, variable or inconsistent PLND templates were used in these studies [3–6]. Consequently, limited resection could have decreased LNC in infirm or elderly patients, inducing selection bias. In contrast, recent LN mapping studies suggest that adherence to a standardized PLND template is more important than LNC in capturing all

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relevant LNs [7,8]. The primary purpose of this study was to establish whether variability in LNC influences survival if surgeons adhere to a standardized PLND template. The second objective was to investigate if potential differences in LNC between different pathology departments or between surgeons affect long-term survival.

2. Materials and methods

2.1. Patients

We extended the series previously described in a study by Meijer et al. [9] and subsequently refined our selection based on the PLND template applied. The cases were derived from the prospective genitourinary cancer database that was maintained by the department of urology at the Netherlands Cancer Institute (hospital A). Firstly, all consecutive patients who underwent open RC and bilateral PLND for urothelial carcinoma from January 2005 until December 2012 were selected ($n = 395$). Patients for whom PLND at RC was not performed according to the standardized template described at 1.2.2. or for whom the PLND template was not clearly defined in surgery or pathology reports were excluded from further analysis ($n = 51$). For 37 of these patients, a superextended template was applied because of suspicion of positive LNs above the true pelvis. In addition, all palliative RCs or RCs following pelvic radiation were excluded, as these factors could have affected LN dissection procedures ($n = 45$). Finally, 25 patients were excluded because their pathology reports were inconclusive regarding the macroscopically and microscopically identified LNC. Tumor stage was classified according to the seventh Union for International Cancer Control (UICC) TNM classification. Patients were initially seen at the BC clinic of the Netherlands Cancer Institute—Antoni van Leeuwenhoek hospital, Amsterdam (hospital A). After multidisciplinary rounds, patients were treated with either RC or neoadjuvant chemotherapy followed by RC. All RCs were performed at either hospital A or St. Lucas—Andreas Hospital, Amsterdam (hospital B). For all patients, follow-up was conducted in hospital A.

2.2. Surgical procedures

A team of 4 experienced urologists (>140 cystectomies performed each) from hospital A had performed all procedures at both hospital A and hospital B. The reason for this unique situation was that hospital B provided extra operation room capacity. All patients underwent a standardized bilateral PLND, which included resection of all nodal and adipose tissue between the genitofemoral nerve, the obturator fossa, along the internal iliac artery, and along the common iliac artery, including the triangle of Marcille, up to the crossing of the ureter, leaving all vascular structures within this template exposed. PLND specimens were sent to

the pathology department in at least 2 separate packages per side (lateral to and medial to the external iliac artery).

2.3. Pathological evaluation

Each pathology department processed the PLND specimens according to its own institutional protocol, as previously described [9]. In brief, protocols for fixation, pathological LN dissection, and packaging in cassettes only slightly differed between the 2 departments. In total, 11 pathology assistants processed the PLND specimens (8 in hospital A and 3 in hospital B). Final evaluation was performed by 11 pathologists in hospital A and 6 in hospital B. All PLND specimens were randomly assigned to each pathology assistant and to each pathologist. Pathology assistants in hospital A identified LNs by palpating the tissue while sweeping strokes of the scalpel were made. Pathology assistants in hospital B searched LNs by manually gently “squashing” the specimens. LN identification within the perinodal adipose tissue therefore depended on the attention of pathology assistants in both the hospitals. Corresponding macroscopic and microscopic LNCs were reported per cassette in pathology reports. For final evaluation, cumulative microscopic LNCs were used.

2.4. Data collection and statistical analysis

Overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) were assessed for all patients. Oncological end points for OS, CSS, and DFS were date of death, date of death due to BC, and the appearance of recurrent disease, respectively. Survival times were defined as the time elapsed from RC to the before-mentioned end points. Cox regression analysis was performed for OS, CSS, and DFS to assess the prognostic value of LNC. The LNC was compared between hospitals and between surgeons using the Mann-Whitney *U* test and the Kruskal-Wallis test, respectively. Patient and tumor characteristics were compared between hospitals and between surgeons using the Pearson chi-square test, the Fischer exact test, independent *t* test, and 1-way analysis of variance. The Kaplan-Meier method was used to generate actuarial survival curves for both the hospitals, which were compared by log-rank tests. The same procedure was performed for comparing between the surgeons. Multivariable Cox regression analysis was performed for LNC as a continuous variable regarding OS, CSS, and DFS to adjust for pT category, pN category, soft tissue margin status (STMS), age, sex, American Society of Anesthesiologists status (ASA), and the administration of neoadjuvant chemotherapy. Positive STMS was defined as the presence of malignant cells at any of the surgical margins, including the ureters, urethra, and circumferential margins. Overall, 3 Cox regression models were generated: model 1 did not include hospital of surgery or surgeon, model 2 included hospital of surgery, and model 3 included surgeon.

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