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Original article

# Incidence and location of lymph node metastases in patients undergoing radical cystectomy for clinical non–muscle invasive bladder cancer: Results from a prospective lymph node mapping study

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## Abstract

**Objectives:** The objective of this study is to investigate the incidence and location of lymph node metastases (LNMs) in patients undergoing radical cystectomy (RC) and lymph node dissection (LND) for clinical non–muscle invasive bladder cancer (NMIBC).

**Methods and materials:** Prospectively collected data of 637 patients who underwent RC and 'superextended' LND with intent-to-cure for urothelial carcinoma of the bladder between 2002 and 2008 were examined. Inclusion criteria were (a) clinical stage Ta, Tis-only, or T1, (b) muscle presence at diagnostic transurethral resection in clinical T1 patients, (c) no prior diagnosis of ≥T2 disease, (d) no neoadjuvant therapy, and (e) lymphatic tissue sample submitted from all 13 predesignated locations. Lymph node mapping was performed in all patients to determine the location of metastatic lymph nodes. Median follow-up time was 4.7 years. Recurrence-free survival and overall survival were reported.

**Results:** A total of 114 patients were included of whom 9 patients (7.9%) had LNM. Stratified by clinical stage, LNM was present in 6/67 (9.0%) patients with cT1, 3/25 (12.0%) patients with cTis-only, and none of the 22 patients with cTa. Of the 9 node-positive patients (33.3%), 3 had LNM proximal to the aortic bifurcation. No skip metastases were found. After RC, 27 patients (23.7%) were upstaged to muscle invasive disease; of whom 16.7% had cT1, 2.6% had cTa, and 4.4% had cTis-only. Of the remaining 87 patients with pathologic NMIBC, 1 patient (1.1%) had LNM, limited to the true pelvis. Five-year RFS was 82.3%, 81.5%, and 62.0% in patients with pathologic NMIBC, clinical NMIBC, and pathologic muscle invasive bladder cancer, respectively.

**Conclusions:** Routine LND is important in patients with cT1 and cTis-only bladder cancer, but may have limited value in patients with cTa. LNM beyond the boundaries of a standard LND occurred in up to one-third of node-positive patients. In the absence of skip metastases, however, performing a standard LND would correctly identify all node-positive patients. Whether removal of LNM proximal to the common iliac vessels provides a survival benefit remains to be evaluated in future prospective studies. 

*Keywords:* Bladder neoplasms; Radical cystectomy; Lymphadenectomy

## 1. Introduction

Most patients who present with urothelial cancer (UC) of the urinary bladder have non–muscle invasive bladder cancer (NMIBC; Ta, Tis-only, and T1). Despite intravesical treatment, patients with NMIBC are at risk of progression to muscle-invasive bladder cancer (MIBC). The risk of progression varies from less than 5% in low-risk patients up to 40% to 50% in high-risk patients with NMIBC [1]. There is accumulating evidence that patients with progression from NMIBC to MIBC have a worse prognosis when compared with patients who had MIBC at the initial presentation [2]. Hence, there is an increasing trend toward performing early radical cystectomy (RC) in NMIBC patients with a high risk of progression and/or patients who have persistent disease despite intravesical therapy.

It is estimated that 6% to 15% of patients who undergo RC for clinical NMIBC (cNMIBC) harbor lymph node metastases (LNMs) [3–5]. Although performing

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lymph node dissection (LND) in patients with cNMIBC may be beneficial, LND is often not performed, even in patients with MIBC [6]. In addition, it is unknown whether the template of LND in patients with cNMIBC should be similar to clinical MIBC, as lymph node (LN) mapping data are lacking. A recent study, however, suggested that with increasing clinical stage, more LNs should be removed, with a minimum of 6 LNs for cTa-cTis disease and a minimum of 25 LNs in patients with ≥cT2 disease [7]. One caveat to the conclusion of the study is that the number of retrieved LNs cannot be translated into a reproducible surgical template as the total number of LNs is influenced by several factors [8,9]. In addition, a recent study suggested the thoroughness of LND to be of more importance than the number of removed LNs [10]. Thus, defining the optimal template of LND would serve the urologist as a better guideline.

In this study, we aimed to investigate the incidence and distribution of LNM in patients undergoing RC and LND for cNMIBC. In addition, we report survival outcomes for this cohort using a standardized 'superextended' LND to the level of the inferior mesenteric artery takeoff.

## 2. Patients and methods

### 2.1. Cohort selection

A total of 637 patients underwent RC with intent-to-cure for UC of the bladder between May 2002 and December 2008. Included patients met all of the following criteria: (a) clinical stage Ta, Tis-only, or T1 prior to RC, (b) muscle presence at diagnostic transurethral resection of bladder tumor (TURBT) in clinical T1 patients, (c) no prior diagnosis of MIBC, (d) no neoadjuvant chemotherapy or radiotherapy, and (e) lymphatic tissue sample submitted from all 13 predesignated locations. A total of 114 patients were included in this study. Patients either had high risk of progression (i.e., high-grade tumor and/or concomitant Tis and/or lymphovascular invasion (LVI) at TURBT) or had recurrent/persistent disease despite intravesical therapy. All patients underwent 'superextended' LND including the following boundaries: the inferior mesenteric artery takeoff proximally, the genitofemoral nerves laterally, the circumflex iliac vein and LN of Cloquet distally, the internal iliac vessels posteriorly, including the obturator fossa and presciatic (fossa Marcille) LNs, and the presacral LNs overlying the sacral promontory. LNs were submitted in 13 predesignated anatomically defined packets and, for analytical purposes, divided in 3 levels as described previously and shown in Fig. 1 [10,13].

### 2.2. Clinical and pathologic staging

Preoperative clinical staging was based on tumor stage at TURBT specimen and results of cross-sectional imaging and physical examination. Pathology specimens were routinely reviewed centrally at our institution. Multiple sections and histologic evaluation were performed on the primary bladder tumor, bladder wall, and all LNs. LNs were identified visually and by palpation without clearing techniques, solvents, or special stains. Pathologic tumor staging and grading were standardized to the 2010 TNM classification of the American Joint Committee on Cancer and 1973 World Health Organization recommendations, respectively [11,12].

## 3. Data management and statistical analysis

Data were prospectively collected by a dedicated data entry team, double-checked by an experienced database

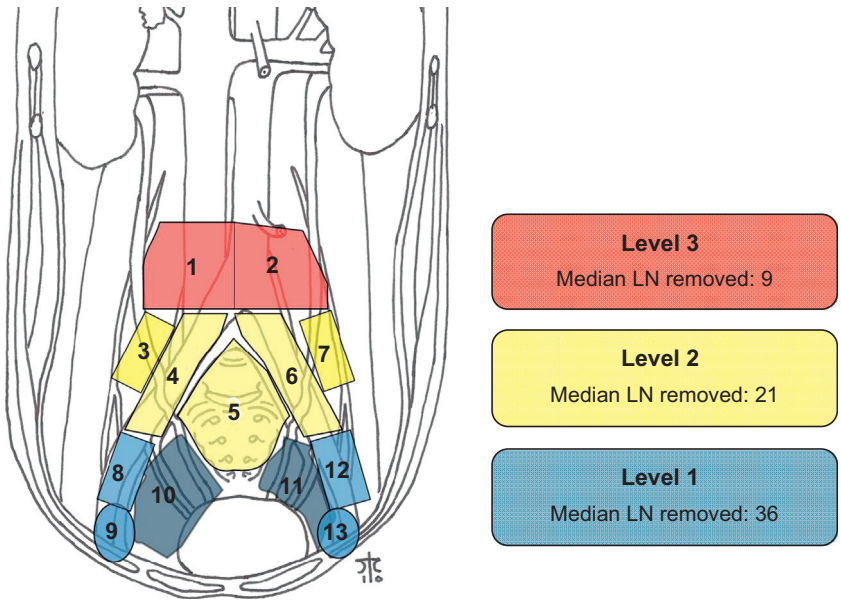


Fig. 1. Anatomical boundaries of lymph node packets and corresponding level of lymph node dissection.