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Original article

Pattern of node metastases in patients treated with radical cystectomy and extended or superextended pelvic lymph node dissection due to bladder cancer

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Abstract

Background: Pelvic lymph node dissection (PLND) has a diagnostic and therapeutic role during radical cystectomy in bladder cancer patients. However, at the time, no prospective data supports the value of extended PLND in improving survival expectances. We sought to describe incidence and location of node metastases in patients treated with extended and superextended PLND.

Methods: We evaluated 653 contemporary patients with clinically nonmetastatic high risk nonmuscle invasive or muscle-invasive bladder cancer treated with radical cystectomy and extended or superextended PLND without neoadjuvant chemotherapy at a single tertiary referral center between 1990 and 2013. Limited PLND is defined as the removal of obturator and internal iliac nodes. Standard included also the external iliac nodes. Extended includes also common and presacral nodes. Finally, superextended PLND includes all the nodes removed along the inferior mesenteric artery. We evaluated incidence of pathologically node metastases. Logistic regression analyses evaluate preoperative and pathologic characteristics to the risk of harboring node metastases in the extended and superextended template.

Results: Overall, 191 (29.3%) patients were found with pathologically node confirmed metastases. Of these, 56 (29.3%) patients were found with a single node metastasis, while 135 (70.7%) had multiple node metastases. The vast majority of patients were found with node metastases standard template (n = 172, 26.3%), on the other hand 30 (4.6%) and 21 (3.2%) patients had node metastases in extended and superextended templates, respectively. However, of these only 2 patients were found without concomitant lymph node metastases in the limited or standard templates. On multivariable analyses, cN+ status (odds ratio = 4.40, P < 0.001) and cT3-4 vs. cT1-2 (odds ratio = 2.25, P < 0.001) were associated with an increased risk of harboring node metastases in the extended or superextended template.

Conclusions: We found that the majority of patients harbored node disease in the limited or standard node dissection pattern. On the other hand, only a minority of patient were found with a disease in extended or superextended template without harboring a concomitant node disease in the limited pattern. © 2018 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Radical cystectomy; Node metastases; PLND; ePLND

1. Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the standard treatment for muscleinvasive and high risk recurrent nonmuscle invasive bladder cancer (BCa) [1]. PLND is a fundamental part of the procedure as it has been estimated that 18.0% to 30.4% [2] of patients harbor node metastases during RC. Retrospective series support the role of extended PLND in improving survival in both node positive and node negative BCa patients [3,4]. On the other hand, available prospective evidences [5] failed to prove any survival benefit of extended PLND when compared to limited PLND but

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showed on a post-hoc analyses a survival benefit limited for patients who harbored an organ confined disease.

The primary lymphatic landing site of metastasis various greatly with BCa, and a limited PLND (including external iliac vessels and the obturator fossa) may only identify 50% of primary lymphatic metastatic sites [6]. However, large series validating these findings are still required. Understanding incidence and patterns of node metastases in patients treated with RC and extended or superextended PLND would be pivotal to assess the necessity of extend PLND. To address these needs, we are presenting here a large single center experience of patients treated with RC and extended PLND regardless of preoperative characteristics. Aim of the study is to describe incidence and location of node metastases in patients treated with extended and extended PLND.

2. Materials and methods

This was an institutional review board approved study (bladder/2012). A prospectively maintained institutional RC registry was queried for clinically nonmetastatic clinical node negative and positive urothelial BCa between 1990 and 2013. A retrospective chart review was conducted on the final cohort to ensure the location of node metastases. All patients who received Neoadjuvant chemotherapy (NAC) (n = 58) had incomplete data (n = 85) or were without proper informed consent (n = 29) were excluded. Patients were staged preoperatively with pelvic/ abdominal computerized tomography, bone scan when indicated and chest x-ray. Clinical N status was defined as pelvic nodes > 8 mm and abdominal nodes > 10 mm in maximum short-axis diameter, as detected by computer tomography or magnetic resonance imaging within 3 months prior RC [7]. Lymph nodes were removed and evaluated separately and subsequently processed by a dedicated experienced uro-pathologist. Briefly, fat tissue containing lymph nodes were fixed in 10% buffered formalin. The macroscopic specimen assessment was based on tactile and visual criteria. Large nodes (>2 cm) were sampled in multiple blocks. If no lymph nodes were macroscopically detected, all fat tissue was processed. All blocks were embedded in paraffin, cut at 3 µm, and stained with hematoxylin-eosin. Pathologic data included tumor grade (according to 1998 WHO/ISUP consensus classification), tumor and nodal stage (according to VI edition TNM classification) [8], lymphovascular invasion (LVI) [9], carcinoma in situ, and soft tissue surgical margin status [10].

All patients included in the study underwent open RC with extended or superextended PLND. Standard PLND is defined as the removal of obturator, internal and external iliac nodes. Extended includes also common and presacral

nodes. Finally, superextended PLND includes all the nodes removed within inferior mesenteric artery.

3. Primary and secondary end points

The primary end-point was to describe incidence and location of node metastases after RC and extended/super-extended PLND. The secondary end-point was to evaluate predictors of the presence of node metastases in the extended and superextended pattern.

4. Statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and interquartile ranges were reported for continuously coded variables. The Mann-Whitney test and chi-square test were used to compare the statistical significance of differences in medians and proportions, respectively. Univariable and multivariable logistic regression analyses tested the impact of preoperative and pathologic features in predicting the possibility to harbor node metastases on extended or superextended PLND pattern. Statistical significance was considered at P < 0.05. Statistical analyses were performed using SPSS v.22.0 (IBM Corp., Armonk, NY) and STATA 13 (Stata Corp., College Station, TX).

5. Results

5.1. Baseline characteristics

Patients' characteristics of the cohort are depicted in Table 1. Of the 653 individuals included in the study, 191 (29.2%) harbored node metastases at RC. The median number of nodes removed was 20. Considering separately the standard, extended, and superextended areas, the median number of nodes removed were 16, 4, and 3, respectively. Patients who harbored node metastases had more lymph nodes removed (median: 26 vs. 20, P < 0.001), worse pathologic T stage (pT2–4: 82.7% vs. 68.9%, P < 0.001), had a higher positive soft tissue surgical margin rate (11.0% vs. 2.4%, P < 0.001), higher LVI (47.1% vs. 15.2%, P < 0.001), and are more prone to be treated with adjuvant chemotherapy (52.3% vs. 29.1%) than their counterparts who did not harbored node positive disease.

5.2. Description of incidence and location of node metastases

Fig. 1 depicts incidence of node metastases in standard, extended, and superextended lymphadenectomy area. Overall, 172 (26.3%), 30 (4.6%), and 21 (3.2%) patients harbored node metastases in the standard, extended, and superextended

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