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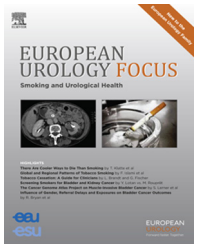

Bladder Cancer

Clinical Lymphadenopathy in Urothelial Cancer: A Transatlantic Collaboration on Performance of Cross-sectional Imaging and Oncologic Outcomes in Patients Treated with Radical Cystectomy Without Neoadjuvant Chemotherapy

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Abstract

Background: Data regarding clinical node metastases (cN+) in patients undergoing radical cystectomy (RC) are scarce.
Objective: To evaluate the performance of conventional imaging in detecting cN+ and analyze the impact of cN+ on survival among patients treated with RC without neoadjuvant chemotherapy (NAC).
Design, setting, and participants: Data from three independent centers of consecutive patients with bladder cancer treated with RC without NAC were analyzed.
Outcome measurements and statistical analysis: cN+ was defined as pelvic nodes >8 mm or abdominal nodes >10 mm in maximum short-axis diameter as detected via preoperative computed tomography or magnetic resonance imaging. Performance characteristics were evaluated considering pN+ disease as the reference standard. Multivariable Cox regression analyses were performed for prediction of survival.
Results and limitations: Overall, 196 patients (7.1%) had cN+ disease before RC and pN+ status was confirmed for 122 of them (62.2%). cN+ status in the overall population had sensitivity of 18% and specificity of 96% with a calculated area under the curve of 57%. The median follow-up was 108 mo. On multivariable analyses, cN+pN+ (hazard ratio [HR] 1.84, 95% confidence interval [CI] 1.26–2.68) and cN−pN+ (HR 2.36, 95% CI 1.90–2.92) were predictors of CSM (both $p < 0.001$). Conversely, cN+pN− status was not associated with worse survival outcomes ($p > 0.2$).
Conclusions: Our study confirms the poor accuracy of conventional preoperative imaging in assessing nodal disease status. cN status had no independent impact on survival when all confounders were evaluated, and potentially curative treatments should not be withheld on the basis of clinical nodal status alone.
Patient summary: The accuracy of conventional imaging techniques for detection of pathologic lymph node–positive disease before radical cystectomy for bladder cancer is suboptimal. The presence of clinical lymph node positivity on preoperative imaging is not an independent predictor of oncologic outcomes, and if the node invasion is not confirmed at radical cystectomy, these patients may have good long-term outcomes.
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1. Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is considered the standard of care for high-risk non–muscle-invasive bladder cancer unresponsive to intravesical therapies, and for muscle-invasive bladder cancer [1]; however, life expectancy even after RC is only 58% at 5 yr [2,3]. It has been found that lymph node metastases are the pathologic features with a greater impact on mortality after RC [2,4,5].

PLND is considered the most reliable procedure for assessing the presence of nodal invasion [6], and it has been shown that extended PLND is related to survival outcome in patients with and without pathologic nodal metastasis (pN+) [7–11]. Previous studies reported a limited ability of computed tomography (CT) and magnetic resonance imaging (MRI) in predicting pN+ disease; this limitation is mainly because of an inability to localize small-volume, micrometastatic nodal disease [12–14]. However, these reports are based on small historical cohorts. The presence of clinical lymph node metastasis (cN+), in fact, can be relevant for subsequent oncologic and surgical management. Notwithstanding, at present no study has directly assessed the impact of cN+ on survival outcome. Promising results have been reported by Zargar-Shoshtari et al [15], who described a survival benefit for selected patients treated with neoadjuvant chemotherapy (NAC) followed by consolidation RC for cN1–3 bladder cancer.

The purpose of the present study was to assess the performance characteristics of conventional preoperative imaging in finding pN+ disease, and to assess the impact of cN+ disease on survival among patients treated with RC without NAC.

2. Patients and methods

After institutional review board approval in each center, 3713 patients with cM0 urothelial bladder cancer who were treated with RC and PLND between 1980 and 2013 at three tertiary care centers (Mayo Clinic, Rochester, MN, USA; San Raffaele Hospital, Milan, Italy; University of Southern California, Los Angeles, CA, USA) were included in the study. Overall, 421 patients were excluded because they underwent NAC and 514 patients were excluded because fewer than ten nodes were removed during RC. The remaining 2778 patients were included in the final analysis. Patients were staged preoperatively using abdominopelvic CT, a bone scan (when indicated), and chest imaging (X-ray or CT). Several surgeons performed RC using a standard technique with PLND. Lymph nodes were removed and evaluated separately, and were subsequently processed at every center by experienced uropathologists. In brief, fat tissue containing lymph nodes were fixed in 10% buffered formalin. 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. Clinical N status was defined as pelvic nodes >8 mm and abdominal nodes >10 mm in maximum short-axis diameter, as detected by CT or MRI within 3 mo before RC [16,17]. Adjuvant treatments were decided by the treating physician on the basis of tumor characteristics and patient preferences. According to the initial agreement between the participating institutions, all patient and center identifiers were removed from the database. Thus, no center-specific results are reported.

2.1. Variable definition

All patients included had complete clinical and pathology data: age at surgery, gender, number of nodes removed, number of positive nodes, pathologic stage (pT0–2 vs pT3 vs pT4), carcinoma in situ, soft tissue surgical margin (STSM) status, lymphovascular invasion, lymph node invasion, grade, and adjuvant chemotherapy.

2.2. Statistical analyses

Descriptive statistics for categorical variables comprise the frequency and proportion. Mean, median, and interquartile range (IQR) are reported for continuous variables. We used χ^2 and Mann-Whitney tests to compare proportions and medians, respectively. Our statistical analyses consisted of several steps. First, the sensitivity and specificity of cN+ status were analyzed considering pN+ status as the reference. Sensitivity was defined as the number of true-positive cN+ results divided by the overall number of positive pN+ results at final pathology evaluation. Specificity was defined as the number of true-negative cN+ results divided by the overall number of true-negative pN+ results. We used the area under the curve (AUC) of the receiver operating characteristic (ROC) curve to quantify the discriminative ability of CT or MRI in prediction of pN+ disease at final pathology evaluation. Second, using multivariable Cox regression analyses, we assessed the value of clinical and pN+ status in predicting recurrence, cancer-specific mortality (CSM), and overall mortality (OM). Covariates included age, gender, cN stage, STSM status, pathologic stage, number of positive nodes, number of nodes removed, lymphovascular invasion, presence of concomitant carcinoma in situ, and adjuvant chemotherapy administration. Third, we used Kaplan-Meier curves to estimate cancer-specific survival (CSS), overall survival, and recurrence-free survival after stratifying patients according clinical and pathologic N status. Finally, Harrell's concordance statistic was calculated to evaluate the ability of cN status to predict recurrence, CSM, and OM. Statistical analyses were performed using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria) and SPSS v. 20.0 (IBM Corp., Armonk, NY, USA), and statistical significance was set at $p < 0.05$ with two-tailed tests.

3. Results

3.1. Baseline characteristics

Clinical and pathologic characteristics of our cohort stratified by cN+ status are reported in Table 1. Overall, 196 patients (7.1%) had cN+ status before RC. At final examination, pN+ status was found in 122 (62.2%) of the cN+ patients and 570 (22.1%) of the cN0 patients. In comparison to cN0, patients with cN+ were younger (median age 66 vs 67 yr; $p = 0.03$), had a higher probability of pN+ disease (mean pN+ 6.8 vs 1.3; $p < 0.001$), had higher rates of pT4 stage (27.6% vs 9.5%; $p < 0.001$), positive STSM (12.2% vs 1.2%; $p < 0.001$) and lymphovascular invasion (33.7% vs 21.4%; $p < 0.001$), and had a lower rate of carcinoma in situ (25.0% vs 43.5%; $p = 0.001$).

3.2. Performance characteristics in detection of nodal metastases

Table 2 shows performance characteristics for prediction of pN+ disease in the overall population and stratified for the number of lymph nodes removed. Overall, sensitivity, specificity, negative predictive value (NPV), positive

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