BJU Int 2024 doi:10.1111/bju.16440

BJUI
BJU International

Original Article

Assessing risk of lymph node invasion in complete responders to neoadjuvant chemotherapy for muscle-invasive bladder cancer

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Objectives

To investigate the lymph node invasion (LNI) rate in patients exhibiting complete pathological response (CR) to neoadjuvant chemotherapy (NAC) and to test the association of CR status with lower LNI and better survival outcomes.

Materials and Methods

We included patients with bladder cancer (BCa; cT2-4a; cN0; cM0) treated with NAC and radical cystectomy (RC) + pelvic lymph node dissection (PLND) at our institution between 2012 and 2022 (N = 157). CR (ypT0) and LNI (ypN+) were defined at final pathology. Univariable and multivariable logistic regression analysis was performed to test the association between CR and LNI after adjusting for number of lymph nodes removed (NLR). Kaplan–Meier and Cox regression analyses were used to assess overall survival (OS), metastasis-free survival (MFS) and disease free-survival (DFS) according to CR status.

Results

Overall CR and LNI rates were 40.1% and 19%, respectively. The median (interquartile range [IQR]) NLR was 26 (19–36). The LNI rate was lower in patients with CR vs those without CR (2 [3.2%] vs 61 [29.8%]; $P < 0.001$). After adjusting for NLR, CR reduced the LNI risk by 93% (odds ratio 0.07, 95% confidence interval [CI] 0.01–0.25; $P < 0.001$). Kaplan–Meier plots depicted better 5-year OS (69.7 vs 52.2%), MFS (68.3 vs 45.5%) and DFS (66.6 vs 43.5%) in patients with CR vs those without CR. After multivariable adjustments, CR independently reduced the risk of death (hazard ratio [HR] 0.44, 95% CI 0.24–0.81; $P = 0.008$), metastatic progression (HR 0.41, 95% CI 0.23–0.71; $P = 0.002$) and disease progression (HR 0.41, 95% CI 0.24–0.70; $P = 0.001$).

Conclusion

Based on these findings, we postulate that PLND could potentially be omitted in patients exhibiting CR after NAC, due to negligible risk of LNI. Prospective Phase II trials are needed to explore this challenging hypothesis.

Keywords

muscle-invasive bladder cancer, radical cystectomy, pelvic lymph node dissection, neoadjuvant chemotherapy, complete response

Introduction

Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) with extended pelvic lymph node dissection (PLND) represents the standard of care for muscle-invasive bladder cancer (MIBC) [1]. Specifically, cisplatin-based NAC chemotherapy has been shown to improve survival with a 5% benefit in terms of 5-year overall survival (OS) [1,2]. Notably, data from randomised controlled trials (RCTs) showed that patients experiencing complete response (CR), defined as the complete eradication of the tumour from the bladder after NAC, had 5-year OS of approximately 85% [2].

Based on the favourable survival outcomes observed in patients achieving CR, the urological community is questioning the need for an invasive, high-morbidity-associated surgical procedure such as RC with extended PLND and is considering the potential non-inferiority of bladder-sparing approaches, including active surveillance in terms of oncological outcomes [3,4].

While these approaches are still under investigation, RC remains the standard of care despite its high morbidity load [5]. In the attempt to reduce the impact of surgery, which can be viewed as an attempt to reduce RC toxicity, RCTs have supported the use of robot-assisted surgery [6,7], as well as restriction of the PLND template [8,9]. Specifically, Lerner et al. [9] demonstrated the non-inferiority of standard vs extended PLND in terms of recurrence-free survival while reporting lower complications in the experimental arm.

Considering the excellent oncological outcomes in MIBC patients achieving CR after NAC, and with increasing evidence suggesting that the optimal lymph node template is still to be determined, we postulated that a pathological CR could serve as a strong predictor of pN0 disease at the final pathology. This perspective, pending the results of ongoing trials evaluating bladder-sparing management in MIBC, could fuel the debate on the necessity of PLND in patients who are fully responsive after NAC. Before running a Phase II trial testing a similar hypothesis, we evaluated lymph node invasion (LNI) at RC in patients exhibiting CR after NAC to assess the real need for PLND in this scenario. We hypothesised that LNI rate was negligible among patients with CR and that CR was associated with reduced risk of LNI and survival advantages.

Material and Methods

Study Design, Setting and Participants

This retrospective cohort study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (File S1). Within our prospectively maintained database, we identified patients with a diagnosis of cT2-4acN0cM0 bladder cancer (BCa) treated with NAC followed by RC and extended PLND at the IFO Regina Elena National Cancer Institute, Rome, Italy between January 2012 and December 2022. Patients with unretrievable data or who received preoperative radiation therapy or non-platinum-based NAC were excluded. The research was conducted according to the declaration of Helsinki ethical guidelines.

Procedure-Specific Features and Follow-Up

In this study, all patients selected for inclusion underwent transurethral resection of bladder tumour (TURBT) confirming the diagnosis of MIBC. Thereafter, a whole-body CT scan was performed for initial staging. Patients were then referred to a urology-dedicated oncologist for cisplatin-based NAC. After the completion of NAC, RC was performed with an open or robot-assisted approach by two highly experienced surgeons who had previously performed more than 50 cases; the choice of urinary diversion was chosen based on patient age and life expectancy, respecting the patient's preference after adequate preoperative discussion. An extended PLND was consistently performed, defined as the removal of lymph nodes within the anatomical boundaries set by the aortic bifurcation and common iliac vessels proximally, the genitofemoral nerve laterally, the circumflex iliac vein distally, and the internal iliac vessels posteriorly [10]. Patient follow-up was conducted in compliance with institutional protocols, which were in alignment with the national guidelines prevailing at that time, with the treating physician's discretion applied as necessary.

Variables

The following baseline characteristics were recorded: age, sex, Charlson Comorbidity Index (CCI) [11], previous intravesical BCG administration, chemotherapy protocol and number of cycles administered. The following peri-operative variables were considered: surgical approach, type of urinary diversion, length of hospital stay, and complications according to the Clavien–Dindo classification system [12]. The pathological characteristics considered were T stage, N stage, number of lymph nodes removed (NLR), lymph node density, and surgical margin status. Additionally, we defined CR as the absence of residual tumour at final pathological report (ypT0). The American Joint Committee on Cancer 7th edition was used for stage assessment [13].

Endpoint

The primary endpoint was the presence of LNI, defined as the detection of tumour cells in one or more lymph nodes, detectable even at a microscopic level. Specimens were evaluated according to our institution's standard protocol. Lymph nodes were processed using a standard method that included the dissection of nodes away from the adipose tissue under bright light. No fat-clearing solutions were used. All identified nodes were sectioned and pathologically evaluated.

The secondary endpoints included: OS, defined as the time from initiation of radical treatment to death from any cause; disease-free survival (DFS), measured from the date of surgery to the first evidence of recorded clinical recurrence – either local/regional or distant metastases, confirmed by imaging or histological analysis – or death from any cause; and metastasis-free survival (MFS), defined in the same way as DFS but not including local/regional recurrence such as metastasis to pelvic lymph nodes. DFS and MFS were censored at the date of the last follow-up.

Statistical Analysis

Continuous variables were reported as median and interquartile range (IQR), while categorical variables were reported as absolute numbers and percentages.

Initially, univariable and multivariable logistic regression analysis were conducted to investigate the association between CR and LNI, after adjusting for NLR (continuous variable). Indeed, although an extended PLND template was employed, the NLR – as assessed by the pathologist – was considered a potential confounder in the detection of LNI [14]. Kaplan–Meier plots were created to depict OS, DFS and MFS according to CR status. A Cox regression model was then applied to assess the association between CR and the following survival outcomes: (1) death from any cause (n = 53); (2) distant metastatic progression or death from any cause (n = 60); (3) recurrence or death from any cause (n = 63) after adjusting for lymph node density and CCI (continuous variables). All tests were two-sided with a level of significance set at $P < 0.05$ and the R software environment for statistical computing and graphics (v.3.4.3) was used for all analyses.

Results

Baseline Characteristics

Overall, 157 patients were included in our analysis: 120 men and 37 women, with a median (IQR) age of 63 (58–68) years and a median (IQR) CCI score of 4 (3–4). The 157 patients received platinum-based NAC with a median (IQR) of 3 (3–4) cycles. Data regarding the preoperative characteristics of patients are summarised in Table 1. Specifically, 71 vs 86 patients underwent an open vs a robot-assisted approach, with most patients receiving an orthotopic neobladder (70.1%). Extended PLND was performed in all patients, with a median (IQR) NLR of 26 (19–36).

Lymph Node Invasion Rates According to Complete Response Status

Overall, CR and LNI were observed in 63 (40.1%) and 30 patients (19.1%), respectively. Patients with CR had significantly lower LNI rates than their counterparts (3.2% [2/63] vs 29.8% [28/94]; $P < 0.001$). After adjusting for NLR, CR reduced the risk of LNI by 93% (odds ratio 0.07, 95% CI 0.01–0.25; $P < 0.001$).

Overall, Disease-free and Metastasis-free Survival According to Complete Response Status

For the entire study cohort, the median follow-up was 48 (95% CI 20–66) months. On Kaplan–Meier analysis, patients with CR were found to have better 5-year OS (69.7% [95% CI 57.1%–85.0%] vs 52.2% [95% CI 41.5%–65.6%]; $P = 0.008$), 5-year MFS (68.3% [95% CI 83.8%–55.6%] vs 45.5% [95% CI 58.5%–35.4%]; $P = 0.001$) and 5-year DFS (66.6% [95% CI 54.0%–82.2%] vs 43.5% [95% CI 56.3%–33.6%]; $P < 0.001$) than their counterparts (Fig. 1). After multivariable adjustments for lymph node density and CCI, CR independently reduced the risk of death from any cause (hazard ratio [HR] 0.44, 95% CI 0.24–0.81; $P = 0.008$), metastatic progression or death from any cause (HR 0.41, 95% CI 0.23–0.71; $P = 0.002$) and disease progression or death from any cause (HR 0.41, 95% CI 0.24–0.70, $P = 0.001$).

Discussion

In the present study, pathological CR emerged as a strong negative predictor of lymph node positivity in patients undergoing RC with extended PLND.

Given the increased operating time and higher risk of peri-operative complications associated with PLND [9,15], and considering the low probability of LNI, patients who achieve a CR after NAC may face an unbalanced risk–benefit profile; the removal of clinically negative nodes could potentially constitute significant overtreatment.

Herein, we hypothesised that LNI rate was negligible among CR patients and that CR was associated with reduced risk of LNI and survival advantages.

In this study, we first examined the CR and LNI rates among patients treated with NAC; these were 40.1% and 19.1%, respectively. These outcomes align with results from RCTs [2], lending credibility to our observations despite the constraints of a small sample size and the study's single-centre design. A notable finding was the minimal percentage of LNI observed among CR patients (3.2%, n = 2), indicating that more than 95% of patients in whom ePLND was performed have potentially been overtreated. Although it may be argued that this rate was derived from a small single-centre series, similar proportions were observed when examining data from two large cohort studies [16,17]; specifically, Nassiri et al. reported an LNI rate of 4.9% (16/349) and van Hoogstraten et al. reported a rate of 4.6% (8/179).

Second, we examined the association between CR and LNI considering the NLR. This consideration is crucial, as the literature indicates a significant impact of lymph node count on the sensitivity of LNI detection, with a removal of 25 nodes achieving a 75% detection sensitivity [14]. In our study, the median NLR was 26, adhering to guidelines that recommend an extended dissection template. This methodology not only complies with best practice but also substantiates the validity of our findings on CR and LNI correlation.

Table 1 Baseline description of the overall cohort of cT2-4acN0cM0 bladder cancer patients treated with neoadjuvant chemotherapy prior to radical cystectomy plus pelvic lymph node dissection.

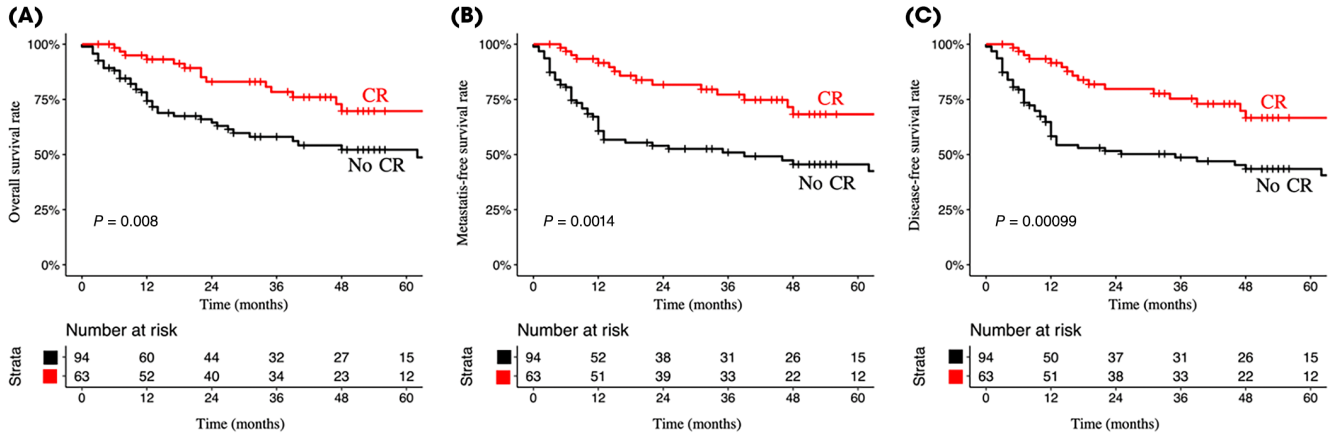
Characteristic	*N*	Overall, *N* = 157
Age, median (IQR), years	157	63 (58, 68)
Male, *n* (%)	157	120 (76.4)
Charlson Comorbidity Index, median (IQR)	157	4 (3, 4)
Previous BCG exposure, *n* (%)	157	14 (8.9)
Neoadjuvant chemotherapy, *n* (%)		
Gemcitabin and Cisplatin	157	135 (86.0)
MVAC		22 (14.0)
Number of cycles, median (IQR)	157	3 (3, 4)
Approach, *n* (%)		
Open	157	71 (45.2)
Robot-assisted		86 (54.8)
Urinary Diversion, *n* (%)		
Ureterocutaneus	157	14 (8.9)
Ileal conduit		33 (21.0)
Continent neobladder		110 (70.1)
Nodes removed, median (IQR)	157	26 (19, 36)
Length of hospital stay, median (IQR), days	157	7 (6, 10)
Overall 90-day complications, *n* (%)	157	82 (52.2)
ypT stage, *n* (%)		
T0	157	63 (40.1)
Ta/is/1		20 (12.8)
T2		24 (15.3)
T3		42 (26.7)
T4a		8 (5.1)
ypN stage, *n* (%)		
N0	157	127 (80.9)
N1		3 (1.9)
N2		22 (14.0)
N3		5 (3.2)
Lymph node density, mean (SD), %	157	4% (12)
Negative surgical margins, *n* (%)	157	157 (100)

IQR, interquartile range; MVAC, methotrexate, vinblastin, adriamycin and cisplatin.

Third, our analysis corroborated the survival benefit of CR, after multivariable adjustments, reflecting data from RCTs [2,18]. Interestingly, the favourable prognosis associated with CR also extends to patients foregoing RC. Indeed, retrospective studies investigating surveillance after TURBT plus NAC in patients with clinical CR, reported 5-year OS rates of 69% (N = 37) [3] and 86% (N = 148) [8], respectively. Recently, a Phase II trial conducted by Galsky et al. [4] reported a strong association between clinical CR and OS, with >90% of patients who had clinical CR after TURBT plus NAC (N = 33) being alive without metastasis at 2-year follow-up, despite the majority forgoing RC and opting for maintenance nivolumab (32/33). Similarly, the RETAIN trial reported a 2-year OS rate of 89% in patients with clinical CR after TURBT plus NAC who opted for active surveillance alone [3]. In summary, survival outcomes for these highly selected cohorts are promising, albeit preliminary, when compared to the standard of care (RC plus PLND).

To our knowledge, this study is among the first to critically evaluate the necessity of performing extended PLND in patients with CR after receiving NAC. Given the low incidence of LNI and the favourable prognosis in patients with CR, the value of PLND in this context warrants reconsideration. Particularly, the impact of PLND on survival outcomes has been under scrutiny for a long time [19]. More recently, in two randomised trials, it was observed that extension of the PLND template greatly affects the magnitude of overall complications without improving oncological outcomes in a general population of RC-treated BCa patients with an LNI prevalence between 22% and 28% [8,9]. In consequence, avoiding PLND, in patients with far lower LNI prevalence, as is the case for patients with CR (3%–5%), may have no statistically significant impact on survival outcomes. Conversely, we strongly believe in the fundamentally

Fig. 1 Kaplan–Meier plots depicting overall survival (**A**), metastasis-free survival (**B**) and disease-free survival (**C**) according to complete response (CR) at final pathology (ypT0 any yCpN). Log-rank test was performed.



important role of RC even when CR after NAC is achieved. Recent findings by Strandgaard et al. [20] have shown an association between field cancerisation—defined as the presence of mutated cellular clones within apparently normal tissues—and progression, immune response, and clinical outcomes in BCa. Therefore, despite no detectable residual disease and the achievement of CR, the extensive field cancerisation could potentiate the risk of tumour recurrence. Additionally, patients with clinical CR might harbour microscopic residual disease or carcinoma *in situ*, which is challenging to detect, as well as circulating tumour cells, which are not routinely screened for. The presence of field cancerisation, microscopic residual disease, carcinoma *in situ* and circulating tumour cells must therefore be carefully considered when contemplating the possibility of forgoing immediate cystectomy.

Robust data from the studies by Galsky et al. [4] and the RETAIN trial [3] revealed that within a median follow-up period of 2 years, 30% and 56% of patients with clinical CR who delayed cystectomy experienced metastatic progression or required salvage cystectomy. The discrepancy between these two outcomes may be attributable to the administration of adjuvant nivolumab in the study by Galsky et al. [4].

Taking the above findings and those of our study together, we believe that omitting PLND during RC in patients achieving CR after TURBT plus NAC may represent an effective strategy that should be tested in a prospective multicentre Phase II trial. There are several advantages to be gained from omitting PLND, such as reduction of operating time, prevention of ureter devascularisation and decreasing the risk of vascular injury and postoperative sequelae related to lymph node removal. Intra-operative frozen section may further improve the assessment of CR, thus guiding the ultimate choice of performing PLND intra-operatively while mitigating the difference in LNI rates associated with the pathological (3%–5%) vs clinical CR (12.7%) based on our study vs that of Kukreja et al. [21]. Additional tools, such as fluorodeoxyglucose positron emission tomography/CT [22], MRI and a standardised scoring system (i.e., Node-rads, Nac-Rads, Vi-rads) [23–25], biomarkers [26–28], artificial intelligence [29] and radiomics [30], may further improve the diagnostic accuracy of CR and LNI preoperatively, thus refining the selection of a target population with a high probability of CR and a negligible risk of LNI. Finally, even if bladder-sparing strategies demonstrate oncological efficacy, minimising the morbidity associated with RC would provide a valuable alternative for patients who struggle with the frequent monitoring and side effects of conservative therapies.

This study has some limitations. First, the monocentric retrospective design may represent a potential limitation. Nonetheless, the comparability of our results supports the reliability of our findings. Second, the non-univocal chemotherapeutic scheme may have influenced our results, with some schemes proven to be more effective than others in terms of survival benefit and CR. Third, our study is hypothesis generating with the aim of questioning clinical practice and preparing the foreground for further studies.

In conclusion, in this study we recorded a negligible LNI rate among patients with a diagnosis of MIBC who are fully responsive after NAC. Moreover, we corroborated the survival benefit of CR. Thus, we believe that the option for patients with a diagnosis of MIBC who are fully responsive after NAC not to undergo PLND should be explored through appropriately designed studies.

Acknowledgement

Open access funding provided by BIBLIOSAN.

Disclosure of Interests

None of the authors conducted the current research in the presence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This research received no external funding.

Authors Contributions

All authors contributed to the current study according to the ICJME guidelines.

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Abbreviations: BCa, bladder cancer; CCI, Charlson Comorbidity Index; CR, complete pathological response; DFS, disease-free survival; HR, hazard ratio; IQR, interquartile range; LNI, lymph node invasion; MFS, metastasis-free survival; NAC, neoadjuvant chemotherapy; NLR, number of lymph nodes removed; OS, overall survival; PLND, pelvic lymph node dissection; RC, radical cystectomy; RCT, randomised controlled trial; TURBT, transurethral resection of the bladder tumour.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. STROBE statement—checklist of items that should be included in reports of observational studies.

