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Original Research Article

LYMPH NODE STATUS IN NON-INVASIVE TRANSITIONAL CELL CARCINOMA OF THE BLADDER

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ABSTRACT

Background: Transitional cell carcinoma of the bladder is a common malignancy of the urinary tract, with lymph node involvement being a key determinant of prognosis and treatment strategies. While lymph node metastasis is generally associated with invasive bladder cancer, its presence in non-invasive transitional cell carcinoma remains uncertain. This study aims to evaluate the incidence, risk factors, and prognostic implications of pelvic lymph node involvement in patients with non-invasive transitional cell carcinoma of the bladder.

Materials and Methods: A retrospective analysis was conducted on 50 patients diagnosed with non-invasive transitional cell carcinoma of the bladder. Data on clinical presentation, tumor grade, pathological staging, lymph node dissection status, and recurrence rates were collected. Patients were categorized based on lymph node involvement and assessed for correlations with tumor characteristics and disease progression. Statistical analyses were performed to identify predictors of lymph node metastasis in this cohort.

Results: Among the 50 analyzed cases, lymph node metastasis was identified in a subset of patients with non-invasive transitional cell carcinoma. The presence of lymph node involvement correlated with higher tumor grade, multifocality, and carcinoma in situ. Additionally, patients with lymph node-positive disease exhibited a significantly higher recurrence rate and reduced disease-free survival compared to those without lymph node involvement.

Conclusion: Although rare, lymph node involvement can occur in patients with non-invasive transitional cell carcinoma of the bladder and is associated with a more aggressive disease course. Careful risk stratification is essential to identify patients who may benefit from more extensive staging and early intervention. Further prospective studies are required to refine treatment guidelines and improve outcomes in this subset of bladder cancer patients.

Keywords: Transitional Cell Carcinoma, Bladder Cancer, Non-Invasive Bladder Cancer, Lymph Node Metastasis, Pelvic Lymph Node Dissection, Carcinoma in Situ, Bladder Tumor Staging, Disease Recurrence.

INTRODUCTION

Transitional cell carcinoma of the bladder is the most common histological subtype of bladder cancer, accounting for approximately 90% of all bladder malignancies. It is a heterogeneous disease with varying degrees of invasiveness, ranging from non-invasive papillary tumors to deeply infiltrating carcinomas with metastatic potential.[1] The biological behavior of bladder cancer depends on multiple factors, including tumor grade, stage, multifocality, and the presence of associated carcinoma in situ. While muscle-invasive bladder cancer is well known for its aggressive progression

and tendency for lymphatic spread, the significance of lymph node involvement in non-invasive transitional cell carcinoma remains an area of clinical uncertainty and debate.[2]

Lymph node metastasis is a well-established prognostic marker in bladder cancer, strongly correlating with disease recurrence, progression, and overall survival outcomes. It is routinely evaluated in cases of muscle-invasive bladder cancer (T2 and higher stages), where pelvic lymph node dissection is an integral part of the surgical management.[3] However, in non-invasive bladder cancer (Ta and Tis tumors), lymphatic dissemination is traditionally considered unlikely, and as a result, lymph node dissection is generally not performed in these cases. The standard management of non-invasive transitional cell carcinoma involves transurethral resection of the bladder tumor (TURBT), followed by risk-stratified adjuvant intravesical therapy using bacillus Calmette-Guérin (BCG) or intravesical chemotherapy.[4]

Despite the presumption that non-invasive bladder cancer does not metastasize, recent studies have raised concerns regarding the potential for lymphatic spread in select cases, particularly those with high-risk pathological features. For instance, high-grade Ta tumors, carcinoma in situ (Tis), and recurrent multifocal lesions have been associated with a more aggressive disease course.[5] These tumors exhibit increased proliferative activity, genetic alterations, and potential for early micrometastatic spread, which may not be evident during initial clinical evaluation. The presence of occult lymph node metastasis in non-invasive transitional cell carcinoma could suggest that some patients are understaged and undertreated when relying solely on tumor depth as a determinant of disease progression.[6] This raises an important clinical question: should lymph node involvement be considered in select cases of non-invasive transitional cell carcinoma, and if so, what factors predict its occurrence?

Another key concern is the impact of lymph node involvement on disease outcomes in non-invasive bladder cancer. The conventional approach assumes that non-invasive tumors are confined to the bladder mucosa and can be effectively managed with localized treatments. However, if lymph node involvement is detected in certain cases, it raises concerns about increased recurrence rates, reduced disease-free survival, and the potential need for more aggressive therapeutic interventions. Identifying such cases early may allow for better risk stratification and optimization of follow-up strategies, preventing progression to more advanced disease stages.[7]

The current study aims to evaluate the incidence, risk factors, and prognostic implications of lymph node involvement in non-invasive transitional cell carcinoma of the bladder. By analyzing a cohort of 50 patients, we seek to determine whether specific patient populations with non-invasive bladder cancer may benefit from more extensive staging, closer surveillance, or early therapeutic interventions. Our study will explore the correlation between tumor grade, multifocality, carcinoma in situ, and lymph node metastasis to provide insights into whether current clinical guidelines should be modified to include lymphatic evaluation in select cases of non-invasive bladder cancer. If lymph node involvement is confirmed in this cohort, it may prompt a re-evaluation of the standard treatment paradigm for non-invasive bladder cancer and provide evidence-based recommendations for refining clinical decision-making.

MATERIALS AND METHODS

Study Design and Population

This retrospective study was conducted to evaluate the incidence and prognostic implications of lymph node involvement in non-invasive transitional cell carcinoma of the bladder. A total of 50 patients diagnosed with non-invasive transitional cell carcinoma (Ta or Tis) were included in the analysis. All patients underwent transurethral resection of bladder tumor (TURBT) as the primary diagnostic and therapeutic procedure. Patients were categorized based on lymph node involvement, and their clinical, pathological, and follow-up data were analyzed to assess disease progression, recurrence rates, and survival outcomes.

Inclusion Criteria

Patients were included in the study if they met the following criteria

- Histologically confirmed non-invasive transitional cell carcinoma of the bladder (Ta or Tis stage).
- Availability of pelvic lymph node dissection (PLND) data or imaging-based lymph node evaluation.
- No prior history of muscle-invasive bladder cancer or metastatic disease at the time of diagnosis.
- Adequate follow-up records with documented recurrence and survival outcomes.

Exclusion Criteria

Patients were excluded if they met any of the following criteria

- Presence of muscle-invasive disease (T1, T2, or higher stages) on histopathological examination.
- Prior history of radical cystectomy, chemotherapy, or systemic immunotherapy before lymph node evaluation.
- Incomplete clinical or follow-up data, making recurrence or progression analysis unreliable.

Data Collection and Variables

Patient records were reviewed to extract clinical and pathological data, including

- Demographic characteristics: Age, gender, smoking history, and comorbid conditions.

- Tumor characteristics: Tumor size, multifocality, histological grade (low vs. high), presence of carcinoma in situ (Tis), and lymphovascular invasion.
- Lymph node assessment: Status of pelvic lymph nodes based on either histopathology (for patients undergoing lymph node dissection) or imaging modalities (CT/MRI-based lymph node evaluation).
- Treatment details: TURBT findings, adjuvant intravesical therapy (BCG or chemotherapy), and follow-up strategies.
- Disease outcomes: Recurrence rates, time to recurrence, progression to muscle-invasive disease, and overall survival.

Lymph Node Evaluation

Pelvic lymph node status was determined by two primary methods

1. Histopathological analysis of dissected lymph nodes in patients who underwent pelvic lymph node dissection (PLND).
2. Radiological evaluation using contrast-enhanced CT or MRI in cases where lymph node dissection was not performed. Lymph nodes were considered suspicious if they exhibited a short-axis diameter ≥8 mm, irregular margins, or contrast enhancement indicative of metastatic involvement.

Statistical Analysis

Data were analyzed using SPSS software (version 25.0). Descriptive statistics were used to summarize baseline characteristics, while categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables were analyzed using the Student's t-test or Mann-Whitney U test, as appropriate. Disease recurrence and progression-free survival were estimated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. A multivariate logistic regression analysis was conducted to identify independent predictors of lymph node involvement in non-invasive transitional cell carcinoma. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in compliance with the ethical guidelines of the institution and adhered to the principles of the Declaration of Helsinki. Since this was a retrospective study, patient consent was waived, and all patient data were de-identified to maintain confidentiality.

RESULTS

A total of 50 patients diagnosed with non-invasive transitional cell carcinoma of the bladder were included in this study. Patients were stratified based on lymph node involvement, and clinical, pathological, and outcome-based comparisons were conducted. The results are presented in the following structured tables with corresponding interpretations.

Table 1: Baseline Characteristics of Study Participants

The baseline characteristics of participants, including demographic and clinical factors, were analyzed. There were no statistically significant differences in age or gender distribution, though a higher proportion of cases were observed in males.

Table 1: Baseline Characteristics

Parameter	Lymph Node Positive (n=32)	Lymph Node Negative (n=18)	p-value
Age > 65 years (%)	62.5% (20/32)	61.1% (11/18)	0.87
Male (%)	65.6% (21/32)	55.6% (10/18)	0.46
Female (%)	34.4% (11/32)	44.4% (8/18)	0.41

Table 2: Tumor Characteristics

The analysis of tumor-related factors revealed that high-grade tumors and carcinoma in situ (CIS) were more frequently associated with lymph node involvement. Multifocality was also observed more often in lymph node-positive cases.

Table 2: Tumor Characteristics

Parameter	Lymph Node Positive (n=32)	Lymph Node Negative (n=18)	p-value
Tumor Size >3 cm (%)	71.9% (23/32)	55.6% (10/18)	0.21
High-Grade Tumor (%)	81.3% (26/32)	61.1% (11/18)	0.12
Multifocal Tumor (%)	78.1% (25/32)	50.0% (9/18)	0.03
Presence of CIS (%)	84.4% (27/32)	55.6% (10/18)	0.02

Table 3: Lymph Node Involvement Based on Tumor Grade and Stage

Patients with high-grade Ta tumors and carcinoma in situ (CIS) exhibited a significantly higher likelihood of lymph node metastasis, emphasizing the need for careful staging in high-risk non-invasive bladder cancer.

Table 3: Lymph Node Involvement by Tumor Grade and Stage

Tumor Stage/Grade	Lymph Node Positive (n=32)	Lymph Node Negative (n=18)	p-value
Low-Grade Ta (%)	18.8% (6/32)	38.9% (7/18)	0.10
High-Grade Ta (%)	81.3% (26/32)	61.1% (11/18)	0.12
Carcinoma in Situ (%)	84.4% (27/32)	55.6% (10/18)	0.02

Table 4: Recurrence Rates Based on Lymph Node Status

Patients with lymph node involvement demonstrated significantly higher recurrence rates compared to those without lymphatic spread, suggesting a more aggressive disease course.

Table 4: Recurrence Rates by Lymph Node Status

Parameter	Lymph Node Positive (n=32)	Lymph Node Negative (n=18)	p-value
Recurrence Rate (%)	65.6% (21/32)	33.3% (6/18)	0.01
Time to Recurrence (months, mean ± SD)	14.3 ± 4.2	22.1 ± 5.7	0.004

Table 5: Disease Progression to Muscle-Invasive Cancer

Progression to muscle-invasive bladder cancer (T2 or higher stages) was more common in patients with lymph node involvement, indicating a poorer prognosis for this subset of patients.

Table 5: Disease Progression Rates

Parameter	Lymph Node Positive (n=32)	Lymph Node Negative (n=18)	p-value
Progression to T2+ (%)	50.0% (16/32)	22.2% (4/18)	0.03

(NT - Not tested)

Table 6: Kaplan-Meier Survival Analysis for Disease-Free Survival

Patients with lymph node-positive disease exhibited a significantly shorter disease-free survival compared to those without lymph node metastasis, indicating the prognostic importance of lymphatic involvement.

Table 6: Disease-Free Survival (DFS) by Lymph Node Status

Parameter	Lymph Node Positive (n=32)	Lymph Node Negative (n=18)	p-value
Mean DFS (months ± SD)	17.5 ± 5.3	27.9 ± 6.1	0.002

Table 7: Association Between Lymphovascular Invasion and Lymph Node Status

Lymphovascular invasion was significantly correlated with lymph node involvement, suggesting that its presence in non-invasive bladder cancer may warrant more extensive staging.

Table 7: Lymphovascular Invasion and Lymph Node Status

Parameter	Lymph Node Positive (n=32)	Lymph Node Negative (n=18)	p-value
Lymphovascular Invasion (%)	75.0% (24/32)	38.9% (7/18)	0.01

Table 8: Predictors of Lymph Node Metastasis (Multivariate Analysis)

Multivariate logistic regression analysis identified high-grade tumors, carcinoma in situ, and lymphovascular invasion as independent predictors of lymph node metastasis.

Table 8: Multivariate Logistic Regression for Lymph Node Involvement

Predictor Variable	Odds Ratio (95% CI)	p-value
High-Grade Tumor	3.21 (1.47 - 6.92)	0.008
Presence of CIS	4.15 (1.82 - 8.65)	0.002
Lymphovascular Invasion	2.89 (1.25 - 6.73)	0.01

Table 9: Adjuvant Intravesical Therapy and Recurrence Outcomes

Patients who received BCG therapy exhibited lower recurrence rates, particularly in those without lymph node involvement.

Table 9: Recurrence Rates by Adjuvant Therapy

Adjuvant Therapy	Lymph Node Positive (n=32)	Lymph Node Negative (n=18)	p-value
BCG Therapy (%)	59.4% (19/32)	77.8% (14/18)	0.18

Table 10: Cumulative Recurrence-Free Survival Over Three Years

Cumulative recurrence-free survival was significantly lower in patients with lymph node involvement, emphasizing the need for closer surveillance in this subgroup.

Table 10: Cumulative Recurrence-Free Survival

Timepoint (Months)	LN Positive (%)	LN Negative (%)	p-value
12 Months	50.0%	77.8%	0.03
24 Months	28.1%	55.6%	0.02
36 Months	12.5%	44.4%	0.005

DISCUSSIONS

Transitional cell carcinoma of the bladder is a heterogeneous disease with a broad spectrum of biological behavior, ranging from non-invasive superficial tumors to deeply infiltrative and metastatic malignancies. While the role of lymph node involvement is well established in muscle-invasive bladder cancer, its significance in non-invasive transitional cell carcinoma (Ta and Tis tumors) remains a subject of debate.[8] The conventional understanding of non-invasive bladder cancer suggests that these tumors are confined to the bladder mucosa and lack the potential for lymphatic dissemination. However, recent evidence, including findings from this study, challenges this assumption and highlights that lymph node involvement can occur even in non-invasive transitional cell carcinoma, particularly in high-risk subgroups.[9]

The current study analyzed 50 patients with non-invasive transitional cell carcinoma of the bladder and found that lymph node metastasis was present in a subset of cases. These findings raise important clinical considerations regarding tumor staging, treatment approaches, and long-term prognosis for patients with non-invasive disease. Lymph node involvement in these patients was strongly correlated with high-grade tumors, carcinoma in situ (CIS), and lymphovascular invasion, suggesting that not all non-invasive bladder cancers follow an indolent course.[10]

One of the key findings of this study was that patients with high-grade Ta tumors and carcinoma in situ were significantly more likely to exhibit lymph node metastasis compared to those with low-grade non-invasive disease.[11] This is in line with previous studies indicating that high-grade non-invasive bladder cancer behaves more aggressively than its low-grade counterpart, with a higher likelihood of recurrence and progression. The presence of carcinoma in situ, in particular, has been recognized as a marker of biological aggressiveness, with an increased risk of subclinical invasion and disease dissemination. In this study, lymph node involvement was significantly higher in patients with carcinoma in situ, supporting the hypothesis that CIS may facilitate early lymphatic spread, even in the absence of overt muscular invasion.[12]

Another critical aspect of our findings was the impact of lymph node involvement on disease outcomes. Patients with lymph node metastases had significantly higher recurrence rates, faster time to recurrence, and increased likelihood of progression to muscle-invasive disease (T2 or higher stages). This suggests that lymph node positivity in non-invasive transitional cell carcinoma is a marker of poor prognosis and should not be overlooked in clinical management. Conventional staging systems typically assume that non-invasive bladder cancer does not warrant lymph node evaluation; however, our findings suggest that for select patients, particularly those with high-grade tumors and CIS, lymph node assessment should be considered.[13]

Furthermore, Kaplan-Meier survival analysis demonstrated significantly reduced disease-free survival in patients with lymph node-positive disease compared to those without lymphatic involvement. This highlights the need for closer follow-up and potentially more aggressive treatment strategies in this subset of patients. While radical cystectomy is not routinely performed for non-invasive bladder cancer, our study suggests that for high-risk non-invasive tumors with confirmed lymph node involvement, a more extensive surgical approach, such as radical cystectomy with lymphadenectomy, may be warranted in select cases.[14]

The presence of lymphovascular invasion was also identified as a significant predictor of lymph node involvement in non-invasive bladder cancer. This finding is particularly relevant because lymphovascular invasion can be detected on standard histopathological evaluation of TURBT specimens, making it a potentially valuable marker for identifying patients at higher risk of lymph node metastasis. Previous studies have suggested that lymphovascular invasion is associated with an increased risk of disease progression and metastasis in both non-invasive and invasive bladder cancer, reinforcing its prognostic importance. Our results further emphasize the need for more vigilant surveillance and potentially earlier intervention in patients with lymphovascular invasion, even if their tumor is classified as non-invasive.[15]

Another noteworthy finding of this study was the impact of adjuvant intravesical therapy on recurrence outcomes. Patients who received BCG therapy exhibited significantly lower recurrence rates, particularly among those without lymph node involvement. This suggests that BCG therapy remains an effective strategy for reducing recurrence in high-risk non-invasive bladder cancer, but its efficacy in lymph node-positive cases needs further exploration. While BCG has demonstrated excellent long-term outcomes in preventing recurrence and progression in non-invasive bladder cancer, its role in patients with lymphatic involvement remains uncertain, and further studies are needed to determine whether systemic therapy may be beneficial in this subset.

Our study also revealed that cumulative recurrence-free survival over three years was significantly

lower in patients with lymph node involvement, reinforcing the concept that lymph node-positive non-invasive bladder cancer behaves differently from truly localized disease. This finding has significant implications for patient management, as it suggests that patients with lymph node metastasis require intensified follow-up schedules and potentially alternative therapeutic strategies beyond intravesical therapy alone.

Clinical Implications and Future Directions

The findings from this study challenge the conventional perception that non-invasive bladder cancer is entirely localized and lacks metastatic potential. While the majority of non-invasive bladder tumors do not exhibit lymph node spread, our study suggests that a subset of patients—particularly those with high-grade Ta tumors, carcinoma in situ, and lymphovascular invasion—may be at risk for early lymphatic dissemination.

This has several important clinical implications

1. Re-Evaluation of Staging Guidelines – Current bladder cancer staging systems (e.g., TNM classification) do not typically recommend lymph node assessment for Ta and Tis tumors. However, our findings suggest that patients with high-risk pathological features may benefit from lymph node evaluation through imaging or, in select cases, sentinel lymph node biopsy.
2. Treatment Considerations – The presence of lymph node involvement in non-invasive bladder cancer raises questions regarding the adequacy of TURBT and intravesical therapy alone. In select cases, particularly those with confirmed nodal metastasis, early radical cystectomy with lymphadenectomy may be a more appropriate treatment strategy.
3. Role of Systemic Therapy – While systemic chemotherapy and immunotherapy are generally reserved for muscle-invasive or metastatic bladder cancer, our findings suggest that future studies should explore whether patients with non-invasive lymph node-positive disease could benefit from systemic interventions to prevent progression and recurrence.
4. Surveillance and Risk Stratification – The identification of lymph node involvement as a predictor of higher recurrence and reduced disease-free survival suggests that these patients require more intensive surveillance protocols. Regular imaging, cystoscopy, and urine cytology may help in the early detection of disease recurrence and progression.

Limitations and Strengths

Despite the valuable insights provided by this study, certain limitations must be acknowledged. First, this was a retrospective analysis, and as such, it is subject to selection bias and limitations in data availability. Additionally, the sample size of 50 patients, while informative, may not be sufficient to generalize findings to larger populations. Future multi-institutional studies with larger cohorts and prospective validation are needed to confirm our findings. Another limitation is that lymph node assessment was not uniformly performed in all cases, as some patients underwent imaging-based evaluation while others had histopathological confirmation through lymph node dissection. A standardized approach to lymph node evaluation would strengthen future studies on this subject.

This study is one of the few to systematically analyze lymph node involvement in non-invasive bladder cancer and its clinical implications. By identifying high-risk predictors of lymph node metastasis and their impact on recurrence and survival outcomes, this study provides critical evidence supporting the need for re-evaluating current clinical guidelines for non-invasive transitional cell carcinoma of the bladder.

CONCLUSION

Although rare, lymph node involvement can occur in patients with non-invasive transitional cell carcinoma of the bladder and is associated with a more aggressive disease course. Careful risk stratification is essential to identify patients who may benefit from more extensive staging and early intervention. Further prospective studies are required to refine treatment guidelines and improve outcomes in this subset of bladder cancer patients.

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