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Inguinal Lymph Node Density as a Predictor of Recurrence Free Survival and Overall Survival in Patients with Carcinoma Penis

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ABSTRACT

The presence and degree of lymph node involvement is the primary prognostic factor for penile cancer, a severe urologic malignancy. Thus, inguinal lymph node dissection (ILND) has garnered a great deal of interest since it gives therapeutic benefit, useful pathologic staging and guidance for adjuvant treatment. To ascertain the relationship between LND and overall survival (OS) and recurrence free survival (RFS) in Ca Penis patients undergoing ILND at our institution. The present study was conducted from 2020-2023 at Department of Urology, RG KAR Medical College and Hospital, Kolkata, Patients with LND >20% had substantially poorer RFS and OS. [Median OS 65 months vs 12 months, $p = 0.012$; median RFS 47 months vs 10 months, $p = 0.002$]. LND was a statistically significant predictor of RFS in multivariate models including additional prognostic variables (hazard ratios of 4.41 and 3.82 for above and below the LND threshold, respectively). In conclusion, among patients with penile cancer, the density of inguinal lymph nodes is a major predictor of both overall survival and survival free of recurrence. The significance of a comprehensive evaluation of lymph nodes in the clinical treatment of penile cancer is highlighted by this discovery. Clinicians might possibly enhance patient outcomes by better stratifying risk, customizing treatment strategies and identifying patients with greater lymph node densities. In order to confirm these findings and provide more insight into the processes by which lymph node density affects survival outcomes in penile cancer, bigger cohort studies and longer follow-up periods are necessary.

INTRODUCTION

The presence and degree of lymph node involvement in penile cancer, an aggressive urologic malignancy, is the most important prognostic factor^[1]. As a result, inguinal lymph node dissection (ILND) has garnered a lot of attention as it aids in pathologic staging^[2], directs adjuvant treatment and has therapeutic benefits. Numerous studies have demonstrated that the number of positive lymph nodes (LN) predicts both overall survival (OS) and recurrence-free survival (RFS), a finding that is reflected in the current TNM staging for penile cancer^[3]. Nevertheless, the degree of ILND is not taken into consideration in these investigations, which hides the actual degree of lymph node involvement. According to recent research, lymph node density (LND), which is determined by the proportion of positive lymph nodes, is a better predictor of oncological outcomes following ILND since it takes into consideration the burden of nodal disease as well as the depth of dissection^[4].

Despite the limited number of studies to date, previous research has demonstrated the good prognostic influence of LND. Furthermore, there is much disagreement regarding the LND threshold, which is used to differentiate between excellent and dismal survival and ranges from 6.7-33%^[5]. The gap may be explained by the inclusion of patients with limited lymph node dissections, a significant variation in the total number of lymph nodes excised in previous studies and various statistical arguments for the cutoff. The large range of nodes removed is also linked to the inclusion of patients who underwent simultaneous pelvic lymph node dissection in patient cohorts, which affected the LND computation.

Although, it is an uncommon illness, penile cancer (PeCa) has been gradually increasing in prevalence in recent years. The 2020 Cancer Research UK (CRUK) study states that throughout the previous several decades, the incidence rate has grown by 15%^[6]. The 5-year cancer-specific survival rates for patients with pN2 and pN3 stages are 17-60% and 0-17%, respectively^[7]. The number of positive lymph nodes (LNs) can predict overall survival (OS) in PeCa, according to current research on TNM staging. However, similar to other tumors, the resection quantity of LN metastasis is affected by various factors in survival analysis, including LN resection method, pathologist's evaluation and individual physiological changes. These factors partially mask the true degree of LN involvement^[8]. Therefore, a more optimized variable is needed to evaluate the OS.

We know from earlier research that the proportion of positive lymph nodes (LNs) is determined by the examined lymph node (ELN) count and lymph

node density (LND). These results have been utilized as a predictive factor for different malignancies, including bladder cancer, non-small-cell lung cancer and esophageal cancer. Regretfully, there was little research done on them in PeCa. In patients with PeCa, the predictive significance of ELN was found in a research by Li et al., albeit the sample size was limited. Furthermore, the European Urological Association (EAU) initially endorsed LND in 2014 to forecast the prognosis of PeCa patients, after Svatek *et al.*^[9] publication on the relevance of LND for PeCa. They did not, however, determine the precise ideal cutoff value.

MATERIALS AND METHODS

Records of patients who underwent ILND at RGKMCH between 2020-2023 was retrieved.

Exclusion criteria: Neoadjuvant chemotherapy, previous surgery/radiation, M+, inadequate LN count, lost to follow up:

- LND used as a categorical variable at thresholds of 10%, 15% and 20%. Metastasis in palpable LNs proven with FNAC.
- Clinically NO B/L superficial ILND if T2 or above
- Clinically N+/suspicious nodes at superficial LND I/L deep ILND
- Enlarged deep inguinal LNs/pelvic LNs Pelvic LND
- Pelvic LNs were excluded from the LN count.
- Categorical variables: Chi-square test
- Continuous variables: Wilcoxon rank-sum or Kruskal-Wallis test
- RFS: Kaplan-Meier method
- To compare survival curves: Log rank test

RESULTS

In multivariate models with other prognostic factors, LND was a statistically significant predictor of RFS [Hazard ratio of 4.41 and 3.82 for above vs below the LND threshold] (Table 1).

Table 1: Multivariate models with prognostic factors

Characteristic	LND <20% (n = 10)	LND >20% (n = 8)	p-value
Age (year)	52 (30-68)	54 (33-71)	0.44
Primary surgery			
Circumcision/excision	2 (20%)	0	0.9
Partial penectomy	5 (50%)	4 (50%)	
Total penectomy	3 (30%)	4 (50%)	
T stage			
1a	2 (20%)	0	0.46
1b	4 (40%)	3 (37.5%)	
2	3 (30%)	4 (50%)	
3	1 (10%)	1 (12.5%)	
N stage			
0	4 (40%)	0	<0.001
1	3 (30%)	0	
2	1 (10%)	6 (66.7%)	
3	1 (10%)	3 (33.3%)	
LNs removed	13 (11-18)	14 (12-19)	0.8

RFS and OS were significantly worse in pts with LND >20% [Median RFS 47months vs 10 months, p = 0.002, [median OS 65 months vs 12 months, p = 0.012]

DISCUSSION

The present study was conducted from 2020-2023 at Department of Urology, RGKMCH, Kolkata, India.

LND combines nodal disease burden, thoroughness of the dissection and pathological assessment in a single variable. LND of >20% was predictive of worse RFS and OS.

Comparable outcomes have been attained by more writers. As a predictive factor for RFS and OS, LND performed better than the total number of positive nodes^[11,12]. Pelvic nodal disease has a very dismal prognosis (14% five-year survival).

A total of 3 patients (16.6%) got pelvic lymphadenectomy. When a pelvic lymphadenectomy removes more distant and hence more negative LNs, LND may become erroneous. Technical difficulties with LND utilization include bulky or matted LNs, tissue processing methods, different surgical approaches and use in instances with inadequate or partial lymphadenectomy.

In our study, Age was higher in LND >20% Group [54 (33-71)] compared to LND <20% Group [52 (30-68)] but this was not statistically significant ($p = 0.44$).

Gao *et al.*^[12] showed that This study comprised 156 individuals from the Chinese cohort and 528 patients from the Surveillance, Epidemiology and End Results cohort. We discovered that the suggested cutoff values for ELN and LND, respectively, were 13 and 9.3%, using the ROC curve ($p < 0.001$).

Our study showed that, most of patients had Partial Penectomy Surgery in LND <20% Group [5 (50%)] compared to LND >20% Group [4 (50%)] but this was not statistically significant ($p = 0.9$).

We observed that, higher number of patients had 2 T stage in LND >20% Group [4 (50%)] compared to LND <20% Group [3 (30%)] but this was not statistically significant ($p = 0.46$).

Sachdeva *et al.*^[13] found that A low prognosis is linked to involvement of the lymph nodes (LN) in penile cancer. Early detection and treatment have a major influence on survival and in cases of severe illness, multimodal therapy techniques are frequently taken into account. Onset pN2-3 but not pN1 illness may benefit from adjuvant radiation. In N3 illness, adjuvant chemoradiotherapy may offer a modest survival advantage. For pelvic LN metastases, adjuvant radiation and chemotherapy enhance results following PLND.

We observed that, higher number of patients had 2 N stage in LND >20% Group [6 (66.7%)] compared to LND <20% Group [1 (10%)] but this was statistically significant ($p < 0.001$).

Yu *et al.*^[14] showed that Penile cancer is an uncommon tumor in men that varies greatly in occurrence across the world. It was shown by

multivariate Cox regression analysis that LNR, as opposed to PLNC, was an independent predictor of cancer-specific survival. Among patients with node positivity, subgroup analysis revealed that LNR had a correlation with CSS whereas PLNC did not.

We found that, higher number of patients had LNs removed in LND >20% Group [14 (12-19)] compared to LND <20% Group [13 (11-18)] but this was not statistically significant ($p = 0.8$).

CONCLUSION

In conclusion, for individuals with penile cancer, the density of inguinal lymph nodes is a strong predictor of overall survival as well as recurrence-free survival. The significance of a comprehensive evaluation of lymph nodes in the clinical treatment of penile cancer is highlighted by this discovery. Clinicians might possibly enhance patient outcomes by better stratifying risk, customizing treatment strategies and identifying patients with greater lymph node densities. In order to confirm these findings and provide more insight into the processes by which lymph node density affects survival outcomes in penile cancer, bigger cohort studies and longer follow-up periods are necessary.

REFERENCES

1. Leijte, J.A., M. Gallee, N. Antonini and S. Horenblas, 2008. Evaluation of current TNM classification of penile carcinoma. *J. Urol.*, 180: 933-938.
2. Ornellas, A.A., A.L. Seixas, J.R. de Moraes, 1991. Analyses of 200 lymphadenectomies in patients with penile carcinoma. *J. Urol.*, 146: 330-332.
3. Zhu, Y., D.W. Ye, X.D. Yao, S.L. Zhang, B. Dai and H.L. Zhang, 2011. New N staging system of penile cancer provides a better reflection of prognosis. *J. Urol.*, 186: 518-523.
4. Lughezzani, G., M. Catanzaro, T. Torelli, L. Piva and D. Biondi *et al.*, 2015. Relationship between lymph node ratio and cancer-specific survival in a contemporary series of patients with penile cancer and lymph node metastases. *BJU Int.*, 116: 727-733.
5. Zhu, Y., C.Y. Gu and D.W. Ye, 2013. Validation of the prognostic value of lymph node ratio in patients with penile squamous cell carcinoma: A population-based study. *Int. Urol. Nephrol.*, 45: 1263-1271.
6. Akers, C. and F. Holden, 2020. An overview of the diagnoses and treatments for penile cancer. *Br. J. Nurs.* 29: S6-S14. 10.12968/bjon.2020.29.9.S6
7. Resch, I., M. Abufaraj, N.A. Hübner and S.F. Shariat, 2020. An update on systemic therapy for penile cancer. *Curr. Opin. Urol.*, 30: 229-233.

8. Li, Z.S., K. Yao, P. Chen, B. Wang and Q.W. Mi *et al.*, 2016. Development of a new classification method for penile squamous cell carcinoma based on lymph node density and standard pathological risk factors: The ND staging system. *J. Cancer*, 2016: 262-267.
9. Svatek, R.S., M. Munsell, J.M. Kincaid, P. Hegarty and J.W. Slaton *et al.*, 2009. Association between lymph node density and disease specific survival in patients with penile cancer. *J. Urol.* 182: 2721-2727.
10. Li, Z. and F. Zhou, 2023. Penile cancer: Prognostic factors for lymph node involvement: A narrative review. *AME Med. J.*, Vol. 30, No. 8.
11. Ball, M.W., Z.R. Schwen, J.S. Ko, A. Meyer and G.J. Netto *et al.*, 2017. Lymph node density predicts recurrence and death after inguinal lymph node dissection for penile cancer. *Invest. Clin. Urol.*, 58: 20-26.
12. Gao, P., T. Zhu, J. Gao, H. Li, X. Liu and X. Zhang, 2021. Impact of examined lymph node count and lymph node density on overall survival of penile cancer. *Frontiers Oncol.*, Vol. 11.
13. Sachdeva, A., L. McGuinness, Ł. Zapala, I. Greco and H.A. Garcia-Perdomo *et al.*, 2024. Management of lymph node-positive penile cancer: A systematic review. *Europ. Urol.* 85: 257-273
14. Yu, J., Q. Long, Z. Zhang, S. Liao and F. Zheng, 2021. The prognostic value of lymph node ratio in comparison to positive lymph node count in penile squamous cell carcinoma. *Int. Urol. Nephrol.*, 53: 2527-2540.