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Clinical-prostate cancer

Prognostic significance of histomorphologic features of lymph node metastases in prostate cancer patients treated with radical prostatectomy: A single center study

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Abstract

Objective: We assessed the prognostic value of histomorphologic features of lymph node (LN) metastases in patients with prostate cancer treated with radical prostatectomy

Materials and Methods: We evaluated the effect of the features of LN metastasis on the risk of biochemical recurrence (BCR) in 280 LN-positive patients who underwent radical prostatectomy between 2006 to 2018. LN specific parameters recorded included number of metastatic LNs, size of the largest metastatic focus, Gleason Grade (GG) of the metastatic focus, and extranodal extension (ENE).

Results: A solitary positive LN was found in 166/280 (59%), 95/280 (34%) patients had 2-4 positive LNs, and 19/280 (7%) had 5 or more positive LNs. The size of the largest metastatic focus > 2 mm (macrometastasis) in 154/261 (59%). GG of the metastatic focus was as follows: GG 1-2: 29/224 (13%); GG 3: 27/224 (12%); and GG 4-5: 168/224 (75%). ENE was identified in 99/244 (41%). We found the number of LNs positive (2-4 vs. 1 Hazard ratio (HR) = 1.60; 95% CI: 1.02 to 2.5; $P = 0.04$) and GG of the metastatic focus (GG 4&5 vs. 1-3 HR = 1.90; 95% CI: 1.14-3.2; $P = 0.014$) to be independent predictors of the risk of BCR after surgery on multivariate analysis.

Conclusions: Our study showed the number of LNs positive and GG of the LN metastatic focus to be significant independent predictors of BCR after radical prostatectomy. We recommend reporting histomorphologic parameters of LN metastasis as they may help in defining BCR risk categorization.

Keywords: Prostate; Neoplasms; Lymph nodes; Metastasis; Lymph node excision

1. Introduction

The prognosis of patients with prostate cancer showing lymph node (LN) metastasis at radical prostatectomy is variable [1,2]. Various easily recordable histomorphologic features, e.g., the number of positive LN, the size of metastatic focus, the presence of extranodal extension (ENE), and grade group (GG) of metastatic focus, identified within these positive LN might explain some of this variability in outcome. Moreover, in recent years, the adoption of the

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surgical extended pelvic LN dissection has resulted in an increase in the rate of detection of LN metastasis [3], including occult metastases [4], which otherwise would have gone undetected. Therefore, risk stratification by LN features has been proposed to improve the management of these patients and potentially spare those with favorable features the side effects of unnecessary adjuvant treatment [5].

Several prior studies [5-9] have shown variable association of these histomorphologic features with the outcome of cancer treatment, and the predictive value of these features has remained controversial. Hence the current version of American Joint Committee on Cancer system [10] does not currently take into account the number of these features and only substratifies the patients into LN negative (pN0) and LN positive (pN1). We aimed to determine the prognostic value of histomorphologic features of lymph node (LN) metastases in patients with prostate cancer treated with radical prostatectomy

2. Material and Methods

The Institutional Review Board approved this study at Henry Ford Hospital. We reviewed all node positive robot-assisted radical prostatectomy cases between 2006 and 2018. Cases with prior neoadjuvant therapy or cases with known metastasis at the time of surgery were excluded.

In every case, the prostate gland and the LN specimens were entirely submitted for microscopic evaluation. GG of the dominant tumor nodule, pathologic stage, margin status, and tumor volume were recorded. Clinical information about biochemical recurrence (BCR) was collected using serum prostate-specific antigen based on American Urological Association guidelines (biochemical recurrence defined as an initial PSA value = 0.2 ng/mL followed by a subsequent confirmatory PSA value = 0.2 ng/mL) [11].

2.1. LN recorded pathologic features

The number of positive LNs: For statistical analysis, we grouped the number of positive LNs into 3 categories: 1, 2-4, and 5 or more LN.

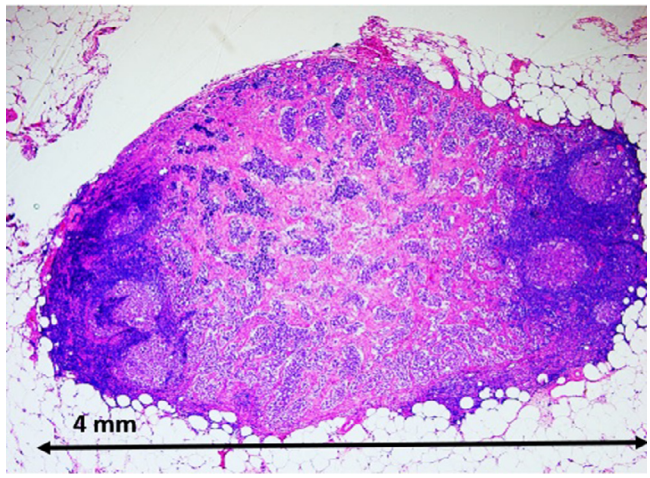

Fig. 1. Size of the entire positive lymph node was recorded (arrow). (Hematoxylin and eosin stain, 2X magnification).

The size of positive LN: This parameter refers to the overall size of the LN with the largest metastatic focus (Fig. 1).

The size of the largest metastatic focus: The size of the single largest metastatic focus was recorded in a linear, two-dimensional fashion. The presence of minute metastatic focus up to 2 mm was labeled as micrometastasis, similar to some of the other organ sites such as breast and endometrium, and > 2 mm metastasis was labeled as macrometastasis (Fig. 2).

The GG of metastatic focus: Although grading of prostate cancer is not recommended outside of prostate, we found a wide spectrum of grades in metastatic foci. Hence, we used GG to assess the differentiation of the metastasis, the same way it is currently used in prostatic cancer (Fig. 3).

Extranodal extension: Defined as unequivocal tumor perforation of the LN capsule into the surrounding pericapsular adipose tissue (Fig. 4).

2.2. Statistical analysis

The association between positive LN features and BCR was examined using Kaplan-Meier curves (log-rank test) and multivariate analysis using Cox proportional hazards model by R software.

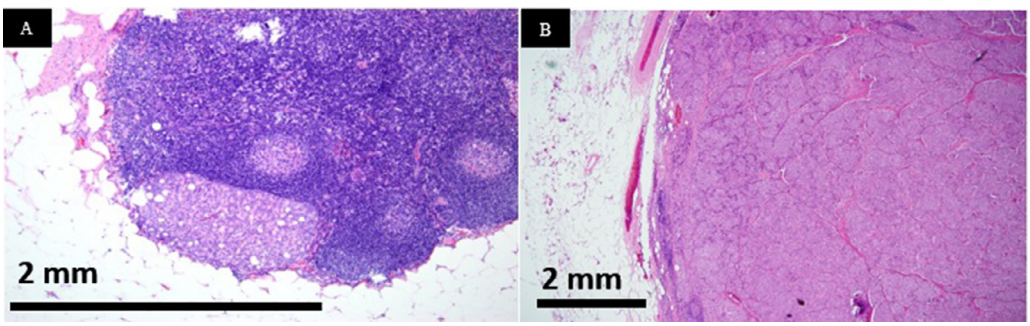

Fig. 2. Size of the largest metastatic focus. A. minute focus or micrometastasis (0.1-2 mm) and B. >2 mm metastasis or macrometastasis. (Hematoxylin and eosin stain).

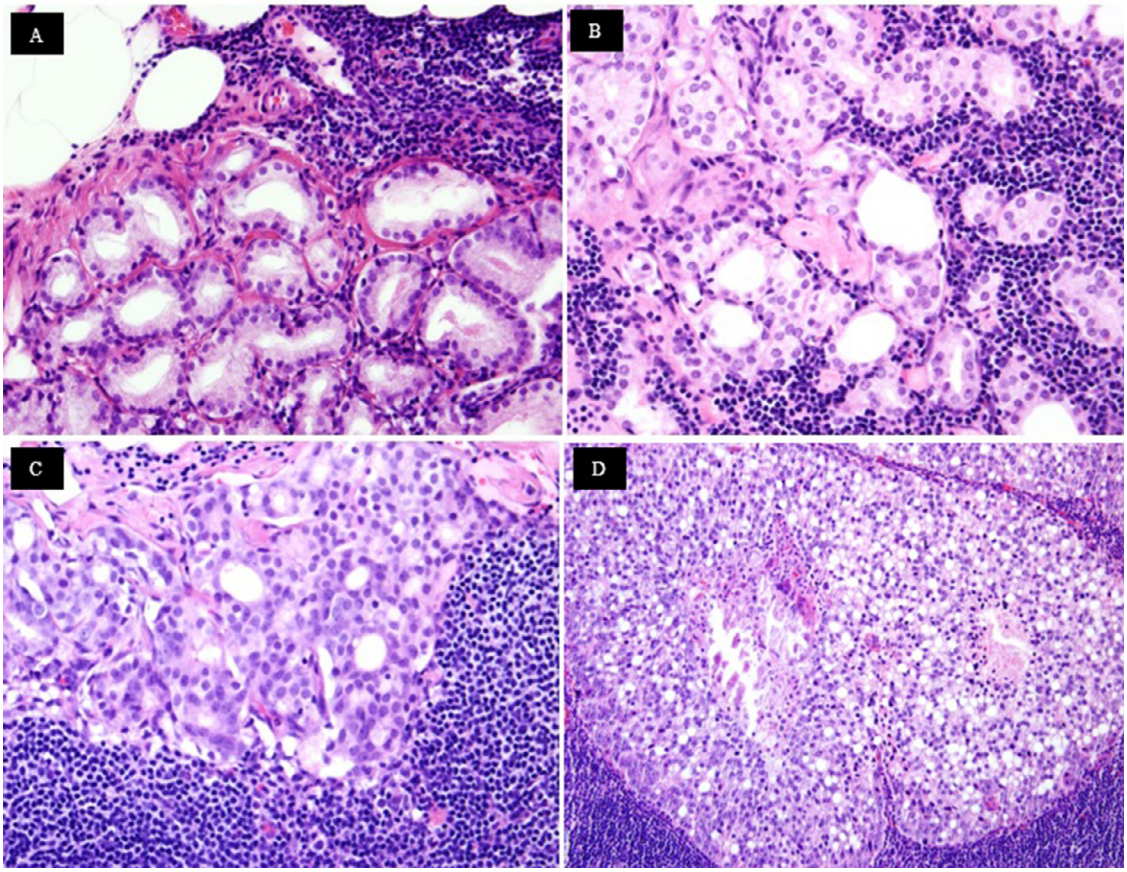

Fig. 3. Examples of different grade groups. A. Grade group 1, B. grade group 2, C. grade group 4, and D. grade group 5 (Hematoxylin and eosin stain A-C: 20X magnification, D: 4X magnification).

3. Results

We identified a total of 280 patients after excluding 18 cases with neoadjuvant therapy and 2 with LN metastases diagnosed before surgery. The median age was 64 years old (range 41-83). The pathologic findings collected from the prostate and the LN dissection are illustrated in Tables 1 and 2.

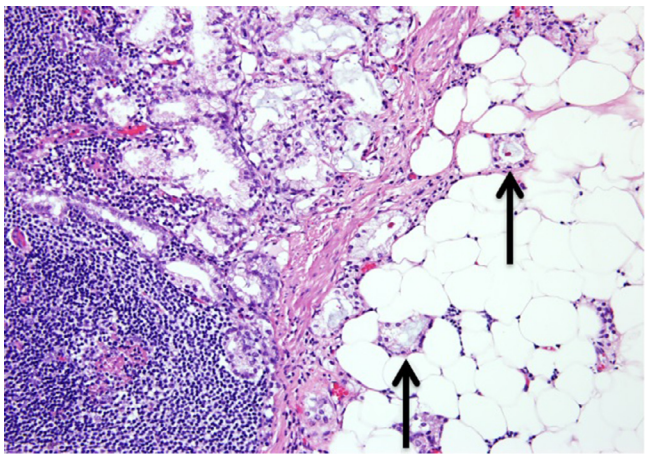

Fig. 4. The tumor invades through the lymph node capsule and extends to the pericapsular adipose tissue (arrow) (Hematoxylin and eosin stain, 10X magnification).

The median number of LN retrieved was 13 (range 1-42). A solitary positive LN was found in 166/280 (59%), 95/280 (34%) patients had 2-4 positive LNs, and 19/280 (7%) had 5 or more positive LNs. The median size of the largest metastatic focus was 3 mm (range 0.1-65). Two-thirds of our cohort (167/234) had largest positive LN measuring less than or equal to 1 cm in size, and 107/261 (41%) cases only comprised of micrometastatic foci (< 2 mm), either single or multiple. Interestingly, 94/107 (88%) cases of the micrometastasis (< 2 mm) cases had involvement of only a single LN and around 20% of which had ENE. However, it is important to indicate that these minute metastatic foci involved tiny LNs, which in many cases did not show a well formed capsule, were predominantly fatty and any involvement by the tumor resulted in spreading into the adipose tissue. ENE positive LNs was equal to or less than 10 mm in 87% of the cases.

The follow-up period ranged from 1.5 to 100 months (median 7 months). BCR developed in 155 (55%) patients. On univariable analysis, The number of positive LNs was significantly associated with BCR ($p < 0.001$; Fig. 5A). BCR increased as the number of LN metastasis increased. Forty-one percent of our cohort of high-risk patients had

Table 1
Radical prostatectomy data (grade group, pathologic stage, surgical margins, and tumor volume) in 280 patients found to have lymph node metastasis after radical prostatectomy

Pathologic variable	*N* (%) (*n* = 280)
Grade group of the prostate	
2	30 (11%)
2 with minor pattern 5	13 (5%)
3	34 (12%)
3 with minor pattern 5	45 (16%)
4	36 (13%)
5	122 (44%)
Pathological stage (pT)	
T2	11 (4%)
T3a	98 (35%)
T3b	170 (61%)
T4	1 (0.4%)
Surgical margins	
Negative	128 (46%)
Positive	152 (54%)
Tumor volume	
1%-14%	65 (23%)
15%-49%	155 (55%)
50%-100%	60 (21%)

micrometastasis (up to 2 mm). The latter was associated with lower BCR rates compared to metastatic focus of > 2 mm in size (macrometastasis) ($P < 0.001$; Fig. 5B).

The vast majority of patients (75% of the cases) had GG 4 and 5 within the LN. Most foci of metastatic prostate cancer were present as cohesive cribriform clusters, solid nests, or sheets even when the primary tumor in the prostate was predominantly formed by discohesive single cells. The differentiation of prostate cancer within the LNs was significantly associated with BCR ($P = 0.001$; Fig. 5C). The GG of LN metastasis matched the GG of the prostate in only 40% of the patients. The GG of the primary tumor was lower than the GG of the LN metastasis in 33% and higher than the GG of the LNs in 27%.

Table 2
Lymph node data (number of positive lymph node(s), size of largest metastatic focus, grade group of metastases, presence of extranodal extension, and unilateral vs. bilateral involvement) in 280 patients found to have lymph node metastasis after radical prostatectomy.

Pathologic variable	N (%) (*n*=280)
Number of positive lymph node(s)	
1	166 (59%)
2-4	95 (34%)
≥5	19 (7%)
Size of largest metastatic focus (*n*=261)	
Micrometastasis (up to 2mm)	107 (41%)
Macrometastasis (>2 mm):	154 (59%)
Grade group of lymph node metastasis (*n*=224)	
1 -3	56 (25%)
4 & 5	168 (75%)
Extranodal extension (*n*=244)	
Negative	145 (60%)
Positive	99 (40%)
Unilateral and bilateral involvement (*n*=273)	
Unilateral	198 (73%)
Bilateral	75 (27%)

Most LNs (60%) were negative for ENE, and the presence of ENE was significantly associated with BCR ($P = 0.02$; Fig. 5D). Unilateral LN involvement was seen in almost three-fourths of our cases. However, no difference was observed between unilateral and bilateral involvement ($P = 0.09$).

We also analyzed patient group with solitary micrometastasis and no ENE ($n = 71$, 25% of our cohort). These "favorable group," of patients had a significantly lower rate of BCR compared to the "unfavorable group," ($P < 0.001$) who had more than 1 LN metastasis, metastatic focus more than 2 mm, and ENE. Similar analysis was also done for patients with negative resection margins ($n = 37$), and it did not show significant difference in BCR rates between the two groups ($P = 0.06$).

From our multivariable analysis, two features of LN metastasis were independently associated with BCR in our cohort: Higher number of positive LNs was associated with BCR (2-4 vs. 1 Hazard ratio (HR) = 1.60; 95% CI: 1.02-2.5; $P = 0.04$). In addition, GG of the metastatic focus was an independent predictor of the risk of BCR (GG 4&5 vs. 1-3 HR = 1.90; 95% CI: 1.14-3.2; $P = 0.014$) (Table 3).

4. Discussion

LN status is a crucial prognostic indicator in cancer in general. In prostate cancer, it is well understood that the presence of LN metastasis after radical prostatectomy is not uniformly associated with poor prognosis [5]. The current American Joint Committee on Cancer TNM staging do not stratify the LN stage based on the extent of LN involvement and merely categorizes all patients with positive LN into a single pN1 category [12]. Table 4 highlights a few studies published in the English literature that have studied different LN features and have found that some of these features are significant and independent predictors of outcome and overall prognosis.

Passoni et al., in a study including 484 patients with prostate cancer, found that patients with 1 or 2 positive LNs have better survival rates than men with ≥ 3 LN metastases. In their multivariable analysis, the diameter of the largest LN metastasis and the dichotomised number of positive LNs were independent predictors of early BCR. At the same time, ENE did not reach statistical significance as an independent predictor. Overall, they found that patients with ≥ 3 positive LNs have 2.7 times the probability of having early BCR than men with 1 or 2 positive LNs [5]. In another study, Briganti et al looked at cancer specific survival (CSS) in 703 LN positive patients treated with radical prostatectomy and extended pelvic LN dissection between 1988 and 2003 at two large academic institutions. The authors found that the number of positive nodes represents

a key variable for CSS predictions. Patients with up to 2 positive nodes in this cohort had an excellent CSS rate, which was significantly higher compared to patients with more than 2 positive nodes ($P< 0.001$). The authors concluded that these results reinforce the need for stratification of node positive patients according to the number of positive nodes proposing a revision of the pathologic TNM classification [13]. In our study, we were also able to demonstrate a difference in BCR rates between patients with solitary positive LN vs. multiple positive LNs. Single LN involvement was seen in the majority (59%) of our cases, in spite of our cohort consisting of more advanced prostate cancer within the prostate gland with 57% of cases belonging to Gleason score 8-10 compared to only 29.5% in the Briganti et al. study and 44% in the Passoni et al. study.

In another study, Fleischmann et al. looked at 102 prostate cancer patients with positive LN metastasis, the author concluded that the presence of ENE in node positive prostate cancer is an indicator lesion for more aggressive disease; however, the only independent prognostic information they found was the size of largest tumor metastasis [8]. The same author in another study [14] looked at survival in patients with LN positive prostate cancer, and their results showed that substaging is possible in LN positive prostate cancer, which is in contrast to the current TNM

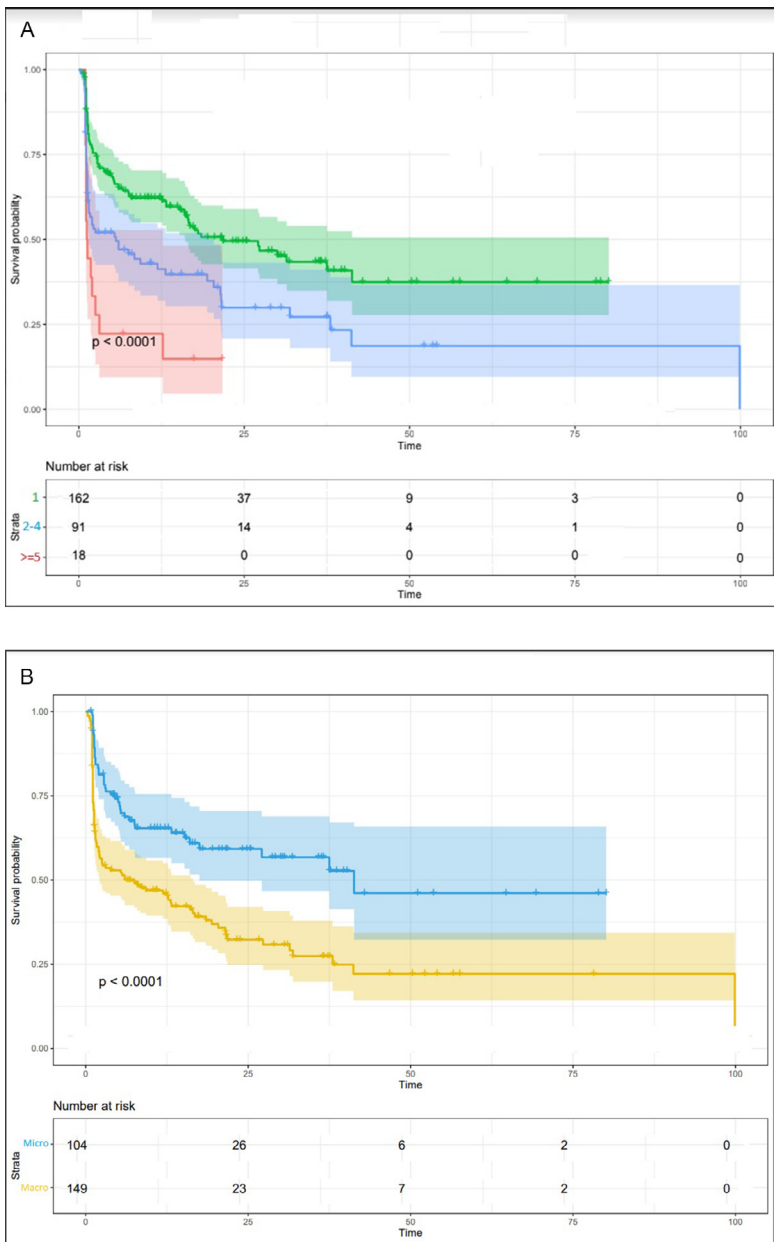

Fig. 5. Kaplan-Meier plots of BCR by A. number of positive lymph node(s), B. size of largest metastatic focus, C. grade group of metastatic focus, D. presence of extranodal extension.

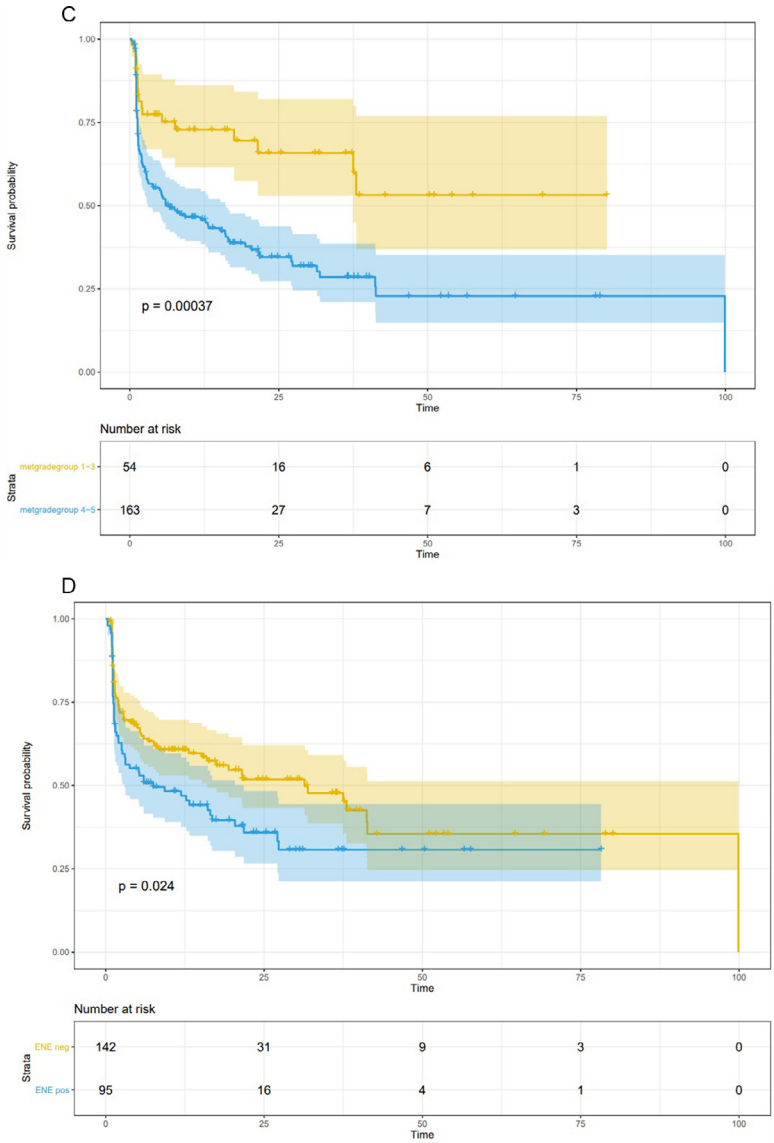

Fig. 5.. Continued

classifications. In this study, the authors found that higher nodal tumor burden, ENE, and less differentiated primary tumor and LN metastases are more likely to experience an adverse outcome. They proposed using the size of the largest metastases of 10 mm as a cut-off for substaging basing their suggestion on the fact that the largest metastasis size showed independent prognostic value, and it is simple to assess. In our study, 87% of LN metastasis were 10 mm or smaller with a median size of 3 mm compared to 73% with a median size of 6 mm in their study. Their median LN count was 21, which was much higher than our median of 13. We evaluated the entire LN packets microscopically for possible LNs. The differences in the LN yield are perhaps attributable to either difference in LN counting methodology, the extent of LN dissection by the urologists, or differences in yield between robotic and non-robotic surgical techniques. The size of the largest metastatic focus was significantly associated with BCR but did not reach statistical significance as an independent predictor of BCR in our study.

Another suggestion from Fleischmann et al. was to use the category "micrometastasis only," because of its favorable prognosis [14]. In our study, a large cohort of patients (94 patients, 88%) within solitary metastasis group showed micrometastasis. Our findings support their conclusion, as our analysis showed that patients with micrometastasis (up to 2 mm) are associated with lower BCR rates compared to metastatic foci >2 mm in size (macrometastasis). Interestingly, we showed that patients who belonged to the favorable group (1 LN metastasis, micrometastasis, and no ENE), constituting 25% of our patients, had far better outcomes in terms of BCR as opposed to patients in the unfavorable group. This finding is in keeping with the literature that showed that patients with a single LN metastasis had

Table 3
Results of the multivariate analysis of predictors of biochemical recurrence after prostatectomy in patients with lymph node metastasis

Variable	Hazard ratio (95% confidence interval)	*P* value
Primary tumor characteristics		
Grade group of the prostate		
2	Reference	
3	2.03 (0.90-4.62)	0.09
4	4.26 (1.79-10.15)	0.001*
5	3.74 (1.65-8.49)	0.002*
Pathological stage (pT)		
T2	Reference	
T3a	1.62 (0.49-5.40)	0.43
T3b and T4	1.70 (0.52-5.65)	0.38
Surgical Margins		
Negative	Reference	
Positive	1.35 (0.91-1.99)	0.14
Histopathologic features of lymph node metastasis		
Number of positive lymph nodes		
1	Reference	
2-4	1.6 (1.02-2.5)	0.04*
≥ 5	2.4 (1.15-5.1)	0.02*
Size of largest metastatic focus		
Micrometastasis (≤ 2 mm)	Reference	
Macrometastasis (> 2mm)	1.3(0.79-2.1)	0.32
Grade group of lymph node metastasis		
1-3	Reference	
4&5	1.9 (1.14-3.2)	0.014*
Extra nodal extension		
Negative	Reference	
Positive	1.30 (0.85-2.00)	0.50

* significant predictor of biochemical recurrence after radical prostatectomy.

favorable prognosis [2,15]. Potentially instead of relying on a single histomorphologic criterion, such as size or number of positive LNs, patients with LN metastasis may need further stratification based on all of these features into two (favorable or unfavorable) or more categories. This stratification should be further explored in multiple larger studies in relationship to BCR, disease specific survival, and overall survival.

While grading of tumors at the metastatic sites is not very common in pathology, prostate cancer is unique in the sense that the grading is entirely based on architectural patterns and not related to cytologic features. Multiple grading tiers compared to tumors arising from other organ sites makes it easy to recognize the change in the differentiation of prostate cancer within the LN metastasis. Very few studies have explored the significance of grading prostatic adenocarcinoma within the LNs or other metastatic sites. Boormans et al. looked at CSS in 146 patients with confirmed LN positive prostate cancer, the two only independent predictors of clinical outcomes were nodal Gleason score and diameter of the largest metastasis. The presence of nodal Gleason score of > 7 and a diameter of the largest metastasis of > 3 mm was correlated with poor CSS [9]. Our study supports their findings, and we were able to demonstrate that GG of metastasis is an independent predictor of BCR.

Sub-centimeter LNs detected on imaging in the preoperative setting are often presumed to be free of metastasis. Our cohort had positive LNs measuring ≤ 10 mm in two-thirds of our patients. This observation is essential as these LNs (≤ 10 mm) often harbor small metastatic foci or micrometastasis and often escape detection as abnormal on conventional imaging in the preoperative setting or by intraoperative palpation. Hence decision making for pelvic LN dissection should be based on other preoperative risk factors, and less weight should be placed on negative imaging characteristics. Furthermore, the standard gross dissection protocols usually include submitting only palpable LNs for histological examination [16], this procedure has the potential of overlooking small and impalpable LNs [6,16]. At our center, we submit the entire LN packets, starting with

Table 4
Summary of lymph node histopathologic features studies.

Study	Year	Lymph Node Features Studied	Significant Independent Predictor	Statistical Analysis
Passoni et al. [5]	2014	Number of positive LN(s); Size of metastatic focus; ENE	Number of positive LN(s) Size of metastatic focus	HR = 2.80; 95% CI 1.99-3.93; *P* = 0.001 HR = 1.48; 95% CI 1.16-1.89; *P* = 0.002
Luchini et al. [6]	2017	ENE	ENE	HR = 1.40, 95% CI 1.12-1.74; I2 = 0%
Carlsson et al. [7]	2013	Number of positive LN(s); Size of metastatic focus; ENE	Number of positive LN(s)	HR = 1.84; 95% CI 1.24-2.73; *P* = 0.002
Fleischmann et al. [8]	2008	Number of positive LN(s); Size of metastatic focus; ENE; Gleason score of metastasis	Size of metastatic focus	HR = 2; 95% CI 1.3-3.2; *P* = 0.002
Boormans et al. [9]	2008	Number of positive LN(s); Size of metastatic focus; ENE; Gleason score of metastasis	Size of metastatic focus Gleason score of metastasis	HR = 2.173; 95% CI 1.01-4.66; *P* = 0.046 HR=1.85; 95% CI 1.09-3.11; *P*=0.021

ENE, extranodal extension; HR, hazard ratio; LN, lymph node.

identifying palpable LNs followed by submitting the remainder of tissue entirely. A study published from our group looked at the effectiveness of the submission of entire LN tissue [17], and we found that it improves the number of LN yield by 37% and positive LN detection by 2%, hence this protocol is critical in detecting micrometastasis.

Our study's limitations include the following: short follow-up, BCR was the only oncologic outcome measured, and disease specific or overall survival was not studied. The lack of standardized postsurgical treatment with adjuvant/anti-androgen therapy is another limitation that could not be controlled in our study. Only 30% of our patients received adjuvant treatment and any analysis of the effects of adjuvant therapy on BCR would have been an under estimate of the effects of such treatment. In fact, we tested for the effect of adjuvant treatment on BCR in our cohort of patients and found it non-significant.

Further studies with longer follow-up periods and a more inclusive set of cancer population may be helpful to further substratify patients with LN metastasis in prostate cancer and to identify patients who will require adjuvant therapy while those who could be followed.

5. Conclusion

Our multivariable analysis showed that the the number of positive LNs and GG of the LN metastasis are independent predictors of BCR after radical prostaetctomy. LN metastasis can easily be stratified into favorable and unfavorable groups based on these histomorphogic features within LN. To further evaluate the significance of our findings and the need for their incorporation into the TNM staging, larger prospective studies with longer follow-up are needed.

Conflicts of interest

None declared

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