# Risk Factors for Pathologically Confirmed Lymph Nodes Metastasis in Patients With Clinical T2N0M0 Stage Prostate Cancer

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**Objective:** To explore the risk factors for postoperatively pathological lymph node metastasis in patients with clinical T2N0M0 stage prostate cancer (PCa).

**Methods:** We retrospectively analyzed clinicopathological data of 316 patients with clinical T2 stage PCa and preoperative negative lymph nodes [LN(−)] indicated by imaging (cT2N0M0) between January 2014 and May 2019. Multivariate logistic regression analysis was performed to determine risk factors for postoperatively pathological pLN(+) in patients with cT2N0M0 stage PCa. Spearman correlation analysis was used to explore the relationship between tumor burden and Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) score.

**Results:** A total of 45 patients (14.2%) were confirmed by postoperative pathology to have LN metastasis. Univariate analysis indicated that total prostate-specific antigen (tPSA), PI-RADS v2 score, postoperative Gleason grade group (GGG), intraductal carcinoma of the prostate (IDC-P), clinical T2 substaging, and postoperative pathological tumor burden were risk factors for pLN(+) in all patients. Multivariate analysis showed that tPSA and postoperative GGG were risk factors for pLN(+) in all patients. Univariate analysis revealed that tPSA, PIRADS v2 score, clinical T2 substaging, IDC-P, postoperative pathological tumor burden, and postoperative GGG were risk factors for pLN(+) in patients with GGG $\geq$ 3. Multivariate analysis suggested that tPSA, PI-RADS v2 score, clinical T2 substaging, postoperative pathological tumor burden, and GGG were risk factors for pLN (+) in patients with GGG $\geq$ 3. Spearman correlation analysis showed that PI-RADS v2 score was positively correlated with clinical T2 substaging and postoperative pathological tumor burden.

**Conclusion:** There was a high risk of LN metastasis in patients with cT2 PCa if they had high preoperative tPSA or high postoperative GGG. Patients with cT2 PCa and GGG $\geq$ 3 had a high risk of LN metastasis if they had high PI-RADS v2 score, high preoperative clinical stage or high postoperative pathological tumor burden. PI-RADS v2 score predicted tumor burden well in patients with GGG $\geq$ 3.

**Keywords: PI-RADS, tumor burden, Gleason grading group, lymph node metastasis, prostate cancer**

## INTRODUCTION

A low prostate-specific antigen (PSA) threshold for triggering biopsy has increased the number of patients with prostate cancer (PCa) and lymph node (LN) metastasis [LN(+)] confirmed by postoperative pathology, despite being LN(−) by preoperative imaging (1). It is reported that LN metastasis frequently indicates poor prognosis and increases the probability of postoperative biochemical recurrence (2). To the best of our knowledge, LN dissection (LND) is the most direct and standard method to determine the presence of LN(+) (3). However, the incidence of LN(+) is frequently heterogeneous among patients with different Gleason scores (GS) (1). The LN metastasis rate of PCa patients with GS 8–10 is significantly increased compared with those with GS 6–7 (1, 2). Traditional GS scores and associated nomograms for assessing LN metastasis might underestimate the risk of lymphatic invasion because of old samples (4). A previous study demonstrated that LN invasion was finally detected by postoperative pathological findings in 17.9% of patients with clinical organ-localized PCa (4). Therefore, it is important for patients with intermediate- and high-risk PCa to undergo pelvic LND (PLND), which might prevent potential lymphatic invasion (5, 6). However, because the complexity of PLND significantly prolongs operating time (7), there is a tendency to increase the use of robot-assisted radical prostatectomy (RP) and decrease the use of PLND, even in patients with high-risk PCa (6). Compared with the heterogeneity of LN metastatic burden to assess prognosis (5), the pathological features of primary tumors may better predict prognosis (3, 8). Complete resection of the primary tumor might be more important than LND (3, 8). Therefore, it is crucial to explore the risk factors for LN metastasis.

Currently, the risk factors for pathologically confirmed LN metastasis in patients with clinical T2N0M0 stage PCa have not been fully elucidated. This study aimed to determine the risk factors for postoperative pathological LN metastasis in patients with preoperative negative LNs and clinical T2 stage (cT2N0M0). In particular, we explored whether the latest International Society of Urological Pathology (ISUP) Gleason Grading Group (GGG) and Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) score were risk factors.

## MATERIALS AND METHODS

### Patients

We included 316 patients with clinical T2 stage (cT2) PCa and negative LNs indicated by preoperative imaging (cT2N0M0) between January 2014 and May 2019 at our center. All patients underwent whole bone scanning, chest and abdominal computed tomography (CT)/multiparametric magnetic resonance imaging (mpMRI), and were diagnosed with PCa postoperatively pathologically. All patients underwent RP plus standard PLND that included the external iliac and obturator LNs (6). The clinical data and tumor pathological features were retrospectively analyzed. The exclusion criteria were as follows: (1) preoperative neoadjuvant chemotherapy/radiotherapy; (2) incomplete clinical data, unclear pathological diagnosis and lack of prostate MRI

images; (3) inability to determine PI-RADS score [poor image quality; diffusion-weighted imaging (DWI)/dynamic contrast enhancement MRI functional sequence deletion; or DWI $b$ value $< 800$ s/mm$^2$]; (4) capsular infiltration or seminal vesicle metastasis suggested by preoperative imaging and confirmed by postoperative pathology; (5) positive surgical margins; and (6) other types of tumors confirmed pathologically.

### Clinical Data

Clinical data were collected, including total PSA (tPSA), clinical staging, PI-RADS v2 score, postoperative pathological Gleason score, postoperative pathological tumor burden (%), intraductal carcinoma of the prostate (IDC-P)/acinar adenocarcinoma (%) and LN status. Postoperative specimens were evaluated at our center by two pathologists with at least 10 years of experience. The 2014 ISUP GGG system was used (9). The system was divided into 5 groups (9): 1 (Gleason score ≤6), 2 (Gleason score 3 + 4 = 7), 3 (Gleason score 4 + 3 = 7), 4 (Gleason score 8), and 5 (Gleason score ≥9).

### Statistical Analysis

Statistical analysis was conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, United States). Categorical data were presented as frequency (%) and analyzed by chi-square test or Fisher's test. Continuous normally distributed data were represented as mean ± standard deviation and analyzed by $t$-test. Continuous data that were not normally distributed were analyzed by Kruskal–Wallis test. Multivariate logistic regression was performed to determine risk factors for postoperatively pathological lymph node metastasis in patients with preoperative cT2N0M0 stage PCa. Spearman correlation analysis was used to explore the correlation between PI-RADS v2 score and clinical T2 substaging and postoperative pathological tumor burden. $P < 0.05$ was considered statistically significant.

## RESULTS

We included 316 patients with clinical T2N0M0 stage PCa, and 45 patients (14.2%) were confirmed to have LN metastasis by postoperative pathology. The number of patients with pathological LN metastasis in each grading group was as follows: 0 cases in GGG 1 (3 + 3) group; 3 cases (0.9%) in GGG2 (3 + 4) group; 9 cases (2.8%) in GGG3 (4 + 3) group; 15 cases (4.7%) in GGG4 (8) group; and 18 cases (5.7%) in GGG5 (9, 10) group. Univariate analysis indicated that tPSA, PI-RADS v2 score, postoperative GGG, intraductal carcinoma of the prostate (IDC-P), clinical T2 substaging, and postoperative pathological tumor burden were risk factors for pathological LN metastasis confirmed postoperatively in all patients (**Table 1**). Multivariate logistic regression analysis showed that tPSA and postoperative GGG were risk factors for pathological LN metastasis confirmed postoperatively in all patients (**Table 2**). Univariate analysis revealed that tPSA, PI-RADS v2 score, clinical T2 substaging, postoperative pathological tumor burden, IDC-P and postoperative GGG were risk factors for pathological LN metastasis confirmed postoperatively in patients with GGG ≥ 3

**TABLE 1 |** Comparison of clinicopathological characteristics between pLN(+) and pLN(−) in all patients.

| PCa | Lymph node status | | P-value |
|---|---|---|---|
| | **Positive** | **Negative** | |
| Age | 67.36 ± 8.49 | 67.44 ± 8.76 | 0.955 |
| tPSA | 11.99 ± 3.49 | 8.45 ± 3.37 | <0.001* |
| PI-RADS v2 score (n.) | | | <0.001* |
| 1 | 1 | 30 | |
| 2 | 7 | 74 | |
| 3 | 11 | 110 | |
| 4 | 10 | 53 | |
| 5 | 16 | 4 | |
| Clinical T2 substage (n.) | | | <0.001* |
| cT2a | 8 | 128 | |
| cT2b | 9 | 93 | |
| cT2c | 28 | 50 | |
| Pathological tumor burden (%) | 36.77 ± 12.51 | 30.06 ± 13.24 | 0.002* |
| IDC-P/acinar adenocarcinoma (%) | 22.89 ± 6.76 | 20.73 ± 6.56 | 0.043* |
| Number of LN removed (n.) | | | 0.281 |
| 5–9 | 10 | 73 | |
| 10–14 | 9 | 80 | |
| 15–19 | 14 | 55 | |
| ≥20 | 12 | 63 | |
| Postoperative GGG (n.) | | | <0.001* |
| 1 | 0 | 27 | |
| 2 | 3 | 29 | |
| 3 | 9 | 87 | |
| 4 | 15 | 70 | |
| 5 | 18 | 58 | |

*P < 0.05. GGG, Gleason grading group; LN, lymph node; PI-RADS v2, Prostate Imaging Reporting and Data System version 2; tPSA, total prostate-specific antigen; IDC-P, intraductal carcinoma of the prostate.

**TABLE 2 |** Multivariate logistic regression analysis of risk factors for LN invasion in all patients.

| PCa | LN status (Positive/Negative) | | |
|---|---|---|---|
| | **P** | **OR** | **95% CI** |
| tPSA | <0.001* | 1.260 | 1.119–1.419 |
| PI-RADS score | 0.066 | 1.563 | 0.970–2.520 |
| Clinical T2 substage | 0.069 | 1.774 | 0.956–3.292 |
| Pathological tumor burden (%) | 0.058 | 1.028 | 0.999–1.057 |
| IDC-P/acinar adenocarcinoma (%) | 0.305 | 1.030 | 0.973–1.090 |
| Postoperative GGG | 0.030* | 1.517 | 1.042–2.209 |

*P < 0.05. GGG, Gleason grading group; LN, lymph node; PI-RADS, Prostate Imaging Reporting and Data System; tPSA, total prostate-specific antigen; IDC-P, intraductal carcinoma of the prostate.

**TABLE 3 |** Comparison of clinicopathological characteristics between pLN(+) and pLN(−) in patients with postoperative GGG ≥ 3.

| PCa | Lymph node | | P-value |
|---|---|---|---|
| | **Positive** | **Negative** | |
| tPSA | 11.63 ± 3.27 | 8.75 ± 3.25 | <0.001* |
| PI-RADS score (n.) | | | <0.001* |
| 1 | 0 | 14 | |
| 2 | 5 | 62 | |
| 3 | 11 | 87 | |
| 4 | 10 | 48 | |
| 5 | 16 | 4 | |
| Clinical T2 substage (n.) | | | <0.001* |
| cT2a | 5 | 95 | |
| cT2b | 9 | 79 | |
| cT2c | 28 | 41 | |
| Pathological tumor burden (%) | 37.97 ± 12.04 | 29.12 ± 13.62 | <0.001* |
| IDC-P/acinar adenocarcinoma (%) | 23.19 ± 6.79 | 20.81 ± 6.46 | 0.032* |
| Number of LN removed (n.) | | | 0.173 |
| 5–9 | 8 | 59 | |
| 10–14 | 8 | 60 | |
| 15–19 | 14 | 43 | |
| ≥20 | 12 | 53 | |
| Postoperative GGG (n.) | | | 0.039* |
| 3 | 9 | 87 | |
| 4 | 15 | 70 | |
| 5 | 18 | 58 | |

*P < 0.05. GGG, Gleason grading group; LN, lymph node; PI-RADS, Prostate Imaging Reporting and Data System; tPSA, total prostate-specific antigen; IDC-P, intraductal carcinoma of the prostate.

(**Table 3**). Multivariate analysis showed that tPSA, PI-RADS v2 score, clinical T2 substaging, postoperative pathological tumor burden, and postoperative GGG were risk factors for pathological LN metastasis confirmed postoperatively in patients with GGG ≥ 3 (**Table 4**). Spearman correlation analysis showed that PI-RADS v2 score was positively correlated with clinical T2 substaging and postoperative pathological tumor burden, and, the higher the grading group, the greater the correlation (**Table 5**).

# DISCUSSION

In 2014, ISUP hosted a consensus conference to make further revisions to the Gleason grading system of PCa. This revision not only defined the morphological criteria for each Gleason grade in more detail, but also proposed a new grading system based on prognosis, called the 2014 International Society of Urological Pathology Consensus Conference on Gleason Grading of Prostatic Carcinoma (2014 ISUP GGG system) (10). Organ-localized PCa does not metastasize to PLNs in patients with GGG ≤ 2 under the premise of negative surgical margins; therefore, there is almost no risk of progression (2, 11). Our study also revealed that patients with cT2 stage and GGG ≤ 2 PCa had a low risk of LN metastasis (0.9%). However, a previous study showed that postoperative GGG ≥ 4 predicted poor cancer-specific survival (CSS) and overall survival (OS) of patients with PCa. The predictive value of the 2014 ISUP GGG system for CSS and OS was significantly better than that of LN metastasis (3, 8). This indicates that the pathological features of the primary tumor are more effective in predicting prognosis. Consequently, complete resection of the primary tumor may be of greater

**TABLE 4 |** Multivariate logistic regression analysis of risk factors for LN invasion in patients with GGG ≥ 3.

| PCa | LN (Positive/Negative) | | |
|---|---|---|---|
| | P | OR | 95% CI |
| tPSA | 0.022* | 1.159 | 1.021–1316 |
| PI-RADS v2 score | 0.033* | 1.812 | 1.050–3.127 |
| Clinical T2 substage | 0.035* | 2.104 | 1.052–4.205 |
| Pathological tumor burden (%) | 0.028* | 1.035 | 1.004–1.067 |
| IDC-P/acinar adenocarcinoma (%) | 0.255 | 1.036 | 0.975–1.100 |
| Postoperative GGG | 0.029* | 1.767 | 1.061–2.943 |

*P < 0.05. GGG, Gleason grading group; LN, lymph node; PI-RADS v2, Prostate Imaging Reporting and Data System version 2; tPSA, total prostate-specific antigen; IDC-P, intraductal carcinoma of the prostate.

**TABLE 5 |** Correlation between tumor burden and PI-RADS v2 score.

| | | cT2 substage | | Pathological tumor burden | |
|---|---|---|---|---|---|
| | | Index | P | Index | P |
| PI-RADS v2 | Overall | 0.566 | <0.001* | 0.154 | 0.006 |
| | GGG ≥ 3 | 0.659 | <0.001* | 0.243 | <0.001* |
| | GGG ≥ 4 | 0.723 | <0.001* | 0.314 | <0.001* |
| | GGG ≥ 5 | 0.703 | <0.001* | 0.371 | 0.001 |

*Spearman correlation analysis, P < 0.05. GGG, Gleason grading group; PI-RADS v2, Prostate Imaging Reporting and Data System version 2.

importance than LND. The present study also demonstrated that poor pathological features of primary tumors indicate a higher risk of pathological LN metastasis in patients with cT2 PCa, and higher tPSA and GGG are more significantly predictive of postoperative LN metastasis.

The 8th edition of the American Joint Committee on Cancer (AJCC) system has modified the pT2 staging. The pT2 stage in the 7th edition of the AJCC system was divided into 3 substages according to the extent of tumor involvement and single/double sidedness. However, the substages did not convey prognostic information and there was no difference in prognosis between various substages (10). The relationship between clinical and pathological T stages is poor (10). Large unilateral tumors may be classified as low pT stage, whereas small bilateral tumors may be classified as high pT stage (10). Therefore, organ-localized PCa is no longer subclassified but attributed pathologically to pT2 in the 8th edition of the AJCC system although the substages (cT2a, cT2b, and cT2c) are retained in clinical T2 staging (10). However, we found that pathological LN metastasis was more likely in the cases with higher preoperative cT2 substage or greater postoperative pathological tumor burden in patients with GGG ≥ 3 and cT2 stage PCa. Therefore, whether to remove pT2 substage remains controversial. In patients with GGG ≥ 3, we might further substage pT2 according to tumor burden to guide subsequent more precise follow-up and treatments strategies, such as performing prostate-specific membrane antigen (PSMA) -PET/CT or salvage lymph node dissection (12, 13).

High PI-RADS v2 score frequently indicates high probability of clinically significant PCa, and the lesions are commonly

visible and large in multiparameter MRI (mpMRI) or surgical specimens. Christopher et al. (14) reported that MR-derived tumor volume ≥2.1 cm$^3$ generally predicted invasion of prostate capsule (sensitivity/specificity = 78.4/73.5%). These imaging and pathological features are inevitably associated with PCa aggressiveness or prognosis (15). In general, high PI-RADS v2 score suggests high aggressiveness and poor clinical prognosis of PCa and high risk of pLN(+) in patients with preoperative LN(−) indicated by mpMRI (16–18). However, misdiagnosis by mpMRI often occurs in patients with tumor volume <1.0 cm$^3$ because these small-volume tumors are difficult to detect by mpMRI (19, 20). It is reported that patients with tumors which are not visible on MRI are frequently confirmed to have small-volume tumors and low GS after RP (0.15 vs. 1.45 cm$^3$ in apparent tumors) (21). Vargas et al. (17) showed that >50% of PCa with GS ≥ 4 + 3 were underestimated in patients with tumor volume <0.5 cm$^3$. Seo et al. (22) also revealed that >50% of clinically significant PCa (PI-RADS v2 score <4) was underestimated in patients with tumor volume <1.0 cm$^3$. Therefore, it is still uncertain whether the parameters of mpMRI function well in predicting GS score. It is reported that PI-RADS v2 score is associated with GS score, tumor volume, and extracapsular invasion. However, a recent study demonstrated that the positive predictive value of PI-RADS v2 = 5 for predicting LN metastasis was only 20%, while the negative predictive value was 99% (16). Therefore, PI-RADS v2 could only be used to exclude patients with an extremely low risk of LN metastasis (16). Any PI-RADS v2 score may contain more than one GS; that is, there may be overlap of various GSs between adjacent PI-RADS v2 scores (23). However, the tumor size (e.g., 1.5 cm) might become an important factor for predicting LN(+) in patients with PI-RADS v2 score of 4 or 5. In patients with GS ≥ 7, PI-RADS v2 score was 4 for small-volume PCa but could be 5 in cases with large tumors. Thus, PI-RADS v2 score performed well in predicting tumor burden to some extent, although it had poor performance in predicting GS (24). The present study revealed that PI-RADS v2 was positively correlated with preoperative clinical substage and postoperative pathological tumor burden, and the correlation was even higher in patients with higher GGG. Besides, high tumor burden indicates high risk of LN invasion, which was consistent with the previous study. Consequently, PI-RADS v2 score performed well in predicting preoperative or postoperative tumor burden in patients with GGG ≥ 3, although it was not associated with LN metastasis in the whole population. High PI-RADS v2 scores frequently suggest a high tendency toward LN metastasis.

Intraductal carcinoma of the prostate is commonly regarded as a highly aggressive malignancy, although GS cannot be applied to IDC-P (25–27). It has been suggested that whether it is IDC-P should be routinely included in pathological reports (9, 28). Hollemans et al. (8) reported that IDC-P is more prone to LN metastasis in patients with GGG = 2. The present study indicated that IDC-P was not a risk factor for LN metastasis in patients with cT2 stage PCa. This may have been because the invasive pathological features were uncommon in very-low-risk patients (GGG = 1), whereas the effect of the invasive feature of IDC-P in the risk of LN(+) was inconspicuous in high-risk PCa

(GGG $\geq$ 3). Multicenter research with a large sample is needed to verify these results.

There were several unavoidable limitations to this study. Firstly, this was a single-center retrospective study with a small sample size. Further investigation into the relationship between primary tumor characteristics and LN metastasis in patients with organ-localized PCa is needed. Secondly, we only included patients undergoing standard LND, and patients with expanded or modified LND were not included. Therefore, it is unclear whether there is a correlation between the extent of LND and positive LN metastasis. Thirdly, biopsy cases were not included because the limited tissue could not fully reflect the pathological features of the whole glandular tissue (8). However, Antonio et al. (4) reported that the percentage of preoperative positive needles and GS of biopsy specimen >4 + 3 were predictors of LN metastasis.

## CONCLUSION

There was a high risk of LN metastasis in patients with cT2 PCa if they had high preoperative tPSA or high postoperative GGG. Patients with cT2 PCa and GGG $\geq$ 3 experienced a high risk of LN metastasis if they had high PI-RADS v2 score, high clinical stage, or high postoperative pathological tumor burden. PI-RADS v2 score performed well in predicting tumor burden in patients with GGG $\geq$ 3 PCa.

## DATA AVAILABILITY STATEMENT

All relevant data of the study are included in the article. Further inquiries of the original data can be directed to the corresponding authors.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Fujian Medical University and all procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional Ethics Committee of First Affiliated Hospital of Fujian Medical University and with the 1964 Helsinki declaration and its later amendments or comparable Ethical Standards. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional Requirements.

## AUTHOR CONTRIBUTIONS

Q-SZ: conceptualization. NX and Y-HC: data curation. S-HC: investigation. Z-BK: methodology. X-YX: project administration. S-HC and X-DL: resources. Y-PW: software. YW and J-BH: supervision. YW: validation. NX, Z-BK, Y-HC, and Y-PW: writing – original draft. X-DL and X-YX: writing – review and editing. All authors contributed to the article and approved the submitted version.

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