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Original Article

Effect of Gleason scores of lymph node metastases on prognosis of patients with prostate cancer

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Abstract: The long-term mortality risk from prostate cancer increases in lymph node (LN) positive patients. This study was done to assess the effect of lymph node Gleason score (LNGS) on prognosis in patients with LN-positive prostate cancer. Among the 1,415 patients who received pelvic lymph node dissection (PLND), 117 (8.4%) patients had a positive LN. The PGS of the prostate specimens and the LNGS of the positive LNs were assessed by uropathologists. The median age of patients at surgery was 67 years (interquartile range [IQR], 62-71 years) and the median follow-up duration was 44.3 months (IQR, 27.0-78.5 months). Pathologic Gleason scores (PGS) of 6-9 included one (0.9%), 53 (49.5%), 22 (20.6%), and 31 (29.0%) patients. The median total number of retrieved LNs was 9.0 (IQR, 5.3-12.8). The median number of positive LNs was one (IQR, 1-2). Cancer architecture with a Gleason pattern and score were observed in LNs as in ordinary prostate specimens. LNGS 6-9 included nine (8.1%), 57 (51.4%), 31 (27.9%), and 14 (12.6%) patients. The speaman's analysis showed the meaningful correlation between PGS and LNGS ($P = 0.249$, $P = 0.011$). The univariate analysis showed that the number of positive LNs and LNGS were significantly associated with prostate cancer-specific survival ($P = 0.028$; $P = 0.005$). The same architecture that is seen in the prostate was seen in positive LNs, and LNGS may be a significant prognostic factor in patients with LN-positive prostate cancer.

Keywords: Gleason score, prognosis, lymph node metastasis, prostate cancer, radical prostatectomy

Introduction

Prostate cancer is the most common malignancy in the US [26] and the fifth-ranking malignancy in Korea. However, in Korea, the 13.5% annual increase in prostate cancer incidence is the fastest of all malignancies. The incidence of prostate cancer increased from 8.5 in 1999 to 24.9 per 100,000 in 2009 [1]. Prostate cancer in Korea exhibits more aggressive characteristics than the disease in the US [27]. For example, prostate cancer in a Korean man tends to present at a more advanced stage, exhibits a higher Gleason score (GS), displays a higher level of prostate-specific antigen (PSA), and is more likely to involve more lymph node (LN) invasion [9, 15].

Radical prostatectomy is the gold standard treatment for localized prostate cancer, and pelvic lymph node dissection (PLND) is an important surgical procedure for accurate LN staging and to improve surgical outcomes [3, 18, 24]. LN-positive prostate cancer indicates an aggressive disease progression. The long-term mortality risk from prostate cancer increases in LN-positive patients [8]. However, few studies have investigated the prognostic factors for LN-positive prostate cancer, although age, size of metastatic LN, extent of PLND, number of LNs, number of positive LNs, pathologic stage, pathologic Gleason score (PGS), surgical margin (SM) status, and seminal vesicle invasion (SVI) have been studied [11, 12, 15, 16, 18, 24, 29]. However, their influence remains controversial. Thus, optimal management for LN-positive prostate cancer has not been defined. Identifying prognostic factors for LN-positive prostate cancer is very important because patients with a poor prognosis must

Table 1. Clinicopathologic variables

	n (%)
Age (IQR)	67 (62-71)
Neoadjuvant therapy (%)	16 (13.8)
Adjuvant therapy (%)	91 (78.4)
Initial PSA, ng/mL (IQR)	18.7 (9.7-36.1)
Tumor stage	
pT2/pT3a/pT3b/T4	13 (11.6%)/28 (25.0%)/65 (58.0%)/6 (5.4%)
Extra-prostatic extension (%)	93 (80.2)
Seminal vesicle invasion (%)	71 (61.2)
Positive surgical margin (%)	85 (73.3)
No. of lymph nodes removed (IQR)	9.0 (5.3 -12.8)
No. of positive lymph nodes (%)	n = 116
1	71 (61.2)
2	22 (19.0)
≥ 3	23 (19.8)
Pathologic Gleason score (%)	n = 107
6	1 (0.9)
7	53 (49.5)
8	22 (20.6)
9	31 (29.0)
Lymph node Gleason score (%)	n = 111
6	9 (8.1)
7	57 (51.4)
8	31 (27.9)
9	14 (12.6)

immediately commence androgen deprivation treatment (ADT) that confers a survival benefit. This treatment, which can have a variety of adverse effects, can be delayed or avoided entirely in low-risk patients.

GS is one of the most important prognostic factors for both localized and advanced prostate cancer [13]. However, information concerning the GS for LNs is lacking. Thus, we evaluated GS for LNs to study the effect of lymph node Gleason score (LNGS) on cancer-specific survival in patients with LN-positive prostate cancer.

Materials and methods

This retrospective study was conducted with 1,415 patients who underwent radical prostatectomy and PLND for localized prostate cancer at two tertiary hospitals from January 1998 to December 2009. Institutional review board approval was obtained for the retrospective analysis of this patient population.

All patients were monitored for PSA level, and received a digital rectal examination, transrectal ultrasound guided biopsy, chest X-ray, pelvic magnetic resonance imaging scan, and a bone scan to rule out advanced prostate cancer prior to surgery. PLND was performed in patients with intermediate risk (cT2b, GS = 7, 10 < PSA ≤ 20) or high risk (≥ cT2c, GS ≥ 8, PSA > 20) according to the D'amico classification [5]. Although the extent of PNLD varies according to surgeons and hospitals, at least the external iliac and obturator LNs were included. A pathologist postoperatively evaluated the prostate specimens according to the criteria of the 2010 Seventh Edition Cancer Staging Guidelines of the American Joint Committee on Cancer.

All of Radical prostatectomy specimens (1,415) were routinely cut in 4-mm transverse slices with perpendicular sections from the apex to the base, fixed in 10% neutral buffered formalin, and embedded in paraffin. All freshly embedded PLND specimens were sent *en bloc* for pathological dissection by a pathologist. Sections were obtained at a thickness of 5-μm and stained with hematoxylin and eosin (H&E) in the typical manner. The PGS of the prostate specimens and the LNGS of the positive LNs were assessed by uropathologists (KC Moon, JH Suh, and Y Park) in accordance with the 2005 criteria developed at the International Society of Urological Pathology (ISUP) Consensus Conference. Gleason score based on Gleason pattern for first and second most predominant patterns with a comment on the tertiary pattern.

Among the 1,415 patients, 117 (8.4%) had a positive LN. One patient whose pathology had

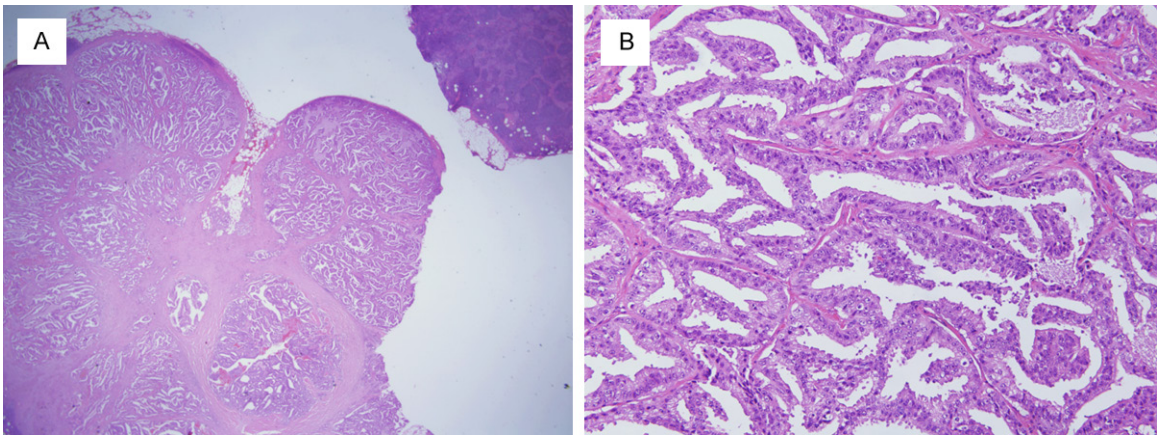

Figure 1. Metastatic prostatic adenocarcinoma in the lymph node showing cribriform gland formation (Gleason score 8 (4+4)). (A) A low power scan. Left lower; positive lymph node, right upper; normal lymph node. (B) Higher magnification of (A) (Original magnification in (A), ×1.25 and (B) ×200).

both squamous cell carcinoma and adenocarcinoma (GS 3+3) was excluded from the study. Sixteen patients received neoadjuvant treatment and 91 patients received adjuvant treatment (70 hormone treatment and 21 hormone and radiation treatment) postoperatively 1 month later. Nine patients had only LNGS and did not have a PGS for their prostate specimen. Because four patients had a positive LN at frozen biopsy during the radical prostatectomy, subsequent procedures were cancelled, and five patients who received neoadjuvant ADT before radical prostatectomy had an undeterminable PGS. Thus, these patients and five patients with missing LNGS were excluded from the survival analysis.

Median follow-up duration was 44.3 months (interquartile range [IQR], 27.0-78.5 months). Patients were followed-up to determine PSA recurrence at 1 month postoperatively and every 3 months thereafter during the first year. If PSA was not elevated, it was followed-up biannually. Biochemical recurrence (BCR) was defined by an elevated serum PSA level (> 0.2 ng/mL) on two consecutive occasions, or the initiation of adjuvant therapy due to PSA elevation.

SPSS ver. 19 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The Mann-Whitney test, Fisher's exact test, and Spearman's correlation analysis were used to assess the relationship among clinicopathologic variables. The Kaplan-Meier method and log-rank test were performed for the univariate survival analysis. A Cox-proportional hazard regression was performed for prostate cancer-specific survival. Each hazard ratio (HR) was given including the 95% confidence intervals (CIs). A P-value < 0.05 was considered significant.

Results

The median age of the 116 patients at surgery was 67 years (IQR, 62-71 years), and the median preoperative PSA level was 18.7 ng/mL (IQR, 9.7-36.1 ng/mL) (**Table 1**). Extra-prostatic extension was evident in 93 patients (80.2%), and SVI was evident in 71 patients (61.2%). A positive SM was noted in 85 patients (73.3%). The median total number of retrieved LNs was 9.0 (IQR, 5.3-12.8). The median number of positive LN was one (IQR, 1-2). Twenty-three patients (19.8%) had more than three positive LNs. According to the PGS, Gleason 6 included one (0.9%) patient, Gleason 7, 53 (49.5%), Gleason 8, 22 (20.6%), and Gleason 9, 31 (29.0%) patients. According to the LNGS, Gleason 6-9 included nine (8.1%), 57 (51.4%), 31 (27.9%), and 14 (12.6%) patients. Twenty-three patients with a positive LN died during the follow-up period. Among them, seven died from prostate cancer. The 5 year cancer-specific survival rate was 91.0% (95% CI, 83.4-98.6, data not shown).

The cancer architecture with the Gleason pattern and score was seen in LNs as in ordinary prostate specimens (**Figure 1**). LNGS 6-9 were associated with well-formed glands, discrete glandular formation and an ill-defined glandular

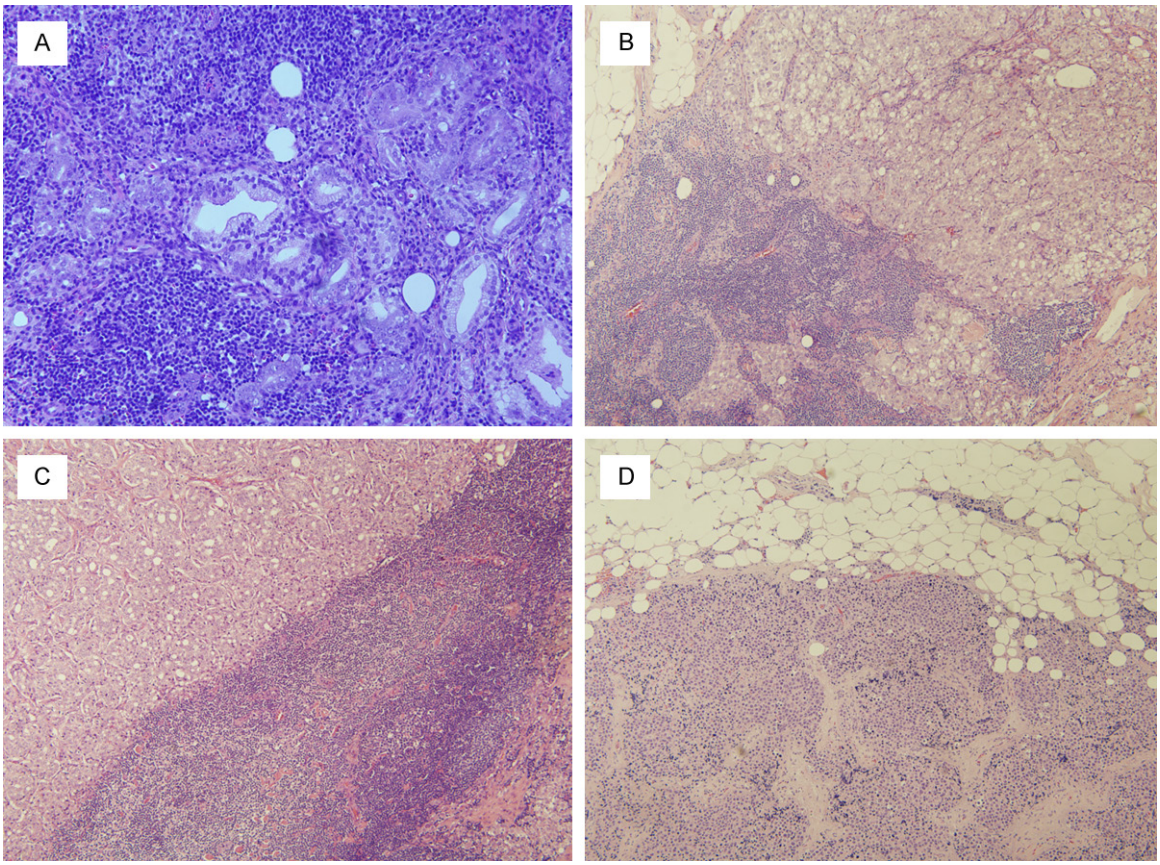

Figure 2. Examinations of metastatic carcinoma. A. Metastatic adenocarcinoma in lymph nodes showing Gleason score 6 (double sum of pattern 3). Well formed glands are observed in lymphoid tissue. (Original magnification = ×200). B. Metastatic adenocarcinoma in lymph nodes showing Gleason score 7 (pattern 4 and pattern 3). Both discrete gland formation and ill defined glandular unit are observed in lymphoid tissue. (Original magnification = ×200). C. Metastatic adenocarcinoma in lymph nodes showing Gleason score 8 (double sum of pattern 4). The large cribriform glands are observed in lymphoid tissue. (Original magnification = ×200). D. Metastatic adenocarcinoma in lymph nodes showing Gleason score 9 (pattern 4 and pattern 5). Poorly differentiated gladular cells with solid proliferation or single cell infiltration is observed in lymphoid tissue. (Original magnification = ×200).

unit, large cribriform glands, and solid proliferation or single cell infiltration, respectively. Forty-five (38.8%) patients had multiple positive LNs (**Figure 2**). These LNs had the same LNGS regardless of PGS and the number of positive LNs except one patient who had three positive LNs (PGS 9, two LNGS 8, and one LNGS 9).

The speaman's analysis showed the meaningful correlation between PGS and LNGS (P = 0.249, P = 0.011, **Table 2**). However, LNGS exhibited a down-graded tendency compared to PGS. Among the 51 patients with PGS 7, seventeen patients (33.3%) showed the higher LNGS. But to the contrary, nineteen patients (67.9%) showed lower LNGS at PGS 9 patients. The univariate analysis showed that initial PSA, PGS, extra-prostatic extension, SVI, positive SM, and extent of PLND were not related to prostate cancer-specific survival. The number of positive LNs and LNGS were significantly associated with prostate cancer-specific survival (HR, 7.59; 95% CI, 1.25-46.11, P = 0.028; HR, 11.533; 95% CI, 2.10-63.35, P = 0.005; **Table 3**).

Discussion

In bladder and obstetrical cancer, some patients with positive LNs are expected to be cured by PLND. Prostate cancer overlaps with bladder cancer and obstetrical cancer in the involvement of lymphatic channels. Some patients with prostate cancer and a positive LN can be cured by PLND [17]. Several studies have reported that patients with LN-positive

Table 2. Correlation between pathologic Gleason score and lymph node Gleason score (Spearman's correlation analysis, $P = 0.249$, $P = 0.011$)

			Lymph node Gleason score			
			6	7	8	9
		Total 102	8	51	30	13
Pathologic Gleason score	6	1	0	1	0	0
	7	51	5	29	15	2
	8	22	1	10	9	2
	9	28	2	11	6	9

Table 3. Univariate analysis of risk factors associated with prostate cancer-specific survival

Risk Factor	HR	95% CI	*P* value
Initial PSA	0.96	0.90-1.03	0.236
Extra-prostatic extension	2.21	0.27-18.40	0.464
Seminal vesicle invasion	0.64	0.16-3.12	0.638
Positive surgical margin	1.28	0.25-6.60	0.769
Extent of PLND(standard vs. extended)	1.05	0.13-8.73	0.967
No. of positive Lymph nodes			
1	Reference		
2	3.44	0.48-24.46	0.217
≥ 3	7.59	1.25-46.11	0.028
Pathologic Gleason score			
≤ 7	Reference		
8	5.49	0.50-60.90	0.165
9	6.00	0.67-53.87	0.109
Lymph node Gleason score			
≤ 7	Reference		
8	0.00	0.00	0.980
9	11.53	2.10-63.35	0.005

prostate cancer who received PLND had long BCR free survival without adjuvant treatment [2, 6, 19, 25]. However, prognostic factors for LN-positive prostate cancer have remained unclear. Cheng et al reported that dedifferentiation in the metastatic progression of prostatic carcinoma was statistically significant only in univerate analysis in 1999, but there was no further study after then [4]. This is the first study to investigate the effect of GS in positive LNs. We could see the prostate gland in positive LNs. Cancer-specific survival differed according to LNGS.

BCR occurred in more than three-quarters of the patients (81.0%) within 1 month postoperatively. This was because our patients had more aggressive disease. Several clinicopathologic studies on LN-positive patients reported a prevalence of PGS exceeding 7 (63.9-95%), median preoperative PSA level (11.6-16 ng/mL), SVI (50-65.5%), positive SM (51-62.1%), more than pathologic stage T3 (76.2-87%), and median number of removed LNs (11-22) [2, 7, 25]. In comparison, nearly all of the present patients had a PGS > 7 (99.1%), higher PSA (18.7 ng/mL; IQR, 9.7-36.1 mg/mL), more SVI (74%), and greater prevalence of positive SM (85%). Additionally, 88.4% of the patients had more than pathologic stage T3 disease.

Schumacher et al. reported that the number of positive LNs after extended PLND related to poor BCR free survival and patients with more than three positive LNs had poor cancer-specific survival [25]. Boorjian et al. reported that a single positive LN increases the risk of BCR and more than two positive LNs after extended PLND was an adverse predictor of cancer-specific survival [2]. Touijer et al. argued that a subclassification of patients with positive LNs is needed. Their data and our data were similar; more than three positive LNs were associated with death from prostate cancer [28].

Bodman et al. reported that PGS is a prognosis factor for patients with LN-positive prostate cancer. Those with < GS 7 had 72% recurrence free survival vs. > GS 8, with 36% recurrence free survival at 24 months [29]. Boorjian et al. reported that PGS (≤ 7 and ≥ 8) was a prognostic factor for systemic progression and cancer-specific survival, whereas PGS was not a prognostic factor for BCR or local recurrence [2]. In our study, PGS was not statistically related to cancer-specific survival. However, the PGS showed a high HR (HR, 6.00; 95% CI, 0.67-53.87, $P = 0.109$). If the more data were accumulated, our data maybe show the similar results like as previous studies.

Some patients with LN-positive prostate cancer show a good prognosis. Several studies have reported that 4-40% of LN-positive patients have long BCR-free survival without ADT [2, 6, 19, 21, 25]. This result indicates that some patients with positive LN could be cured by radical prostatectomy and PLND only. Our data that LNGS exhibited a down-graded tendency compared to PGS may be related. However, we do not know which patients have long BCR free survival and why patients remain cancer free. Furthermore, appropriate management of patients with LN-positive cancer has not been confirmed.

GS was the sum of the predominant Gleason pattern and the second most common Gleason pattern. The Gleason pattern was based just on tumor morphology and not on immunochemical staining or polymerase chain reaction or nucleic acid analyses. However, the GS reflects biologic aggressiveness well. It was recommended at the 2005 ISUP consensus conference that higher grade tertiary pattern at TRUS biopsy should be included in the GS [10]. After radical prostatectomy, if there is tertiary pattern 5 in GS 7 prostate cancer, patients have a higher pT stage, SVI, EPE, and BCR than GS 7 without a tertiary pattern 5 [14, 20, 22, 30]. This result means that GS and Gleason pattern itself are important prognostic tools anywhere. Recent study showed that, with sequential comparisons of GS 7 to 10, Gleason pattern 5 is independent prognostic factors in metastatic cancer [23]. Thus, we believe that the GS for a positive LN is also meaningful for prognosis. LNGS 9, that included the Gleason pattern 5, showed very poor cancer-specific survival (HR, 11.53; 95% CI, 2.10-63.35, $P = 0.005$) in our study.

This study had several limitations. First, we did not discuss BCR. However, almost all patients with a positive LN received adjuvant ADT or lifelong ADT (continuous or intermittent) after radical prostatectomy. A fair number of patients who did not receive ADT did not fall to the nadir (0.2 ng/mL). In these cases, BCR resumed immediately. Thus, a BCR analysis is very difficult for LN-positive prostate cancer. ADT decreases the risk of BCR, but ADT does not significantly affect cancer-specific survival [2]. We analyzed survival, although death from prostate cancer was small. Second, the extent of PLND varied according to the surgeon even if at least the external and obturator LNs were contained. Because 21% positive LNs were discovered at the internal iliac LN, the extent of PLND could affect BCR free survival [25]. Finally, the LNs retrieved 9.0 (IQR, 5.3-12.8) might have been insufficient to remove all metastatic LNs.

Disclosure of conflict of interest

None.

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