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An Investigation of the Pathology Report of Prostate Cancer Patients with Radical Prostatectomy in Southern Iran: A Cross-sectional Study

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Abstract

Background: Prostate cancer is a major malignancy worldwide among men; it is the fourth leading cancer in both genders. This study investigated the pathologic factors of radical prostatectomy (RP) specimens.

Method: About 578 men underwent RP during five years in Shiraz University hospitals. We recorded the following clincopathological parameters: tumor type and stage, Gleason score (GS), grade, tertiary pattern, ISUP, surgical margin, lymph node (LN) involvement, lymphovascular invasion, seminal vesicle involvement, extraprostatic extension (EPE), vas deferens invasion, perineural and pseudocapsular invasion, bladder neck involvement, and age.

Results: The mean age of participants was 63.87 ± 6.95 years. Most had pathologic T2N0Mx (73 %) diseases; the most GS was low-risk GS ≤ 6 (47.4%). Surgical margin status was free of tumors in 72.5% and among those with positive margins; the most involved site was the apex in 18.3%. Single and dual LN involvements were the most prevalent patterns. 5.9% of the patients had EPE. We found perineural and pseudocapsular invasions in 59.9% and 29.9%, respectively. There was a strong correlation between the clincopathological parameters, stage, and ISUP. Perineural invasion, pseudocapsular invasion, and tertiary pattern 5 increased with advanced age ($P < 0.0001$). The GS 8 to 10 increased with the increase in age ($P = 0.001$).

Conclusion: A strong correlation existed between the clincopathological parameters, stage, and ISUP. Additionally, perineural and pseudocapsular involvement and tertiary pattern 5 had a strong relationship with advanced age.

Keywords: Prostate cancer, Radical prostatectomy, Pathology

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Introduction

Prostate cancer is a major malignancy worldwide among men and the fourth leading cancer in both genders.[1] The incidence rate is obtained based on the geographical area and ethnic group. African-American men showed the highest incidence rate (234.6:100, 000), earlier age onset of prostate cancer, and more aggressive presentation and pathology (tumor volume, more advanced stage, higher Gleason score, and higher prostate specific antigen (PSA) levels).[2-4] The incidence of prostate cancer is 9.6:100,000 in Iran, which is more than several countries in Asia.[5, 6] From an epidemiologic aspect, since 1992, the incidence trend of prostate cancer has been dramatically increasing by approximately 1% annually. This is partially due to early detection through screening modalities comprising serum PSA, which is the most important factor, digital rectal examination, and transrectal ultrasonography.[7-10]

Several factors are involved in selecting the treatment of choice. Among these factors mention can be made of pretreatment serum PSA, digital rectal examination, tumor, node, and metastasis (TNM), histologic grading (Gleason score/grade group), molecular and genomic profile of the tumor, extraprostatic extension and metastases by imaging studies, symptomatic appearance, probable complications of each procedure, patient's preferences, and general conditions affecting treatment tolerance, including age, life expectancy, and presence of comorbidities.[11]

Accurate data from the histopathological examination of radical prostatectomy (RP) specimens play a pivotal role in predicting the risk of recurrence, surveillance, and decided to adjuvant radiotherapy or hormonal therapy. Structured pathology report regarding all components of specimen was shown to significantly enhance the competence and quality of data provided for clinicians and was recommended in North America and the United Kingdom.[12] Therefore, we aimed to review the prognostic factors derived from the pathological examination of radical prostatectomy in a cross-sectional study.

Material and Methods

Ethics statement

The Ethics Committee of Shiraz University of Medical Sciences approved this study with the

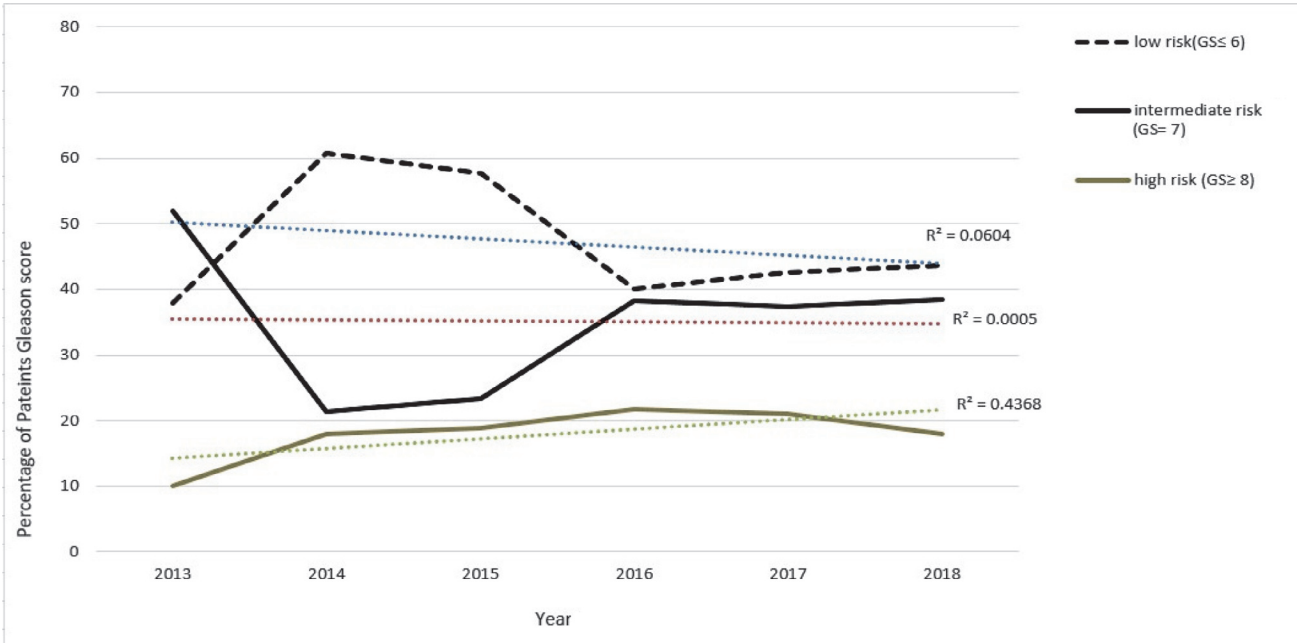

Figure 1. This figure shows the number of patients with prostatic cancer undergoing radical prostatectomy (RP) between 2013 and 2018.

Note: In the final years, almost all the patients had clinically significant cancer, indicating that overtreatment of prostate cancer decreased (P=0.004).

Table 1. Patients and tumor characteristics

Age (years) ± SD	63.90 ± 6.95
Gleason score	
Low risk≤ 6	274 (47.4%)
Intermediated risk = 7	195(33.7%)
High risk≥ 8	109(18.9%)
ISUP grade group	
I (GS 3+3)	277 (47.9%)
II (GS 3+4)	158 (27.3%)
III (GS 4+3)	34 (5.9 %)
IV (GS 4+4, 3+5, or 5+3)	65 (11.2%)
V (GS 4+5, 5+4, or 5+5)	44 (7.6%)
Tertiary pattern 5	45 (7.8 %)
PT- stage	
T2Nx	63 (10.6 %)
T2N0	422 (73 %)
T2N1	10 (1.7%)
T3aNx	1 (0.2%)
T3aN0	17 (2.9%)
T3aN1	1 (0.2%)
T3bNx	3 (0.5%)
T3bN0	41 (7%)
T3bN1	20 (3.4%)

SD: standard deviation; ISOP: International society for urologic pathologists

code of: 17229. Additionally, patients signed written informed consent for participation in our study.

Data inclusion

In this retrospective study, we enrolled consecutive patients with prostate cancer, treated with radical prostatectomy between March 2013 and March 2018 in Shiraz University hospitals. Our prostate cancer database prospectively collected clinical and pathological data from patients undergoing RP. We excluded patients who had received neoadjuvant hormonal therapy and previous radiotherapy and had oligometastatic prostatic cancer.

Data gathering

We gathered the following tumor characteristic variables from the patients' medical records and pathology reports: tumor type, Gleason score and grade, tertiary pattern, the International Society for Urologic Pathologists (ISUP) grade group, tumor stage, surgical margin, lymph node involvement, lymphovascular invasion (LVI), seminal vesicle involvement, extraprostatic extension, vas deferens invasion, perineural invasion, pseudocapsular invasion, bladder neck involvement, and age.

Statistical analysis

The mean±SD and frequency percentage described the quantitative and qualitative variables. We assessed the normality assumption of the variables in the study by the Kolmogorov-Smirnov test. For comparison, we either considered the equality of the two mean values in qualitative variables and default equality of variances of independent t-test or applied the non-parametric Mann-Whitney U test. To evaluate the correlation between variables, we utilized Pearson's correlation coefficient. *P*-values less than 0.05 were statistically significant. The statistical software SPSS version 22 analyzed the data.

Results

Patient's characteristics

During the study period, we identified a total of 578 patients meeting our criteria. The mean age of participants was 63.87 ± 6.95 years. All the detected tumors were adenocarcinoma. Most had pathologic T2N0Mx (73 %) diseases; the most Gleason score was low risk GS ≤ 6 (47.4%). Approximately 7.65% of the patients showed tertiary pattern 5 in the specimen. Table 1 shows the patients and tumor characteristics, stage, and grade distribution.

Additionally, in recent years, almost all the patients had clinically significant cancer, suggesting that the overtreatment of prostate cancer decreased (*P*=0.004) (Figure 1).

Clincopathological parameters

Prostate involved by tumor was equal to or less than 50% space in 87%. The surgical margin status was free of tumors in 72.5% and among those with positive margins; the most involved site was the prostate apex 18.3%. Moreover, only 11.9% of the patients had positive lymphovascular invasion.

The mean dissected lymph node (LN) was 8.4 ± 5.2. About 94% of the dissected LNs were free of involvements. Single and dual LN involvements were the most prevalent involvement patterns. Additionally, the right side involvement was slightly higher than the left side (4.5% vs. 3.9%).

Around 5.9 % of the patients had extraprostatic extension (EPE). Perineural and pseudocapsular invasions existed in 59.9% and 29.9%, respectively.

The pattern of vas deferens invasion was mostly bilateral (1.7%). However, the left side involvement was higher than the right side (0.9% vs 0.4%). We observed this pattern in seminal vesicle invasion (bilateral: 6.4%; left: 2.9%; right: 1.6%). Table 2 shows the Clincopathological parameters.

Relationship of age, ISUP grade group, and TNM stage with other pathological parameters

There was a strong correlation between clincopathological parameters, stage, and ISUP grade group. However, only perineural invasion, pseudocapsular invasion, and tertiary pattern 5 significantly increased with advanced age (*P*<0.0001) (Table 3). The probability of a Gleason score of 8 to 10 or high-risk disease significantly increased with the increase in age [66.7±6.78 vs 62.87±6.82 years, *P*=0.001] (Figure 2). Furthermore, a strong association existed between clincopathological parameters and ISUP subgroups (Table 4).

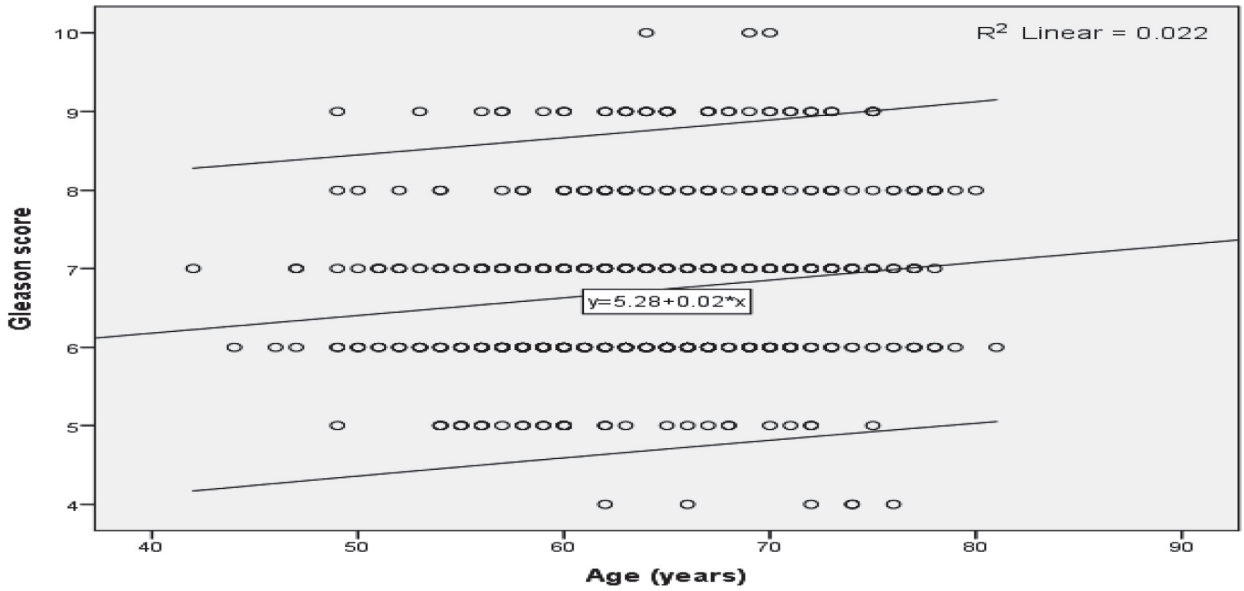

Figure 2. This figure shows the correlation between age and Gleason grade 8.

Table 2. Clincopathological parameters

Tissue involved by tumor	
> 50%	75 (13%)
≤ 50%	503 (87%)
Surgical margin	
Free of tumor	419 (72.5%)
Apex	106 (18.3%)
Base	27 (4.7%)
Apex and base	24 (4.2%)
Left posterolateral	1 (0.2%)
Base and left posterolateral	1 (0.2%)
LVI*	70 (12.1%)
LN* dissected± SD	8.4 ± 5.2
EPE*	34 (5.9%)
Seminal vesicle invasion	
Right	9 (1.6%)
Left	17 (2.9%)
Bilateral	37 (6.4%)
Vas deferens invasion	
Right	2 (0.3%)
Left	5 (0.9%)
Bilateral	10 (1.7%)
Perineural invasion	346 (59.9%)
Pseudocapsular invasion	173 (29.9%)

*LN=lymph node; EPE= extra prostatic extension; LVI= lymphovascular invasion

Discussion

In this study, the most prevalent pathologic stage was T2. Similarly, the most prevalent pattern of Gleason score was low-risk GS≤ 6, about 47.4%. It can be concluded that most participants in our study did not have a poor prognosis or advanced tumors. The potential explanation for our finding is the effective screening system; traditionally, patients with low or intermediate GS do not accept active surveillance and they chose the radical prostatectomy option. A recently published study recommended active surveillance for most patients with low-risk (Gleason score ≤ 6) localized prostate cancer; also, factors such as younger age, prostate cancer volume, patient preference, and ethnicity should be considered when making management decisions.[13]

However, in recent years, almost all the patients had a clinically significant cancer, suggesting that overtreatment of prostate cancer decreased. In addition, our data showed that advanced age had a relationship with high-risk disease or probability of high Gleason score (8-10). Muralida et al. concluded that older men had a very high probability of high-grade or high-risk of prostate cancer.[14]

Moreover, all clinicopathologic parameters were significantly more likely to have a higher TNM and ISUP grade. However, advanced age had a significant association with perineural invasion, pseudocapsular involvement, and tertiary pattern.

ISUP is based on prognostic behavior of prostate cancers with various Gleason scores that are separated by probability of five-year biochemical recurrences (BCR) following RP.

Table 3. Relationship between age, ISUP* grade group, and TNM* stage with clincopathological parameters

	Age	ISUP grade group	TNM stage
ISUP grade group[a]	< 0.0001 [0.16]	-	-
TNM stage[a]	0.27 [0.04]	< 0.0001 [0.42]	-
LN* involvement[b]	0.29 [65.1 vs. 63.7]	< 0.0001 [3.7 vs. 1.9]	< 0.0001 [5.9 vs. 1.6]
Seminal vesicle invasion[b]	0.13 [62.5 vs. 63.]	< 0.0001 [3.5 vs. 1.8]	< 0.0001 [7.2 vs. 1]
Vas deferens invasion[b]	0.41 [62.5 vs. 63.8]	< 0.0001 [3.1 vs. 2.0]	< 0.0001 [7.4 vs. 1.5]
Extraprostatic involvement[b]	0.24 [65.2 vs. 63.1]	< 0.0001 [3.4 vs. 1.9]	< 0.0001 [6.2 vs. 1.4]
Perineural invasion[b]	0.02 [64.4 vs. 63.1]	< 0.0001 [2.4 vs. 1.4]	< 0.0001 [2.1 vs. 1.0]
Pseudocapsular invasion[b]	0.006 [65.1 vs. 63.3]	< 0.0001 [2.6 vs. 1.7]	< 0.0001 [2.7 vs. 1.2]
Tertiary pattern 5[b]	< 0.0001 [65.7 vs. 63.5]	< 0.0001 [3.0 vs. 1.8]	< 0.0001 [2.8 vs. 1.4]
Surgical margin[b]	0.07 [64.7 vs. 63.5]	< 0.0001 [2.6 vs. 1.8]	< 0.0001 [2.7 vs. 1.3]
Bladder neck involvement[b]	0.066 [63.9 vs. 63.0]	0.072 [2.7 vs. 2.0]	< 0.0001 [4.8 vs. 1.6]
Lymphovascular invasion[b]	0.63 [64.27 vs. 63.8]	< 0.0001 [2.9 vs. 1.9]	< 0.0001 [3.8 vs. 1.4]

a: Pearson's correlation coefficient test (*P*-value [r coefficient]); b: Independent *t*-test or Mann-Whitney test (*P*-value [positive gp vs. negative gp]).
* ISUP=The International Society for Urologic Pathologists; LN= lymph node; TNM= tumor, node and metastasis

According to this grading system, prognostic grade group 1 included all prostate cancers with Gleason scores of 6 (or less), which are indolent cancers, in which only active surveillance can be considered. Prognostic grade group 1 and score 6 cancers had individual discrete, well-formed glands and demonstrated a 96% probability of five-year BCR-free progression following RP. Prognostic grade group 2 consisted of tumors with score 3+4=7, predominantly composed of well-formed glands with fewer components of poorly formed, fused, and cribriform glands. The prognostic grade group 2 showed 88% probability of five-year BCR-free progression following RP. Prognostic grade group 3 was comprised of cancers with score 4+3=7, predominantly showing poorly formed, fused, and cribriform glands with fewer components of well-formed glands. Prognostic grade group 3 cancers revealed 63% probability of five-year BCR-free progression after RP. Prognostic grade group 4 included cancers with score 4+4=8, or 3+5=8, or 5+3=8. These cancers showed only poorly formed, fused, and cribriform glands (4+4=8), or they indicated predominantly well-formed glands and fewer components lacking any glands (3+5=8), or they predominantly lacked glands and showed only fewer components of well-formed glands (5+3=8). The prognostic grade group 4 (score 8) cancers behaved similarly whether they were 4+4=8, or 3+5=8, or 5+3=8 and demonstrated 48% probability of 5-year BCR-free progression following RP. Prognostic grade group 5 comprised cancers with score 4+5=9, 5+4=9, and 5+5=10. These tumors showed complete lack of gland formation (or with necrosis) with poorly formed, fused, and cribriform glands (4+5=9 or 5+4=9) or complete lack of gland formation (5+5=10). All the prognostic grade group 5 cancers behaved similarly whether 4+5=9, or 5+4=9, or 5+5=10; they showed 26% probability of five-year BCR-free progression after RP. However, we did not assess the correlation between clinicopathologic parameters and survival rate. Therefore, we recommended that the five-year survival of the same population should be reported.[15, 16]

Our study revealed that 7.65% of the patients had tertiary pattern 5 in RP specimens. There is still controversy as to whether tertiary pattern 5 is associated with aggressive pathological features predictive of advanced pathological stage, worse outcome, and biochemical recurrence-free survival.[17, 18]

In a large population of patients undergone open radical prostatectomy, positive surgical margin rates were 27.6% and the apex was the most common location of positive surgical margin,[19] which is in line with the present study.

In addition, a recently published study suggested that the presence of positive surgical margin was a poor prognostic factor for patients with prostate cancer.[20]

In our study, about 29.9% of the patients had pseudocapsular invasions. Those patients were

Table 4. The relationship between ISUP subgroups and clincopathological parameters

			ISUP* grade group (N=578)					*P*-value
Variable	**Subgroup**	**Total**	**1 (n=277)**	**2 (n=158)**	**3 (n=34)**	**4 (n=65)**	**5 (n=44)**	
Age (year)[a]	-	-	62.87±6.81	64.16±7.01	63.85±6.70	66.65±7.36	65.45±5.82	0.001
Lymph node involvement[b]	No involvement	479(93.9)	239(99.6)	133(95.7)	26(89.7)	51(83.6)	30(73.2)	< 0.0001
	involvement	31(6.1)	1(0.4)	6(4.3)	3(10.3)	10(16.4)	11(26.8)	
Seminal vesicle invasion[b]	No	515(89.1)	274(98.9)	139(88.0)	28(82.4)	52(80.0)	22(50.0)	< 0.0001
	Yes	63(10.9)	3(1.1)	19(12.0)	6(17.6)	13(20.0)	22(50.0)	
Vas deferens invasion[b]	No	561(97.1)	276(99.6)	152(96.2)	31(91.2)	62(95.4)	40(90.9)	< 0.0001
	Yes	17(2.9)	1(0.4)	6(3.8)	3(8.8)	3(4.6)	4(9.1)	
Extraprostatic involvement[b]	Not seen	544(94.1)	273(98.6)	151(95.6)	32(94.1)	53(81.5)	35(79.5)	< 0.0001
	Yes	34(5.9)	4(1.4)	7(4.4)	2(5.9)	12(18.5)	9(20.5)	
Perineural invasion[b]	Not seen	232(40.1)	156(56.3)	59(37.3)	5(14.7)	7(10.8)	5(11.4)	< 0.0001
	Yes	346(59.9)	121(43.7)	99(62.7)	29(85.3)	58(89.2)	39(88.6)	
Pseudocapsular invasion[b]	Not seen	405(70.1)	234(84.5)	103(65.2)	19(55.9)	30(46.2)	19(43.2)	< 0.0001
	Yes	173(29.9).	43(15.5)	55(34.8)	15(44.1)	35(53.8)	25(56.8)	
Tertiary pattern 5[b]	No	487(84.3)	263(94.9)	132(83.5)	25(73.5)	37(56.9)	30(68.2)	< 0.0001
	Yes	91(15.7)	14(5.1)	26(16.5)	9(26.5)	28(43.1)	14(31.8)	
Surgical margin[b]	Free of tumor	419(72.5)	231(83.4)	111(70.3)	21(61.8)	34(52.3)	22(50.0)	< 0.0001
	Tumor involvement	159(27.5)	46(16.6)	47(29.7)	13(38.2)	31(47.7)	22(50.0)	
bladder neck involvement b	No	567(98.1)	276(99.6)	153(96.8)	32(94.1)	63(96.9)	43(97.7)	0.021
	Yes	11(1.9)	1(0.4)	5(3.2)	2(5.9)	2(3.1)	1(2.3)	

a: *P*-value based on ANOVA test, mean ± standard deviation; b: *P*-value based on chi-square test, frequency (relative frequency)
*ISUP= International Society for Urologic Pathologists; Grade group 1: Gleason scores of 6 or less, Grade group 2: Gleason scores of 3+4=7, Grade group 3: Gleason scores of 4+3=7, Grade group 4: Gleason Scores of 4+4=8, 3+5=8, 5+3=8, Grade group 5: Gleason Scores of 4+5=9, 5+4=9, 5+5=10

in the more advanced grade group or stages compared with negative pseudocapsule invasion. The studies in this field are few and far between, and some studies reported that was not a pathological feature associated with an adverse outcome after prostatectomy; however, based on some meta-analyses, it might be concluded that pseudocapsular invasion is associated with high grade and stage disease whether detected in a surgical study or imaging such as T2-weighted MR imaging.[21, 22]

Several meta-analyses suggest that perineural invasion is a significant prognostic indicator, particularly in patients coupled with PSA level and biopsy Gleason score results. In the current study, we detected perineural invasion in 59.9%. Therefore, whether perineural invasion could be a reliable prognostic factor for prostate cancer treatment and clinical care is yet to be investigated. However, our study showed the high-grade and stage disease associated with perineural invasion.[23-25]

Vas deferens invasion is associated with an increased risk of lymph node metastasis and recurrence; it is even suggested to serve as an independent prognostic determinant for adjuvant therapy due to poor prognosis.[26, 27] Similarly, our study showed the high grade and stage disease associated with vas deferens invasion.

Invasion of the muscular wall of the seminal vesicles by prostate cancer is generally regarded as a marker of poor prognosis at the time of pathologic staging after radical prostatectomy.[28] Bilateral seminal vesicle invasion seems to represent an independent prognostic factor.[29] Similar to vas deferens invasion, high grade and stage disease had a relationship with seminal vesicle invasion; also, bilateral seminal vesicle invasion was higher than the left side or right side invasion (bilateral: 6.5%; left: 2.9%; right:

1.5%). However, there is still controversy as to the impact of bilateral or unilateral invasion on the prognosis; for instance, Ohori et al. reported that bilaterality did not correlate with progression.[30]

A study by Kapoor et al. concluded that compared with invasive phenotype (pseudocapsular invasion), EPE into the periprostatic fat (periprostatic adipose tissue) was a more important pathological feature associated with an adverse outcome and prostate cancer recurrence after prostatectomy.[21] Our study showed the high grade and high stage disease associated with extraprostatic extension.

The presence of lymph node metastasis was a poor prognostic variable, and long-term risk of prostate cancer death substantially increased with an estimated range of 20% and 42%.[31, 32] The increase in peritumoral lymphatic vessel density and/or invasion of the tumor cells in the existing peritumoral lymphatic vessels, lymphangiogenic, and growth factors appear to be the major factor in lymph node metastasis of prostate cancer.[33]

In the present study, more than 95% of the patients were free of LN involvement. Furthermore, single and dual LN involvements were the most prevalent patterns.

LVI is a powerful predictor of aggressive prostate cancer behavior, early biochemical failure or relapse after radical prostatectomy in all patients in different stages and grades and even in patients with pT2N0 and pT2N0 negative resection margin.[34, 35] Our results showed that 11.9% of the patients had positive lymphovascular invasion. Urinary bladder neck invasion is defined as the presence of neoplastic glands within the thick smooth muscle bundles of the bladder neck in microscopic investigation. Classified as pT3 disease, bladder neck involvement is a significant predictor of PSA recurrence.[12] Zhuo concluded that bladder neck involvement was associated with other adverse pathologic features; however, it was not an independent predictor of PSA recurrence.[36] Our study showed that high grade and stage disease correlated with urinary bladder neck invasion.

The current study had some limitations. Firstly, we did not assess the correlation between clinicopathologic parameters and survival rate. Therefore, we recommended that the five-year survival of the same population should be reported. Secondly, we did not evaluate clinical outcomes such as recurrence, required for further treatment such as radiotherapy and adjuvant hormonotherapy after surgery. Thirdly, adverse effects such as erectile dysfunction and incontinence were not examined. Fourthly, there was no access to data on prostate gland volume. Finally, PSA biochemical recurrence and metastatic recurrence were unavailable in this study.

Conclusion

Examination of the specimen obtained from radical prostatectomy is essential for patient management and a logical adjuvant therapy.

There was a strong correlation between clinicopathologic parameters, stage, and ISUP grade group. Additionally, perineural invasion, pseudocapsular involvement, and tertiary pattern had a strong relationship with advanced age. Therefore, these variables should be used to better manage and improve the prevention and prognosis of the disease.

We recommend that future studies investigate the correlation between clinicopathologic parameters and survival rate and elucidate the importance of these variables compared to the present study design. To this end, we suggest that the five-year survival of the same population be reported.

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Conflicts of Interest

None declared.

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