Journal of Cancer Therapy, 2016, 7, 239-246
Published Online April 2016 in SciRes. http://www.scirp.org/journal/jct
http://dx.doi.org/10.4236/jct.2016.74025

Pathologic and Prognostic Outcomes of Very Low- and Low-Risk Prostate Cancer According to the National Comprehensive Cancer Network Guidelines in Japanese Patients with Radical Prostatectomy

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Received 24 February 2016; accepted 28 March 2016; published 31 March 2016

Abstract

Background: The purpose of this study was to validate the treatment strategy for a cohort of Japanese patients with very low-risk (VLR) and low-risk (LR) prostate cancer according to the National Comprehensive Cancer Network (NCCN) guidelines. Methods: We studied 751 patients with T1-3N0M0 prostate cancer treated with radical prostatectomy at our institution between 2000 and 2012. Patients with neoadjuvant treatments were excluded. We retrospectively reviewed the clinical and pathological outcomes for patients with VLR or LR prostate cancers that were classified by NCCN guidelines. Results: We identified 45 patients with VLR and 137 with LR prostate cancer. Non-biochemical recurrence rate at 5-year for 45 patients with VLR was 86.9% and 81.2% for 137 patients with LR (p = 0.56). However, none of the 19 patients >65 years old with VLR progressed, while 19% of 26 patients ≤65 years old with VLR cancer, 14% of patients >65 years old with LR cancer, and 17% of patients ≤65 years old with LR cancer progressed during the follow-up period (p = 0.04, p = 0.04 and p = 0.05, respectively). In analyses of prostatectomy specimens, both VLR and LR had similarly favorable outcomes, but patients >65 years old with VLR had the smallest tumors, with a mean of 5 mm in diameter. Conclusions: Our results support the treatment strategy of the NCCN that patients with VLR cancer and age >65 years old are good candidates for active surveillance, and that other treatment options—including active surveillance and aggressive treatments—can be applied to the remaining patients with VLR or LR cancers.

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How to cite this paper: Takizawa, I., *et al*. (2016) Pathologic and Prognostic Outcomes of Very Low- and Low-Risk Prostate Cancer According to the National Comprehensive Cancer Network Guidelines in Japanese Patients with Radical Prostatectomy. *Journal of Cancer Therapy*, **7**, 239-246. http://dx.doi.org/10.4236/jct.2016.74025

Keywords

Prostate Cancer, NCCN Guideline, Very Low-Risk, Low-Risk, Active Surveillance

1. Introduction

With the advent of serum prostate-specific antigen (PSA), prostate cancers can be detected early on; however, difficulty in detecting clinically non-significant disease still exists [1]. Furthermore, treatments for early cancer have been well organized in the last two decades so that patients have many treatments options [1]. While many investigators have been trying to develop prognostic markers or statistical models [2]-[5], the risk groups reported by D'Amico *et al*. [6] and the National Comprehensive Cancer Network (NCCN) guidelines [7] are simple to use, easy to understand by patients, and readily applied by physicians in the clinic. However, intermediate- and high-risk groups include a wide range of pathological features and prognoses [8].

Recently, NCCN guidelines for prostate cancer were updated to include a new category—a very low-risk group—that includes patients with low PSA density, fewer positive biopsy cores and shorter percent maximum cancer length in any biopsy core [9] [10]. For this new category, NCCN guidelines recommend active surveillance as an option for treatment, based on the 2B evidence level [7]. There were several reports to assess the prognostic significance of very low-risk (VLR) and low-risk (LR) prostate cancer by the NCCN, but most of them originated from Europe and the USA [11]-[17]. Recently, it was reported that African Americans with VLR prostate cancer tended to have more aggressive cancer than Caucasians [18]. Therefore, race may affect pathological and/or prognostic significance in patients with a relatively favorable risk cancer.

In the present study, we sought to validate the treatment strategy for patients with VLR and LR prostate cancer according to NCCN guidelines to confirm its clinical usefulness in a Japanese cohort.

2. Materials and Methods

2.1. Patients

We studied 1035 patients who had undergone radical prostatectomy (RP) and pelvic lymph node dissection for clinical stage (T1-3), no regional lymph node metastasis (N0), and no distant metastasis (M0) at Tokyo Medical University hospital during 13 years from 2000 to 2012. Patients who had neoadjuvant hormonal (n = 223) or high-intensity focused ultrasound (n = 1) were excluded from the present study. In addition, we excluded 60 patients who were followed at other hospitals immediately after surgery so that the remaining 751 patients were included for analyses. RP was performed by open retropubic (n = 338), perineal (n = 2), and robot-assisted laparoscopy (n = 411). Lymph node dissection was performed by open retropubic and robot-assisted RP, and none of the patients with perineal RP underwent lymph node dissection. Clinical stage was assigned according to the 2002 TNM staging system. Pathological outcomes such as pathological stage, surgical margin status, and Gleason score in RP specimens were obtained from official pathology reports. The patients were categorized based on the risk groups in the NCCN guidelines [7]. Patients with T1c or T2a classification, a biopsy Gleason score between 2 - 6, and a serum PSA level <10 ng/ml were assigned to the LR cancer group. The VLR group included patients with T1c classification, PSA density <0.15 ng/ml/cc, less than three positive biopsy cores, and <50% of maximum cancer length in any of their biopsy cores.

The present retrospective study was carried out according to the ethical guidelines for clinical studies of the Ministry of Health, Labor and Welfare of Japan, and was approved by the ethics committee of our institution (approval number: 1621).

2.2. Treatment Failure

The time of biochemical recurrence (BCR) was defined as the earliest date that the postoperative serum PSA levels rose to 0.2 ng/mL or higher and was confirmed by a second PSA examination result that was equal to or higher than the first PSA level. The day of surgery was reported as the PSA recurrence day when postoperative serum PSA levels did not fall to 0.1 ng/mL or less. In the present study, five patients whose PSA recurrence day was reported as the day of surgery were treated with adjuvant radiotherapy.

According to the Japanese Government's 21st Life Tables from the Statistics and Information Department of

the Minister's Secretariat, Ministry of Health, Labour and Welfare [19], the life expectancies for 60- and 65-year-old men are 22.75 and 18.74 years, respectively. Therefore, we used 65 years old as a cut-off to divide patients with VLR and LR cancer.

3. Analysis

Non-BCR rates was calculated using the Kaplan-Meier method. The differences in clinical and pathological features among risk groups were evaluated using a rank-sum test and chi-square test.

All statistical analyses were performed using STATA software (Stata Corporation, College Station, TX, USA). For all statistical comparisons, differences with a p value <0.05 were considered significant.

4. Results

Of the 751 patients, 45, 137, 350, and 219 patients were categorized into VLR, LR, intermediate, or high-risk groups according to NCCN guidelines. The clinical and pathological features of the patients with VLR and LR are shown in **Table 1**.

Table 1. Patient characteristics.

		Risk group according to the NCCN guidelines		
	Entire population n = 751	Very low N = 45	Low N = 137	p-value very low vs. low
Age mean (range)	65.3 (46 - 81)	64.2 (51 - 74)	63.8 (47 - 78)	0.69
Age <65	330 (43.9)	21 (46.7)	74 (54.0)	0.32
PSA*, ng/ml mean (range)	9.9 (1.1 - 89.0)	5.4 (1.1 - 8.6)	6.3 (3.0 - 10.0)	<0.05
PSA density ng/ml/cc mean (range)	0.32 (0.02 - 3.30)	0.11 (0.05 - 0.15)	0.22 (0.06 - 0.45)	-
Clinical T stage, n (%) T1c or T2a T2b or T2c T3	659 (88%) 84 (11%) 8 (1%)	45 (100%) - -	137 (100%) - -	-
Biopsy Gleason score, n (%) ≤6 7 ≥8	251 (34%) 328 (44%) 167 (22%)	45 (100%) - -	137 (100%) - -	-
No .of positive cores 1, 2 3, 4 5, 6 ≥7	363 230 86 71	45 - - -	78 42 10 7	-
Pathological stage, n (%) pT2 pT3a pT3b pN+	498 (66%) 181 (24%) 60 (8%) 12 (2%)	40 (89%) 5 (11%) - -	111 (81%) 25 (18%) - 1 (1%)	0.43
Positive surgical margins, n (%)	308 (41%)	11 (24%)	49 (36%)	0.16
Gleason score ≤6 7 ≥8	118 (15.7%) 466 (62.1%) 167 (22.2%)	23 (51.1%) 21 (46.7%) 1 (2.2%)	43 (31.4%) 88 (64.2%) 6 (4.4%)	0.017 for ≤6

*prostate specific antigen.

In the analyses of RP specimens, the frequencies of confined cancer and positive surgical margins were not significantly different between patients with VLR and LR (p = 0.223 and p = 0.161, respectively). Patients with VLR cancer had Gleason scores ≤6 more frequently than those with LR cancer (51% versus 31%, p = 0.017; **Table 1**).

Table 2 shows clinical and pathological features according to patients' age (≤65 and >65 year old). PSA density for patients with VLR cancer and age >65 years old was 0.108 ng/ml/cc, which was significantly less than other groups (p = 0.043- < 0.0005). While the distribution of pathological stages and frequency of positive surgical margins were not different among these groups, patients with VLR cancer and age >65 years old had the smallest diameter of largest tumors in RP specimens and had no tumors with Gleason scores 4 + 3 or ≥8 (**Table 2**).

Table 2. Clinical and pathological features of patients with very low-risk and low-risk prostate cancer according to the NCCN guidelines.

	Risk group according to the NCCN guidelines				p-value
	Very low-risk (VLR)		Low-risk (LR)		
	>65 y.o. N = 19	≤65 y.o. N = 26	>65 y.o. N = 58	≤65 y.o. N = 79	
Age Mean (range)	69.5 (66 - 74)	60.3 (51 - 65)	70.1 (66 - 78)	59.1 (47 - 75)	-
PSA, ng/ml Median Mean (range)	4.9 5.65 (3.2 - 8.6)	5.0 5.18 (1.1 - 8.3)	6.26 6.44 (4.0 - 9.92)	6.0 6.12 (3 - 10)	VLR ≤ 65 vs. LR ≤ 65, p = 0.01
PSA density ng/ml/cc Mean (range)	0.108 (0.08 - 0.14)	0.117 (0.05 - 0.148)	0.20 (0.06 - 0.42)	0.23 (0.07 - 0.45)	VLR > 65 vs. VLR ≤ 65, p = 0.043 vs. LR ≤ 65, p < 0.0005 vs. LR > 65, p < 0.0005 VLR ≤ 65 vs. LR > 65, p < 0.0005 vs. LR > 65, p < 0.00054 LR ≤ 65 vs. LR > 65, p = 0.0589
No. of positive cores 1 2 3, 4 5, 6 ≥7	 16 (84.2%) 3 (15.8%) - - -	 18 (69.2%) 8 (30.8%) - - -	 23 (40%) 13 (22.4%) 16 (28%) 2 (3.5%) 4 (7%)	 25 (31.6%) 17 (21.5%) 26 (32.9%) 8 (10%) 3 (4%)	-
Maximum cancer % In biopsy cores	16.5 ± 13.7 (1 - 40)	20.0 ± 16.8 (3 - 50)	28.6 ± 26.7 (3 - 100)	26.8 ± 23.4 (3 - 95)	n.s.
Pathological stage, n (%) pT2 pT3a pT3b pN+	 16 (84.2%) 3 (15.8%) - -	 24 (92.3%) 2 (7.7%) - -	 49 (84.5%) 8 (13.8%) - 1 (1.7%)	 62 (78.5%) 17 (21.5%) - -	n.s.
Positive surgical margins, n (%)	4 (21%)	7 (26.9%)	21 (36.2%)	28 (35.4%)	n.s.
Gleason score ≤6 3 + 4 4 + 3 ≥8	 11 (57.9%) 8 (42.1%) - -	 12 (46.1%) 13 (50%) 1 (3.9%) -	 20 (34.5%) 24 (41.4%) 9 (15.5%) 5 (8.6%)	 23 (29.1%) 49 (62.0%) 6 (7.6%) 1 (1.3%)	VLR > 65 vs. LR ≤ 65, p = 0.013
Maximum diameter of largest cancer, (mm) Median (range)	5.5 (2 - 20)	12 (3 - 30)	18 (5 - 48)	15 (3 - 42)	VLR > 65 vs. LR > 65, p = 0.0101 vs. VLR ≤ 65, p = 0.0096 VLR ≤ 65 vs. LR > 65, p = 0.032

In the entire population, a total of 212 patients (28.2%) had a BCR, and 69% ± 2% patient had non-BCR at five years after a surgery. Non-BCR rates at five years for VLR, LR, intermediate-, and high-risk groups were 86.9%, 81.2%, 75.1%, 49.0%, respectively (**Figure 1**). Patients with VLR or LR cancer had a better non-BCR rate than those with intermediate or high-risk cancer. However, there was no significant difference in non-BCR rates between patients with VLR and LR cancer (p = 0.56).

Further, we looked at the differences in non-BCR rates for patients with VLR or LR cancer according to age ≤65 and >65 years old. None of the 19 patients with VLR cancer and age >65 years old progressed, while 19% of 24 patients ≤65 years old with VLR cancer, 14% of patients >65 years old with low-risk cancer, and 17% of patients <65 years with low-risk cancer did progress during the follow-up period (p = 0.04, p = 0.04 and p = 0.05, respectively; **Figure 2**).

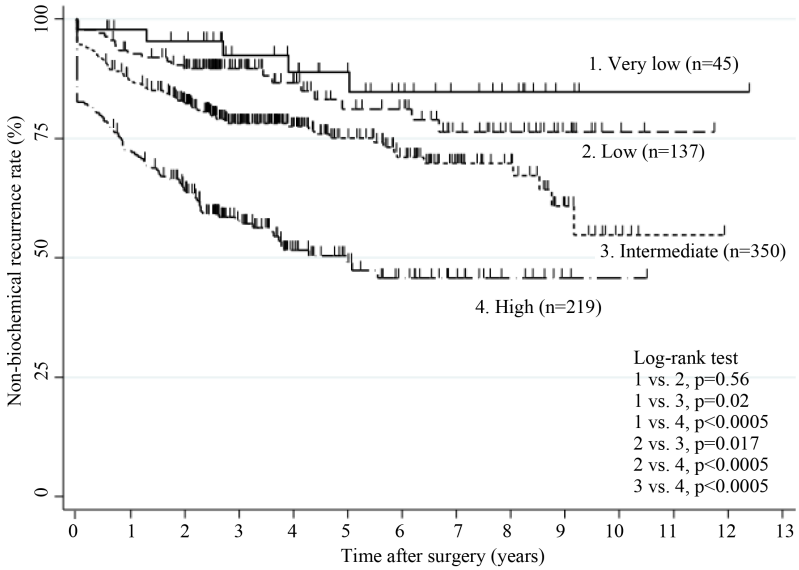

Figure 1. Non-biochemical recurrence rates after radical prostatectomy according to very low-, low-, intermediate- and high-risk prostate cancer based on NCCN guidelines.

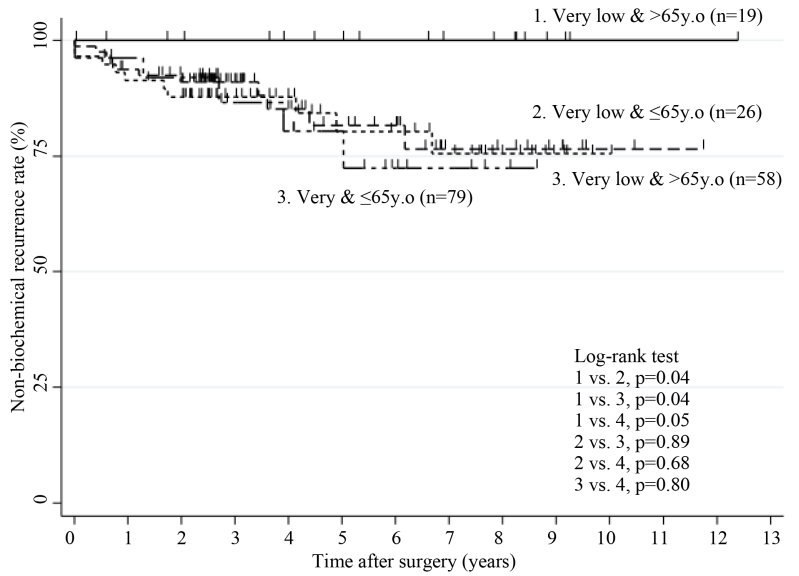

Figure 2. Non-biochemical recurrence rates after radical prostatectomy according to very low- or low-risk prostate cancer and age based on NCCN guidelines.

5. Discussion

In 2010, the NCCN guidelines added the new category VLR prostate cancer and recommends active surveillance for VLR patients with a life expectancy <20 years. It is recommended that VLR patients check their PSA at six months intervals, and have a rectal examination and biopsy at twelve-month intervals [7]. For VLR patients with a life expectancy >20 years, the NCCN recommends the same treatment strategy as for LR patients. The criterion for VLR originated from a report by Epstein *et al*. [9] stating that three pathologic variables on needle biopsy were predictive of significant tumor: Gleason score 4 or 5, three or more core samples with tumor involvement, and any core with more than 50% tumor involvement [9]. Conversely, if these variables are negative, clinically insignificant cancer is likely.

In the present study, 45 patients were categorized as having VLR cancer. Of these 45 patients, five (11%) had pT3a (extraprostatic disease) cancer, 22 (49%) had a Gleason score ≥7, and eleven (24%) had positive surgical margins. More importantly, non-BCR for patients with VLR cancer was similar to those with LR cancer. Therefore, we initially thought that we should recommend similar treatment options for both patients with LR or VLR cancer. However, after incorporating the patient age, we found that patients with VLR cancer who were >65 years old had an excellent outcome of non-BCR compared to patients with VLR aged ≤65 years and patients with LR. Therefore, we agreed with the treatment strategy recommended by NCCN guidelines for patients with VLR and LR cancer. Patients aged >65 years old with VLR cancer are good candidates for active surveillance, while patients with VLR aged ≤65 year old or LR cancer would benefit from a treatment strategy including active surveillance and aggressive treatments.

Tosoian *et al*. identified 7333 patients with LR cancer and 153 patients with VLR cancer among patients who underwent RP at Johns Hopkins Hospital [17]. The frequency of Gleason score upgrade and non-organ confined cancer for those with VLR and LR were 21.8% and 23.1%, and 13.1% and 8.5%, respectively. Therefore, they concluded that men with VLR prostate cancer are appropriate for active surveillance. However, they failed to show the influence of the age. The ages (mean ± SD) for patients with VLR and LR cancer in their series were 53.8 ± 6.0 and 57.3 ± 6.4, respectively, so that the majority of patients was ≤65 years old. In the present study, patients ≤65 years old with VLR cancer had a similar pathological outcome and PSA recurrence to those with LR cancer.

Sundi *et al*. recently compared 87 African-American (AA) men with VLR cancer to 89 Caucasians with VLR cancer and found that AA men were more likely to have significant prostate cancer, a Gleason score ≥7 and tumor volume >0.5 cm^3 [18]. In addition, they found that dominant cancers in AA men were larger and more often anterior than in Caucasians. Therefore, they concluded that enhanced imaging or anterior zone biopsy sampling may detect more significant cancers. While we need to further explore our population to determine the location and size of dominant tumors, it is plausible that race may affect pathology outcomes in VLR and LR cancers.

Life expectancy is one of the most clinically significant issues in prostate cancer. NCCN guidelines recommend dividing patients with a life expectancy <20 and >20 years when deciding on treatment strategy. In general, older patients are more likely to have a worse pathology and prognostic outcome. In a series of 350 RP specimens, Kabalin *et al*. found that 75% of patients aged >70 years had a Gleason score of 4 and/or 5 compared with 62% of those 61 to 70 years old, 54% in the 51 to 60-year-old group, and 35% in those aged 41 to 50 years [20].

Sung *et al*. analyzed 210 men aged ≥70 years who underwent prostate biopsy, and found the cancer detection rate was significantly higher in patients aged ≥80 years than those <80 years. Further, cancer patients aged ≥80 years had a higher rate of poorly differentiated tumors and a larger proportion of high-stage tumors than patients aged <80 years old [21]. Obek *et al*. report a higher biochemical failure rate in 41 patients aged >70 years who underwent RP than in 460 patients aged ≤70 years old, as well as a shorter time until failure [22]. The results in the present study clearly indicate that patients >65 years old had an excellent pathology and prognostic outcome when they had a very early cancer at the initial diagnosis that fit within the criteria of the NCCN guidelines.

There are several possible limitations to the present study. First, the number of patients in the entire group studied was adequate, but the number of patients with VLR and LR cancer was smaller than desired. It may be necessary to expand these studies to include larger numbers of patients with VLR and LR. Second, the follow-up period for patients without PSA recurrence was 50 months, which was long enough to assess non-BCR at five years after a surgery. However, this length of time may not be long enough to draw conclusions about VLR and LR patients at ten or fifteen years after surgery. Third, based on pathology outcomes and non-BCR rates, we

reached several conclusions as to VLR and LR cancer. However, considering the long natural history of prostate cancer, outcomes after RP may not be fully representative of the entire population of patients with prostate cancer. We believe, however, that outcomes after RP are a very important source of information for counseling patients and family.

6. Conclusion

Our results support the treatment strategy of the NCCN that patients >65 years old with VLR cancer are good candidates for active surveillance. Active surveillance and aggressive treatments should provide for the remaining patients with VLR or LR cancer.

Financial Disclosures

None declared.

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