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Radical Prostatectomy in High-Risk Prostate Cancer Patients: Results of a Single-Institution Study

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Abstract:

Objective: To evaluate long-term outcomes of radical prostatectomy and bilateral pelvic lymph node dissection (RP) for high-risk prostate cancer (PC).

Material and Method: A retrospective review of high-risk PC patients who received RP, identified from medical records. We collected data from Songklanagarind Hospital, Prince of Songkla University from 2007 to 2015. The Kaplan-Meier method and Cox proportional regression models were used to analyze clinical recurrence (CR) and biochemical recurrence (BCR).

Results: In 79 patients, the median follow-up was 27.2 months. The 3-year and 5-year biochemical free survival in men with high-risk PC were 67.7% and 62.9% respectively. Multivariate analysis shows that pathologic stage 3a (hazard ratio=4.87; 95% confidence interval=1.01-23.38) was independently associated with cancer control.

Conclusion: Data support the belief that RP has a place in the treatment of high-risk PC. RP was a long-term cancer control in patients with high-risk PC. Only pathologic staging was independently associated with cancer control outcome.

Keywords: high risk, prostate cancer, radical prostatectomy, survival

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Introduction

Prostate cancer (PC) is a commonly diagnosed genitourinary cancer. The incidence in Thailand is 7.2/100,000 of population and the mortality is 3.7/100,000.[1] In Thailand, patients usually present with advanced stage PC when compared with the USA and Europe.[2] Radical prostatectomy and bilateral pelvic lymph node dissection (RP) is the standard treatment for clinically localized prostate cancer patients with a life expectancy of at least 10 yr.[3,4] The current role of RP in patients with high-risk disease or locally advanced PC (LAPC) remains controversial.[5] Although the optimal treatment approach for these patients remains uncertain, there is a tendency for patients who are healthy, younger, and have low-volume tumors to receive radical surgical treatment.[6] There is a paucity of data examining long-term outcomes of RP in high-risk and LAPC.

We used a longitudinal database of patients treated at Prince of Songkla University in order to describe the long-term outcomes after RP for high-risk prostate cancer.

The criteria defined high-risk PC using any of the following three parameters: Prostate specific antigen (PSA)>20 ng/ml, biopsy Gleason score: 8-10, clinical staging ≥T3a.[7,8]

Material and Method

Ethical approval for the study was obtained from the Institutional Review Board of Songklanagarind Hospital. We identified 183 patients who underwent RP. We focused on 79 patients with high-risk adenocarcinoma of the prostate treated between January 1, 2006 and December 31, 2015 at Songklanagarind Hospital, Prince of Songkla University.

Seventy-nine patients met all entry criteria. All data were obtained by reviewing each patient's history, imaging study, operative record, and discharge summary. Patient and disease characteristics, including age, clinical staging, Gleason score, initial PSA, margin status, post-operative PSA, time to biochemical recurrence (BCR) and pathologic staging, were reviewed.

Statistical analyses

Statistical analyses were carried out using the R software 3.2.2 (R Foundation for statistical computing, Vienna, Austria) and p-value<0.05 was considered to be statistically significant. Overall survival was estimated by the Kaplan-Meier method. The log-rank test was used to assess differences between groups. The Cox proportional hazards regression model was used to analyze independent predictors of BCR. Only the variables that were found to be significant in the univariate analyses (p-value<0.05) were entered into the multivariate analysis in order to determine the most significant factors for predicting disease outcome.

Results

Descriptive characteristics

Overall, 79 of 184 patients had complete data and met the inclusion criteria for the current analysis. Table 1 shows demographic and characteristic. Mean age at surgery was 67.7 years (standard deviation=6.1). The median follow-up time was 27.2 months (interquartile range (IQR) 13.9-48.2). The median PSA value was 30.3 ng/ml (IQR 20.9-41.4) with the majority of the patients (78.5%) having a PSA>20 ng/ml. Most patients (59.5%) were classified in the locally advanced prostate cancer group (tumor invaded through prostate capsule). Lymph node status negative and single node positive were 82.3% and 6.3% respectively. Pathologic results show negative margins in 33 (41.8%) of 79 patients. Waiting time for RP was 10 weeks (range 6.6 to 15.1).

Table 1 Baseline characteristics of 79 prostate cancer patients analysed in this study

Demographic	Value (79)
Age (year)	
Mean (S.D.)	67.7 (6.1)
Initial PSA (ng/mL)	
<10	9 (11.4)
10-20	8 (10.1)
>20	62 (78.5)
Median PSA	30.3 (20.9, 41.4)
Postoperative PSA 6 weeks	
Nadir	62 (78.5)
Not nadir	17 (21.5)
Time to BCR (months)	
Median	22.3 (8.4, 34.5)
Biopsy pathological Gleason score	
3+3	22 (27.8)
3+4	13 (16.5)
3+5	3 (3.8)
4+3	17 (21.5)
4+4	12 (15.2)
4+5	5 (6.3)
5+4	6 (7.6)
5+5	1 (1.3)
Final pathological Gleason score	
3+3	7 (8.9)
3+4	17 (21.5)
4+3	22 (27.8)
4+4	7 (8.9)
4+5	20 (25.3)
5+4	6 (7.6)
Pathologic staging	
pT2a	7 (8.9)
pT2b	7 (8.9)
pT2c	18 (22.8)
pT3a	15 (19)
pT3b	29 (36.7)
pT4a	2 (2.5)
pT4b	1 (1.3)
Surgical margin	
Free margin	33 (41.8)
Not free	46 (58.2)
Status lymph node	
No	65 (82.3)
N1	5 (6.3)
N2 (positive >1 node)	9 (11.4)
Waiting time median (weeks)	10 (6.7, 15.1)
Operative type	
RRP	51 (64.6)
LRP	27 (34.2)
LRP conversion to RRP	1 (1.3)
Adjuvant treatment	
NO	33 (42.9)
RT	18 (23.4)
ADT	22 (28.6)
Combination	4 (5.2)
Median follow-up time (months)	27.2 (13.9, 48.2)

S.D.=standard deviation, PSA=prostate specific antigen, BCR=biochemical recurrence, RRP=radical retropubic prostatectomy, LRP=laparoscopic radical prostatectomy, NO=no treatment, RT=tadiation therapy, ADT=androgen deprivation therapy

Cancer control outcomes and predictors of biochemical free survival outcomes

At 3-year and 5-year, the biochemical free survivals were 67.7% and 62.9% respectively show as Table 2. In univariable analysis, examining predictors of BCR were Gleason 5 pattern, high stage, and margin status. In contrast, the result of multivariable analysis, examining predictors of biochemical recurrence, only pathologic stage 3a (hazard ratio=4.87; 95% confidence interval=1.01-23.38) was independently associated with BCR show as Table 3.

Table 2 Shows biochemical recurrence-free survival

	3-year biochemical free survival (%)	5-year biochemical free survival (%)
High-risk PC	67.7	62.9

PC=prostate cancer

Table 3 Uni- and multivariate analyses of several pathological factors for predicting biochemical recurrence-free survival

	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Biopsy Gleason score						
3+3	1	ref.		-	-	
3+4	1.5	0.37-6.05	0.569	-	-	
4+3	3.21	0.86-12.02	0.084	-	-	
4+4	0.88	0.2-3.85	0.86	-	-	
G 5	4.81	1.14-20.25	0.032	-	-	
Margin status						
Free margin	1	ref.	0.034	1	ref.	0.402
Not free margin	2.72	1.08-6.86		1.67	0.5-5.52	
Patho Gleason score						
3+3	1	ref.		1	ref.	
3+4	2.22	0.33-14.8	0.409	0.97	0.12-7.85	0.977
4+3	0.94	0.14-6.2	0.947	0.53	0.06-4.33	0.552
4+4	6.25	0.61-63.54	0.121	2.97	0.25-35.12	0.388
G 5 pattern	6.79	1.06-43.36	0.043	2.79	0.32-24.03	0.35
Pathologic stage						
T2	1	ref.		1	ref.	
T3a	6.05	1.54-23.73	0.01	4.87	1.01-23.38	0.048
T3b	3.12	1.09-8.92	0.034	1.71	0.46-6.4	0.424
T4	4.4	0.36-54.37	0.248	3.31	0.15-73.2	0.449
Operative type						
RRP	1	ref.	0.207	1	ref.	0.383
LRP	1.83	0.71-4.71		1.71	0.51-5.65	
Lymph node status						
No	1	ref.		1	ref.	
N1	4.39	0.46-41.4	0.197	1.7	0.14-20.13	0.673
N2	1.37	0.34-5.57	0.659	0.76	0.13-4.43	0.764

OR=odd ratio, CI=confidence interval, RRP=radical retropubic prostatectomy, LRP=laparoscopic radical prostatectomy

Discussion

Historically, men with high-risk PC, especially if clinically advanced, were often managed with androgen-deprivation therapy (ADT) alone or external beam radiation therapy (EBRT), or both. At present, EBRT alone or combined with brachytherapy plus long-term (2–3 years) ADT and RP are the two main modalities for the primary treatment of high-risk PC.[9] Indeed, at the moment, lots of urologists face the dilemma of deciding which treatment is best, RP or radiation therapy with ADT.[10] It has become attractive for patients with high-risk PC, particularly younger men[11], to consider RP as an alternative option to EBRT combined with hormonal therapy.[12] In fact, there have been several studies showing favorable cancer control by RP in men with high-risk PC.[13-16]

In this research we aimed to study the surgical outcomes in high-risk PC and identify the risk factors for developing BCR. In Thailand, we do not have a policy for screening PC; thus, many cases present with advanced PC. In our series, patient groups were more advanced than in other studies.[17,18] Our baseline PSA and maximum PSA were 30.3 ng/mL and 200 ng/ml respectively. More than 50.0% of patients had locally advanced prostate cancer; however, postoperative PSA could reach to nadir 75.8%. The concern of increased perioperative morbidity and complications in LAPC treated with RP was not realized. Perioperative complications in the LAPC group parallel the outcomes of patients with cT2 disease.[19]

BCR free survival is the main outcome that is comparable with previous studies. Furukawa et al. reported 3- and 5- year BCR free survival rates of 68.4% and 60.1% respectively. In other series, such as Stewart et al,[14] 3-year recurrence-free survival rates ranging from 45.0% to 86.0% were reported. These outcomes are comparable with our findings. Data from the Memorial Sloan-Kettering Cancer Center and Mayo Clinic report that 10-year recurrence-free survival rates were 44.0% and 43.0%, respectively, for patients with T3 LAPC undergoing RP, showing that selected patients can be cured with surgery.[20]

In our series, high pathologic stage is the only independent predictive factor for progression free survival. In contrast, Ploussard et al. also reported that the Gleason score ≥8, pathological stage ≥pT3, positive SM, and lymph node involvement were independently associated with BR-free survival.[21] Patients who had pT3 and were node-negative with undetectable postoperative PSA may be offered two choices of treatment: immediate adjuvant radiation therapy (aRT) or initial biochemical monitoring, followed by early salvage radiation therapy (esRT) before PSA level exceeds 0.5 ng/ml.[22] In our institute, mostly we offer esRT for patients with unfavorable features. Fossati et al. reported no significant differences between aRT and esRT in terms of metastasis-free survival (MFS) and overall survival.[23] On the other hand, Abugharib et al. reported that esRt is not sufficient to preventing BCR and distal metastases. They mention that very early salvage radiotherapy (PSA 0.01-0.2 ng/mL) can prevent these.[24] There is discordance among radiation oncologists and urologists in the postoperative management of unfavorable patients. Radiation oncologists are more likely to offer aRT, whereas urologists prefer esRT.[25] Now-adays, we still look for level 1 evidence for post-operative management of high-risk patients.

Preoperative evaluation for patients with high-risk prostate cancer is important. Prostate magnetic resonance imaging (MRI) is the modality of choice for evaluating this patient group. MRI may show tumor extension into the bladder neck, rectum or urethral sphincter. This information may change preoperative decision making and planning in some cases. We strongly recommend preoperative prostate MRI before surgery.

There are several limitations in our study. First, it was a retrospective analysis and dependent on data that may affect the accuracy of the results. Second, the

sample size was relatively small, and there were few outcomes on which to base statistical analysis. We believe these data could be useful in determining the best treatment strategy for predicting patients who are likely to benefit from RP.

Conclusion

In summary, the treatment of LAPC varies widely. Surgery of LAPC provides accurate pathologic staging to assist with an individualized approach to secondary therapies. RP as monotherapy is not standard treatment in the high-risk group. This group of patients should be treated with combination therapy. RP conferred long-term cancer control in men with high-risk PC. Pathologic staging was independently associated with poorer cancer control.

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