RESEARCH ARTICLE

The Prognostic Factors of Biochemical Recurrence-Free Survival Following Radical Prostatectomy

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Abstract

Objective: To evaluate outcomes, biochemical recurrence-free survival (BCRFS) and to identify parameters influencing BCRFS of radical prostatectomy (RP) and bilateral pelvic lymph node dissection in a single-institution. **Methods:** A retrospective review of prostate cancer (PC) patients received RP was identified from the medical records. Data was collected from 2007 to 2016. 178 patients received RP were enrolled in a study. These patients were evaluated on efficacy of RP by using prostate-specific antigen (PSA) to analyze BCRFS and compared with Gleason score, pathologic staging, margin status and lymph node status with BCRFS. **Results:** The median follow up was 32.5 months (n = 178). Sixty-nine patients had extracapsular extension on pathologic results whereas 93 patients were classified as a high risk group. The median time for biochemical recurrence (BCR) was 22.3 months. The 3-year BCRFS in patients with a Gleason score 6, 3+4, 4+3, 8 and 9-10 were 85.8%, 84.6%, 78.7%, 53.3% and 35.8% . Multivariate analysis showed that extracapsular extension was independently associated with BCRFS. **Conclusions:** New group grading system indicates impact on BCRFS on univariate analysis but show negative impact on a multivariate Cox regression, only pathologic staging was independently associated with the cancer control outcome.

Keywords: Radical prostatectomy- biochemical recurrence-free survival- group-grading system

Introduction

Prostate cancer (PC) is commonly diagnosed as genitourinary cancer in people aged over 50 years. In the United States with 3.3 million men suffered from PC. In 2016, approximately 180,900 cases were diagnosed with PC (Miller et al., 2016). The incidence in Thailand is 7.2/100,000 of a population with a mortality rate 3.7/100,000 (Lojanapiwat, 2015). Although no screening program is observed in the country, hospital base PSA screening leads to an increase in the numbers of candidates for radical prostatectomies (RP) (De Carlo et al., 2014). RP remains the recommended curative treatment for patients with clinically localized prostate cancer (cT1– cT2) and is associated with a survival advantage when compared to watchful waiting (Ryu et al., 2016; Bill-Axelson et al., 2014). RP has been shown to provide excellent local control, accurately stage the disease resulting in a possibility to identify potential patient who will suffer from biochemical recurrence (BCR) and initiate adjuvant treatment within an optimal time frame (Furakawa et al., 2015). Subsequently short to long term oncologic outcomes, including biochemical recurrence-free survival, cancer-specific survival (CSS) and overall survival (OS) were reported from larger cohorts (Mortezavi et al., 2016).

However, the oncologic safety of RP has yet to be fully elucidated in developing countries.

We used a longitudinal database of patients, treated at Prince of Songkla University, in order to describe the outcomes after RP for prostate cancer. The aims of this study were to evaluate the postoperative oncological outcomes and identify parameters influencing biochemical recurrence-free survival (BCRFS) of RP in our institution.

Materials and Methods

Patients and Methods

Ethical approval for the study was obtained from the Institutional Review Board of Songklanagarind Hospital. The medical records of all PC patients treated with RP were reviewed. From the records, we identified 203 patients underwent RP. We focused on 178 patients with adenocarcinoma of a prostate whose bone scan negatively treated between the periods between January the 1st , 2004 and July the 31st, 2016 in Songklanagarind Hospital, Prince of Songkla University. BCR was defined by two consecutive rising PSA values >0.2 ng/ml (Cornford et al.,2017). We classified the risk group as a D'Amico risk classification.

One hundred and seventy-eight patients met all entry

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criteria. All data were obtained by reviewing each patient's history, imaging studies, operative record and discharge summaries. Patient and disease characteristics, including; age, clinical staging, Gleason score, initial prostate specific antigen (PSA), margin status, postoperative PSA, time to biochemical recurrence and pathologic staging were reviewed.

Statistical Analyses

Statistical analyses were carried out using 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 the groups. The Cox proportional hazards regression model was used to analyze independent predictors of BCRFS. Only 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 the disease outcomes.

Results

Descriptive characteristics

Overall, 178 of 203 patients completed data and met the inclusion criteria for the current analysis. (Table 1 shows demographic and characteristic data.) Mean age at surgery was 68.2 years (S.D. = 5.9). The median for follow-up time was 32.5 months (range 13.6 to 51.4). The median PSA value was 23.766 ng/ml (range 0.4 to 205) with the majority of the patients (40.4%) having a PSA > 20 ng/ml.

Ninety-three patients (52.24%) were classified into the high risk prostate cancer group. More than 50% of these patients had a low Gleason score (6, 3+4) on their pathologic results. One hundred and nine patients (61.2%) were classified as having an organ confined disease on final pathologic report. On pathologic result, 4 patients (2.3%) were pathologically at stage 4. Both negative and single node positive Lymph node status were 89.3% and 3.9%, respectively. Pathologic results showed negative margins
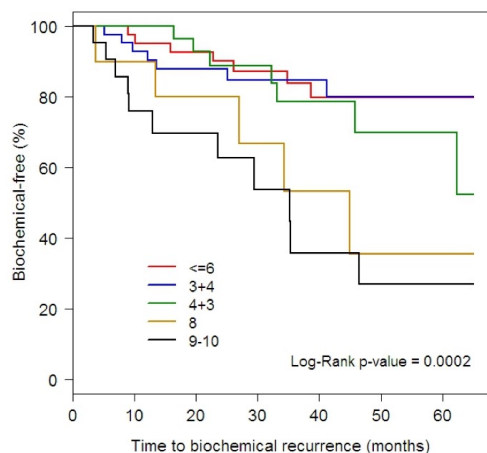

Figure 1. Biochemical Recurrence Free Survival (Pathologic Gleason Sum)

Table 1. Baseline Characteristic Data

Demographic	Value (178)
Age (yr) mean (SD)	68.2 (5.9)
initial PSA (ng/mL) (%)	
<10	54 (30.3)
10-20	52 (29.2)
>20	72 (40.4)
Mean PSA	23.766 (0.4,205)
Median time follow up (month)	32.5 (13.6,51.4)
Postoperative PSA 6 weeks	
nadir	150 (84.2)
not nadir	28 (15.8)
Time to BCR (months) median	22.3 (9.7,34.3)
final patho G(%)	
3+3	45 (25.3)
3+4	47 (26.4)
3+5	1 (0.6)
4+3	41 (23)
4+4	11 (6.2)
4+5	24 (13.5)
5+4	9 (5.1)
Five-group grading	
≤6	45 (25.3)
3+4	47 (26.4)
4+3	41 (23)
8	12 (6.7)
9-10	33 (18.5)
Pathologic staging	
pT2a	26 (14.6)
pT2b	16 (9)
pT2c	67 (37.6)
pT3a	26 (14.6)
pT3b	39 (21.9)
pT4	4 (2.3)
Positive surgical margin	
free margin	102 (57.3)
not free	76 (42.7)
status lymph node	
No	159 (89.4)
N1	7 (3.9)
N2 (positive >1 node)	12 (6.7)
waiting time (wks)	11.4 (7.9,17.2)
Operative type	
RRP	99 (55.6)
LRP	76 (42.7)
LRP conversion to RRP	3 (1.7)

(57.3%; 102 out of 178 patients). One hundred and fifty patients (84.2%) with PSA post-operative reached nadir in 6 weeks. Waiting time for RP was 11.4 weeks (range 7.9 to 17.2).

Table 2. Biochemical Recurrence-Free Survival Data

Gleason BCRFS (%)	6	3+4	4+3	8	9-10	Overall (178)
1 years	95.1	92.8	100	90	75.9	92.5
3 years	85.8	84.6	78.7	53.3	35.8	74.1
5 years	79.8	79.9	69.9	35.6	26.8	67.9

Cancer control outcomes and predictors of biochemical free survival outcomes

At 1-year, 3-years and 5-years, the overall BCRFS were 92.5%, 74.1% and 67.9%, respectively. A five-grade group BCRFS is shown in Table 2 and Figure 1. Univariable analysis displaying the examining predictors of BCRFS were a high Gleason score, high stage lymph node status and margin status. However, the result of the multivariable analysis demonstrated that the examining predictors of biochemical recurrence were pathologically only at stage 3a and 3b (hazard ratio [HR], 8.45; 95% CI, 1.74-40.9 and 7.12, 1.48-34.28) suggesting the independent association with BCR (Table 3).

Discussion

From this study, BCRFS is the main outcome similar to previous studies. Furukawa et al. reported that 3-, and the 5- years BCRFS rates were 68.4% and 60.1%, respectively. In addition, Stewart et al. showed that the 3-year recurrence-free survival rates ranged from 45% to 86% in consistent with our findings. Data from the Memorial Sloan-Kettering Cancer Center along with the Mayo clinic indicated that 10-year recurrence-free rates for patients with T3 LAPC undergoing RP were 44% and 43%, respectively, suggesting that the certain selected patients can be cured or BCRFS may be prolonged with surgery (Kaushik et al., 2016; Lowrance et al., 2011).

Previous studies have reported that the preoperative PSA, a positive surgical margin, pathological stage and other factors are predictors of BCRFS (Negishi et al., 2017). Ploussard et al., (2011) reported that pre-operative criteria of high-risk PC was independently associated with BCRFS. The PSA failure risk was increased by 1.5 and 2.8 fold with 2 and 3 criteria, respectively. Hruza et al., (2012) also reported that only the Gleason score and pT had significant impact on BCRFS. Takeuchi et al., (2017) described that in pre-prostate specific antigen doubling time (PSADT) more than 24 months have lower rate of PSA recurrence following the surgery. In our study, high pathologic stage is the only independent predictive factor for progression free survival.

Currently, Thailand does not have an established policy for screening PC. Thus, many cases presented with advanced PC. In our studies, patient groups were more advanced than in other studies (Roiss et al., 2014; Novara et al., 2012; Gnanapragasam et al., 2016). Baseline PSA as well as maximum PSA were 23.76 ng/mL and 205.12 ng/ml, respectively. Nearly 40% of the patients had locally advanced prostate cancer on their pathologic

Table 3. Uni- and Multivariate Analyses of Several Pathological Factors for Predicting Biochemical Recurrence-Free Survival

	Univariate		multivariate		
variation	OR	CI 95%	OR	CI 95%	p-valve
patho gleason score					
6	1	ref.	1	ref.	
3+4	1.2	0.46-3.14	0.72	0.25-2.12	0.555
4+3	1.69	0.64-4.42	0.86	0.29-2.59	0.788
8	4.9	1.28-18.82	2.34	0.53-10.4	0.264
9-10	8.05	2.9-22.38	2.64	0.77-9.05	0.123
pathologic stage					
T2a	1	ref.	1	ref.	
T2b	1.77	0.31-10.07	2.12	0.33-13.53	0.426
T2c	2.66	0.71-9.99	2.7	0.68-10.71	0.158
T3a	10.45	2.49-43.81	8.45	1.74-40.9	0.008
T3b	12.27	3.13-48.04	7.12	1.48-34.28	0.014
T4	23	1.77-298.44	13.73	0.84-224.99	0.066
Margin status					
Free	1	ref.	1	ref.	
not free	2.57	1.37-4.82	1.08	0.49-2.39	
Lymph node status					
N0	1	ref.	1	ref.	
N1	5.1	0.96-27.15	1.45	0.23-9.07	0.691
N2	4.08	1.17-14.16	1.63	0.39-6.83	0.501

reports. However, overall postoperative PSA could reach to nadir 84.2%. In the group of PSA > 20 ng/mL patients, 36 patients (50%) received RP had PSA nadir. For patients with intermediate to high risk diseases, the acceptable period for treatment should not exceed 3 months if the delay might result in an unfavourable affect (Van den Bergh et al., 2013). Our data showed that the waiting time for RP was 11.4 weeks indicating the border line which may ultimately affect the surgical outcome.

Although positive lymph node patient is the most aggressive condition after RP. There is currently no consensus on the optimal timing for androgen deprivation therapy (ADT). Recent evidences showed that early ADT may improve survival and delays disease progression (Messing et al., 1999; Kunath et al., 2013). Even though patients had positive lymph nodes on their final pathologic results, we prolonged the post-operative PSA to 6 weeks before determining the surgical outcome defined by our policy after RP. If PSA is able to reach to nadir, we closed follow up patients without ADT. However, patients whose PSA were unable to reach to nadir, we began the ADT immediately. Patients having pT3 and 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 exceeding 0.5 ng/ml (Mohler et al., 2016). At our unit, we mostly offer esRT for patients with unfavorable features. Fossati et al., (2017) reported no significant differences between aRT and esRT in term of metastasis-free survival (MFS) and overall survival (OS). On the

other hand, Abugharib et al., (2017) reported that esRt is not sufficient for prevention of BCR and distal metastases. They described that in very early salvage radiotherapy (PSA 0.01-0.2 ng/mL) can prevent even these. There is discord among radiation oncologist and urologist in postoperative management of unfavorable patients. Most radiation oncologists are more likely to offer aRT whereas urologists prefer esRT (Kishan et al., 2017). Nowadays, we still look forward for level I evidence for post-operative management for high risk patients.

Epstein et al., (2016) classified a new PC grading system that is potentially more accurate in grade stratification and reflects prognosis more than the current systems (Pierorazio et al., 2013). In our study, analyses were based on the new Gleason grade grouping demonstrating that the results are comparable with the original article. Our data is beneficial for further meta-analysis study.

There are several limitations in our study. First, our retrospective analysis resulted in data dependent which may affect the accuracy of the results. Second, the sample size was relatively small, thus a few outcome was observed. We believe these data could be useful in determining the best treatment strategy for predicting patients likely to benefit from RP.

In conclusion, the new group grading system showed impact on BCRFS by univariate analysis, however, showed negative impact on a multivariate Cox regression. Only pathologic staging was independently associated with the cancer control outcome.

Acknowledgments

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