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Comparison of biochemical recurrence in prostate cancer patients treated with radical prostatectomy or radiotherapy

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Purpose: We evaluated the biochemical recurrence (BCR) of prostate cancer patients treated by radical prostatectomy (RP) or radiotherapy (RT).

Materials and Methods: Patients who underwent RP or RT as primary definitive treatment from 2007 were enrolled for this study. They were divided into two groups; the low-intermediate risk group and the high risk group according to the National Comprehensive Cancer Network guidelines. We compared differences such as age, prostate specific antigen, Gleason score, follow-up duration, clinical T staging, and BCR. Their BCR-free survival rates were analyzed.

Results: A total of 165 patients were enrolled. There were 115 patients in the low-intermediate risk. Among them, 88 received RP and 27 underwent RT. BCR occurred in 9 of the RP patients (10.2%) and 3 of the RT patients (11.1%). For the high risk group, 50 patients were included. RP was performed in 25 patients and RT in 25 patients. BCR was observed in 4 of the RP patients (16%) and 12 of the RT patients (48%). There were no differences in BCR-free survival for the low-intermediate group (p=0.765). For the high risk group, the RP group had a higher BCR free survival rate (p=0.032).

Conclusions: No difference of BCR and BCR-free survival was seen in the low-intermediate risk group but lower BCR and better BCR-free survival were observed for patients that received RP in the high risk group. RP should be a more strongly considered option when deciding the treatment method for selected high risk patients.

Keywords: Prostatic neoplasms; Prostatectomy; Radiotherapy; Recurrence

INTRODUCTION

Prostate cancer (PCa) is one of the most commonly diagnosed malignancies in men and accounts for a major proportion in cancer deaths [1]. Though known to be more prevalent in Western countries, migrant population data show lifestyle and environment to be contributing risk factors [2,3]. With westernized behavior changes, an increase in occurrence of PCa can be expected from the Asian population. The use of prostate-specific antigen (PSA) screening has also added to increase of localized PCa diagnosis [4]. This overall increase in PCa has resulted in a patient pool that is now more enthusiastic and willing to participate in their treatment. They demand for an

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urologist that can counsel them in deciding which modality of treatment best suits their desires, both in cancer free survival and post-treatment side effects [5].

In order to choose the most appropriate method of treatment, patients are stratified by clinical staging, PSA and pathology results into risk groups, and options such as radical prostatectomy (RP) or radiotherapy (RT) are recommended accordingly [6]. Several retrospective studies exist comparing the results of these treatment options. General consensus shows no significant difference in biochemical recurrence (BCR) free survival between RP and RT [7]. However, a few studies comment on the advantages of RP, especially in patient with lower risk and lower tumor volume [8,9]. These results show that choosing the best treatment method still remains a difficult problem and research on long term outcome is needed.

Most of the studies mentioned above were conducted in Europe and the United States, and there are few reports that evaluate long-term outcome differences between RP and RT patients in Korea [10]. Further data is needed for a more conclusive statement on this subject, especially in the Korean population. We conducted this study to evaluate the BCR-free survival between primary treatment modalities, RP and RT, in Korean patients. Both high and low risk patients were included in our study for a wider perspective in comparing of the treatment methods.

MATERIALS AND METHODS

1. Patient selection

After gaining approval of our Institutional Review Board (KMC IRB no. 1526-10), we reviewed retrospectively the medical charts of patients who had been treated for PCa at a single medical center (Kyung Hee University Medical Center). The patients who had under gone either RP or RT as primary definitive treatment from 2007 were enrolled for this study. The decision for the choice of therapy was decided by mutual consent between the physician and the patient after thorough counseling. RP patients underwent either open radical retropubic prostatectomy, laparoscopic RP or robot-assisted laparoscopic RP with or without bilateral pelvic lymph node dissection. RT patients underwent high dose definitive RT or tomotherapy. Patients who had received androgen deprivation therapy (ADT), or followed up for less than 2 years were excluded from this study.

2. Definition of low, intermediate, and high risk groups

The treatment modality, age, PSA, biopsy Gleason scores, and clinical staging of the patients were evaluated and they were divided into two groups; the low-intermediate risk group and the high risk group according to the National Comprehensive Cancer Network (NCCN) guidelines [11]. The risk groups defined by the NCCN guidelines are as follows; low risk group patients were defined as T1–T2a, Gleason score≤6, and PSA<10 ng/mL; intermediate risk groups were defined as T2b–T2c or Gleason score 7 or PSA 10–20 ng/mL; high risk groups were defined as T3a or Gleason score 8–10 or PSA>20 ng/mL.

3. Definition of BCR

The definition for BCR for RP patients was a PSA of ≥0.2 ng/mL followed by a repeat measurement higher than 0.2 ng/mL or the initiation of salvage treatment [12]. The definition of BCR for RT patients was nadir + 2 ng/mL or the initiation of ADT [13].

4. Statistical analysis

We compared differences between the RP patients and RT patients separately for both risk groups using Student t-test and chi-square test. The BCR free survival was analyzed using the Kaplan-Meier graph. All statistical analyses were performed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) and statistical significance was achieved with a p-value<0.05.

RESULTS

1. Patient characteristics

A total of 165 patients were included in this study. According to their treatment modality, 113 patients were placed in the RP group and the remaining 52 were included into the RT group. The mean age was 66.27±6.76 years, mean PSA was 11.31±11.51 ng/mL, and mean duration of follow-up was 37.19±20.49 months. Stage T1 or T2a was seen in 101 patients (61.2%), stage T2b or T2c in 33 patients (20%), stage T3a in 15 patients (9.1%) and stage T3b in 16 patients (9.7%). For Gleason scores, 3+3 was seen in 89 patients (53.9%), 3+4 in 36 patients (21.8%), 4+3 in 18 patients (10.9%), 8 in 12 patients (7.3%), and 9 or 10 in 10 patients (6.1%). BCR occurred in 28 of the patients (17%) (Table 1).

1) Low-intermediate risk group

From the initial 165 patients, 115 patients were placed in the low-intermediate risk group. There were 88 patients in the RP group and 27 in the RT group. The RP group patients were younger (64.57±6.69 years vs. 71.26±4.99 years, p<0.05), had lower PSA levels (6.58±3.08 ng/mL vs. 8.81±3.49

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ng/mL, p=0.002) and shorter follow-up duration (38.16±18.21 months vs. 51.52±23.89 months, p=0.011). There was no statistical difference in clinical T stage, or Gleason scores between the 2 groups (Table 2).

2) High risk group

A total of 50 patients were placed into the high risk group. Among them, 25 patients were included in the RP group and 25 patients in the RT group. There was no statistical difference in age (65.80±6.42 years vs. 67.36±6.45 years, p=0.395) or duration of follow-up (28.48±15.61 months vs. 27.04±19.55 months, p=0.775), but PSA levels were significantly higher for the RT group (13.04±11.43 ng/mL vs. 28.95±17.62 ng/mL, p<0.05). Both the T stage and Gleason scores were statistically higher for the RT group (p<0.05) (Table 3).

Table 1. Summary of patient characteristics (n=165)

Characteristic	Value
Age (y)	66.27±6.76
Prostate-specific antigen (ng/mL)	11.31±11.51
Follow-up duration or time until BCR (mo)	37.19±20.49
T stage	
T1, T2a	101 (61.2)
T2b, T2c	33 (20.0)
T3a	15 (9.1)
T3b	16 (9.7)
Gleason score	
3+3	89 (53.9)
3+4	36 (21.8)
4+3	18 (10.9)
8	12 (7.3)
9, 10	10 (6.1)
Biochemical recurrence	
Yes	28 (17.0)
No	137 (83.0)

Values are presented as mean±standard deviation or number (%).
BCR, biochemical recurrence.

2. Biochemical recurrence

1) Low intermediate risk group

BCR occurred in 9 of the patients (10.2%) from the RP group and 3 (11.1%) from the RT group, but no statistical difference was seen (p=0.895). The 5-year BCR free survival rate was 82.2% for the RP group and 86.6% for the RT group. There was no difference in BCR free survival between the two groups (log-rank test p=0.765) (Fig. 1).

2) High risk group

BCR was observed in 4 patients (16.0%) from the RP group and 12 patients (48.0%) from the RT group, showing a statistically higher recurrence rate for the RT group (p=0.015). The 5-year BCR free survival rate was also significantly different; 74.2% for the RP group and 27.7% for the RT group (log-rank test p=0.032) (Fig. 2).

DISCUSSION

This study was conducted in order to analyze the difference of BCR between patients either undergoing RP

Table 2. Summary of patient characteristics of the low-intermediate risk group

Characteristic	Total	RP (n=88)	RT (n=27)	p-value
Age (y)		64.57±6.69	71.26±4.99	0.000[a]
Prostate-specific antigen (ng/mL)		6.58±3.08	8.81±3.49	0.002[a]
Follow-up duration or time until BCR (mo)		38.16±18.21	51.52±23.89	0.011[a]
T stage				0.741[b]
T1, T2a	92 (80.0)	71 (80.7)	21 (77.8)	
T2b, T2c	23 (20.0)	17 (19.3)	6 (22.2)	
Gleason score				0.116[b]
3+3	78 (67.8)	64 (72.7)	14 (51.9)	
3+4	27 (23.5)	18 (20.5)	9 (33.3)	
4+3	10 (8.7)	6 (6.8)	4 (14.8)	
Biochemical recurrence				0.895[b]
Yes	12 (10.4)	9 (10.2)	3 (11.1)	
No	103 (89.6)	79 (89.8)	24 (88.9)	

Values are presented as mean±standard deviation or number (%).
RP, radical prostatectomy; RT, radiotherapy; BCR, biochemical recurrence.
[a]:Continuous variables were analyzed using the Student t-test. [b]:Categorical variables were analyzed using the Pearson chi-square and Fisher exact test.

Table 3. Summary of patient characteristics of the high risk group

Characteristic	Total	RP (n=25)	RT (n=25)	p-value
Age (y)		65.80±6.42	67.36±6.45	0.395[a]
Prostate-specific antigen (ng/mL)		13.04±11.43	28.95±17.62	0.000[a]
Follow-up duration or time until BCR (mo)		28.48±15.61	27.04±19.55	0.775[a]
T-stage				0.022[b]
T1, T2a	9 (18.0)	5 (20.0)	4 (16.0)	
T2b, T2c	10 (20.0)	7 (28.0)	3 (12.0)	
T3a	15 (30.0)	10 (40.0)	5 (20.0)	
T3b	16 (32.0)	3 (12.0)	13 (52.0)	
Gleason score				0.004[b]
3+3	11 (22.0)	6 (24.0)	5 (20.0)	
3+4	9 (18.0)	0 (0)	9 (36.0)	
4+3	8 (16.0)	5 (20.0)	3 (12.0)	
8	12 (24.0)	10 (40.0)	2 (8.0)	
9, 10	10 (20.0)	4 (16.0)	6 (24.0)	
Biochemical recurrence				0.015[b]
Yes	16 (32.0)	4 (16.0)	12 (48.0)	
No	34 (68.0)	21 (84.0)	13 (52.0)	

Values are presented as mean±standard deviation or number (%).
RP, radical prostatectomy; RT, radiotherapy; BCR, biochemical recurrence.
[a]:Continuous variables were analyzed using the Student t-test. [b]:Categorical variables were analyzed using the Pearson chi-square and Fisher exact test.

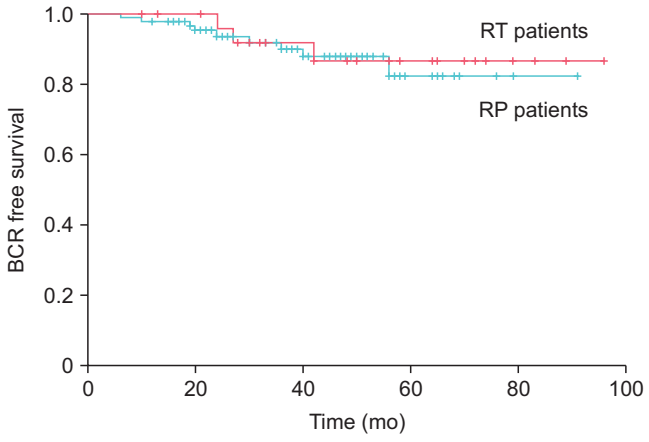

Fig. 1. Kaplan-Meier curve of BCR-free survival between RP and RT patients in low-intermediate risk patients (p=0.765). BCR, biochemical recurrence; RP, radical prostatectomy; RT, radiotherapy.

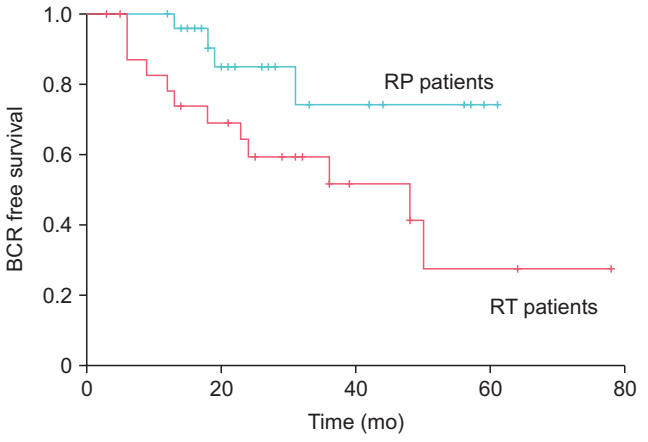

Fig. 2. Kaplan-Meier curve of BCR-free survival between RP and RT patients in high risk patients (p=0.032). BCR, biochemical recurrence; RP, radical prostatectomy; RT, radiotherapy.

or RT in a Korean population. First of all, our study showed that there were no significant differences in BCR free survival of the low-intermediate risk group. According to the European Association of Urology (EAU) guidelines for PCa, in low and intermediate risk patients, RP is recommended for patients with a life expectancy >10 years. External bean RT is offered to all risk groups of non-metastatic PCa [6]. Studies comparing the different outcomes of treatment in low-intermediate risk PCa show diverse results. Potters et al. [14] reported that the 7-year BCR free survival rates for permanent prostate brachytherapy versus external beam RT versus RP were 74%, 77%, and 79%, respectively, showing no difference in BCR failure rates for all three modalities. However, results from the Prostate Cancer Results Study group show superior BCR-free survival for brachytherapy in low risk disease [15]. Therefore, when choosing the optimal treatment choice in low risk patients, all modalities (surgery or radiotherapy) should be considered and offered to the patient during consultation.

For the high risk group, the RP group had a statistically

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higher BCR free rate. Considering the higher PSA, T staging, and Gleason score of the RT group, the patients were relatively of higher risk compared to the RP group, and therefore probably had more chance of recurrence. Several studies agree with our results on the superiority of RP in high grade PCa patients. A review article with meta-analysis on RP or RT in high risk PCa patients by Petrelli et al. [16] reported RP was associated with improved overall survival, PCa specific mortality, and non-PCa specific mortality compared with RT. However, BCR-free survival rates were similar to those of RT. Another article on this subject by Borza and Kibel [17] commented that despite the lack of a randomized data comparing RP and RT, RP demonstrated better survival benefits than RT in many studies. Even when there was no statistical difference in overall survival between RP and RT groups, many authors commented on the advantages of RP in high risk PCa patients. Klein et al. [18] reported in their paper that there was no difference in BCR free survival between RP, external bean RT and brachytherapy. They also pointed out the advantages of RP, such as detailed pathology analysis, and the downside of radiation based therapies such as understaging, undergrading, and higher late local failure rate. A different result was given by Schreiber et al. [19] who analyzed patients undergoing radical retropubic prostatectomy with or without salvage radiation against RT with or without androgen deprivation. Both groups showed equivalent distant metastatic-free survival and PCa-specific survival. But biochemical control rates appeared to be equivalent or better in those receiving RT. The EAU guidelines recommend RP for high risk patients in selected locally advanced cT3a with the emphasis of a multimodality setting. RT is recommended given in combination with long term ADT [6].

The data presented above agrees with our results, and adds strength to the position of RP in the treatment of high risk patients. Kang et al. [20] commented on the role of RP in high risk PCa patients with positive remarks that the RP with extended pelvic lymphadenectomy delivers good cancer-related outcomes in high- and very-high-risk PCa. However, RT is chosen more often in the high risk group due to older age, higher PSA, and economical reasons [21,22]. Considering the BCR free survival benefits that RP may offer, surgery should not be easily discarded and should be recommended if the patient is in an operable state.

A study by Lee et al. [10] reported a similar study to ours. They compared the cancer specific mortality of RP and RT in clinically localized high risk patients of Korean population. Their results also show that the 5-year estimates of cancer-specific survival rates for men treated with RP were higher than RT patients (96.5% vs. 88.3%) with statistically increased cumulative incidences estimates for the RT group was also seen. In our study, we focused on the BCR-free survival of RT and RP groups. We also included lower risk patients to our study for a more comprehensive view on this subject.

There were a few limitations in our study. First of all, this was a retrospective study conducted with patients from a single institution. This limited our study in the size of the initial patient pool and we were not able to randomize our patients, causing decrease in the strength of our statistical results. Considering the limitation of retrospective studies and a small patient pool, a larger scale prospective randomized controlled study will be needed. Second, we limited the treatment modalities of the patients, to the first definitive RT or RP. In doing so, we excluded RP patients who had margin positive pathology reports because they received concurrent adjuvant ADT or RT and therefore interfere in comparing the differences of BCR-free survival after primary treatment. By removing patients from the high risk groups there is the risk of selection bias and could have confounded our data. However this was necessary in order to compare the differences of the primary treatment modalities and the fact that this was a retrospective study also limits the power of our data. Combined ADT or salvage RT was not considered in this study and will need to be looked into in future studies. Third, stratification using the NCCN guidelines could have caused overgrading in some patients. Patients presenting with only high PSA levels while showing low T staging and low Gleason scores could have confounded the data by being placed in the high risk group. Spahn et al. [23] reported that high PSA patients have varying risk levels. In patients with only PSA>20 ng/mL, 33% had pT2 PCa, 57.9% had Gleason scores<7, 54% had negative surgical margins, and 85% were lymph node negative, causing undergrading and consequent elevation in biochemical survival.

Despite these limitations, our study gives ground that RP should be considered as favorable treatment option for selected high risk group patients. Compared to prior studies our data covered all risk groups of PCa in the Korean population. No difference in the low-intermediate group emphasizes that diverse treatment options can be selected for lower risk groups and therefore more consideration on the quality of the patient life after treatment should be done. We add strength to prior studies agreeing with the superiority of RP in treatment of high risk PCa. However limitations in our data suggest caution before approving

of RP in these patients. Selected high risk patients, such as those overgraded due to high Gleason score or patients with low level PSA, are likely candidates to profit from RP and should be counseled on the benefits of surgery. Future prospective studies will be needed to further strengthen our conclusions.

CONCLUSIONS

There is no difference BCR free survival rates between RP and RT in low-intermediate risk groups. However, for high risk group patients, RP has shown superior BCR-free survival rates. Though many patients of the high risk group are undergoing RT due to multiple reasons, RP should not be so easily discarded from the choices of treatment and when plausible, be more actively recommended in selected high risk patients. Future randomized controlled studies will be aid in supporting these results.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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