Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Factors affecting biochemical recurrence time in prostate cancer patients: A single center analysis

Sedef Gokhan Acikgoz[a,*], Ipek Pinar Aral[b], Huseyin Furkan Ozturk[c], Suheyla Aytac Arslan[c], Havva Beyaz[a], Gonca Altinisik Inan[c], Yilmaz Tezcan[c]

[a] *Ankara City Hospital, Clinic of Radiation Oncology, Ankara, Türkiye*
[b] *Hacettepe University, Faculty of Medicine, Department of Radiation Oncology, Ankara, Türkiye*
[c] *Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of Radiation Oncology, Ankara, Türkiye*

ARTICLE INFO

Keywords:
Prostate cancer
Salvage radiotherapy
Biochemical recurrence

Received: Feb 09, 2022
Accepted: Sep 02, 2022
Available Online: 27.09.2022

DOI:
10.5455/annalsmedres.2022.02.047

Abstract

Aim: In this study, patients who underwent salvage Radiotherapy (RT) after biochemical recurrence (BCR) were evaluated retrospectively. The aim of this study was to evaluate the factors affecting the time to biochemical recurrence and salvage RT after radical prostatectomy.

Materials and Methods: In Ankara Atatürk Education Hospital, patients with prostate cancer who received salvage RT between 01.01.2011 and 01.01.2018 were analyzed retrospectively. Patients who had undergone radical prostatectomy for prostate adenocarcinoma, and received salvage RT for PSA (Prostate-specific antigen) recurrence, were included. Patients who received post-surgery hormone therapy, and received definitive or palliative RT, were excluded. SPSS Ver. 22 software package was used for statistical analysis and the statistical significance limit was accepted as $p \leq 0.05$.

Results: Results of 84 patients who met the criteria of the study were analyzed. The median follow-up was 78.5 (range 28-172) months and the median time between surgery and RT was 23.7 (range 5.1-136.9) months. The relationship between the time from surgery to BCR and the Gleason Score (GS) was statistically significant; the median time was 16.3 (2.17-125.9) months in the group with GS $\leq$8, and 8.9 (2.8-20.3) months in the group with GS 9-10 ($p=0.05$). The relationship between the time from surgery to BCR and Tumor (T) stage was statistically significant. In subgroup analysis, this difference was seen between T3A and T3B stages. That time was 17.8 (range 2.17-73.77) months in T3A and 8.7 (range 2.8-29.6) months in T3B stages ($p=0.02$). The relationship between the level of nadir PSA and the median time between surgery and BCR was significant. It was median 20.6 (range 5.4-65.2) months in patients with PSA$<$ 0.03 and 8.8 (range 2.2-125.9) months in patients with PSA $\geq$0.03 ($p<0.0001$).

Conclusion: BCR time is shorter in patients with high GS, advanced T stage, and high postoperative PSA nadir.

Introduction

Prostate cancer (PC) is the most common extracutaneous cancer in men worldwide, according to GLOBACON 2020 data; its incidence is 1,414,259 and 375,304 people died due to prostate cancer [1]. The main treatments are radical prostatectomy, radiotherapy (RT), and hormonal therapy (HT) [2,3]. In the evaluation of the patients diagnosed with prostate cancer in terms of treatment rates; Radiotherapy (RT) is applied to 55% of patients, and radical prostatectomy (RP) to 40% of patients [4]. The rate of biochemical recurrence (BCR) in the 10-year follow-up of patients who underwent RP, is 20-40% [5]. Local salvage radiotherapy (SRT) is the most commonly used treatment option for BCR after RP [6].

The risk of BCR can be affected by different factors such as Gleason score (GS), PSA (Prostate-specific antigen) doubling time (PSA-DT), clinical stage, and surgical margin (SM) status. In many studies, it has been shown that risk factors such as advanced stage (pT3-4), GS 8-10, and SM positivity increase the risk of BCR [7]. Individualized treatments have emerged in patients with BCR, and clinicians have proposed different PSA cut-off levels to define BCR. Thus, it was aimed to intervene at the most appropriate time to achieve the best oncological results [8].

In this study, prostate cancer patients receiving salvage RT

*Corresponding author:
Email address: drsedeff@gmail.com (Sedef Gokhan Acikgoz)

after surgery were analyzed retrospectively. The time from surgery to BCR was measured. It is aimed to evaluate the factors affecting this period and BCR.

Materials and Methods

Patients diagnosed with prostate cancer who received SRT in Ankara Ataturk Education Hospital between 01.01.2011 and 01.01.2018 were analyzed retrospectively. Patients who had undergone radical prostatectomy for prostate adenocarcinoma then received SRT for PSA recurrence were included. Patients who received post-surgery hormone therapy, and definitive or palliative RT were excluded.

The patients were treated with Helical Tomotherapy using the Image Guided-Intensity Modulated RT (IG-IMRT) technique. Age, preoperative (preop) PSA level, SM status, T stage, N stage, GS, postoperative nadir PSA, PSA before RT, and time between surgery and BCR were noted. GS determined by radical prostatectomy, not biopsy, was evaluated. In addition, the relationship between pre-RT PSA and post-RT nadir PSA was evaluated. The PSA level was accepted as $\geq$ 0.2 ng/ml for BCR and the undetectable PSA level was accepted as $\leq$0.1 ng/ml for the patients.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ankara Atatürk Education Hospital with the decision number E1/1535/2021 on 17/02/2021.

Primary and secondary endpoint

The primary endpoint of this study was analysis of factors affecting time to BCR after RP. It is important to identify high-risk subgroups and to monitor this patient group more closely and to refer them to SRT as soon as possible. The second endpoint of the study is the evaluation of the recurrence status after salvage RT.

Statistical analysis

SPSS Ver. 22 (IBM Corp Released 2010. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) software package was used for statistical analysis. Nonparametric tests were used in the study because the data did not fit the normal distribution. Descriptive analyzes were given as the median value for non-normally distributed variables. Chi-square or Fisher exact tests were used for comparative analysis. For statistical analysis of 2 independent groups, the Mann-Whitney U test and 3 or more independent group analyzes were performed with the Kruskal Wallis test, and the significance was evaluated with post hoc analyses after Bonferroni correction. The statistical significance limit was accepted as a p-value of 0.05 or less.

Results

The results of 84 patients who met the criteria of the study were analyzed. The median follow-up time was 78.5 (range 28-172) months and the median time between surgery and RT was 23.7 (range 5.1-136.9) months. The median total dose of RT was 70 (range 59.4-74.0) Gray. Robotic RP (RRP) was performed in 65.5% (n=55) of the patients, and open radical retropubic prostatectomy (ORP) was performed in 34.5% (n=29). GS was determined by biopsy and surgery was recorded. According to the results of this evaluation, the GS determined by operation was found to be higher at 53.5% (n=45) compared to biopsy, and lower at 11% (n=13). The SM was positive in 57.1% (n=48) of the patients. Separately analyzed according to the type of surgery, the SM was positive in 61.8% (n=34) of the pa-

Table 1. Demographic data, disease and treatment details of the patients.

		n (%)
Age (years) Median (range)	61 (44-80)	
PSA (ng/mL) at the time of diagnosis	< 10	45 (53.5)
	10-20	25 (29.8)
	> 20	14 (16.7)
Gleason score	$\leq$ 6	13 (15.5)
	3+4	27 (32.1)
	4+3	20 (23.8)
	8	12 (14.3)
	9-10	12 (14.3)
T Stage	2A	8 (9.5)
	2B	3 (3.5)
	2C	23 (27.4)
	3A	36 (42.9)
	3B	14 (16.7)
Surgical margin status	Positive	48 (57.1)
	Negative	36 (42.9)
Nadir PSA levels after surgery * (ng/mL)	< 0.03	40 (47.6)
	$\geq$ 0.03	44 (52.4)
PSA* (ng/mL) at time of RT	< 0.03	35 (41.7)
	$\geq$ 0.03	49 (58.3)
Last status	Alive	82 (97.6)
	Ex	2 (2.4)

Abbr: PSA=Prostate Specific Antigen; T=Tumor; RT= Radiotherapy.

Table 2. Analysis of factors affecting time from surgery to BCR.

		Period (month) Median(range)	p values
Surgical margin status	Positive	14.8 (3.0-65.1)	0.49
	Negative	15.4 (2.2-125.1)	
PSA (ng/mL) at the time of diagnosis	< 10	16.1 (2.2-125.9)	0.79
	10-20	17.0 (2.8-73.8)	
	> 20	10.2 (2.9-65.2)	
Gleason score	$\leq$ 8	16.3 (2.1-125.9)	0.05
	9-10	8.9 (2.8-20.3)	
T Stage	3A	17.8 (2.1-73.7)	0.02
	3B	8.7 (2.8-29.6)	
Postoperative nadir PSA levels ng/ml)	< 0.03	20.6 (5.4-65.2)	<0.0001
	$\geq$ 0.03	8.8 (2.2-125.9)	
PSA (ng/ml) at the time of RT	< 0.3	15.6 (2.2-125.9)	0.93
	$\geq$ 0.3	14.4 (2.5-91.8)	
Age	< 60	17.1 (3.9-91.8)	0.07
	$\geq$ 60	13.4 (2.2-125.9)	
PSA level of last control (ng/ml)	< 0.2	16.3 (2.2-125.9)	0.30
	$\geq$ 0.2	10.3 (2.8-56.0)	
Undetectable PSA ($\leq$0.1 ng/ml) at last control	Yes	16.4 (2.2-125.9)	0.50
	No	13.9 (2.8-56.0)	

Abbr: PSA=Prostate Specific Antigen; T=Tumor; RT= Radiotherapy.

tients who underwent RRP and 48.3% (n=14) of patients who underwent ORP, but the difference was not statistically significant (p=0.25). Postoperative nadir PSA levels were median 0.03 (range 0.003-15.0) ng/ml. PSA levels at the time of RT were median 0.3 (range 0.003-9.1) ng/ml. The median PSA level of the patients at the last control time was 0.05 (0.003-13.2) ng/ml. Demographic data, disease, and treatment details of the patients are summarized in Table 1.

Analysis of time between surgery and BCR

The median time from surgery to BCR was 14.8 months (range 2.17-125.9) months. According to the GS, the median was 16.3 (2.17-125.9) months in the group with GS ≤8, while the median was 8.9 (2.8-20.3) months in the group with GS 9-10 (p=0.05). The relationship between the median time from surgery to biochemical recurrence and the T stage was statistically significant (p=0.03). In subgroup -analyses, it was seen that this difference was due to the difference between T3A and T3B stages. The median time between surgery and BCR in T3A patients was 17.8 (range 2.17-73.77) months, while it was 8.7 (range 2.8-29.6) months in T3B patients (p=0.02). The median time between surgery and BCR was 20.6 (range 5.4-65.2) months in patients with nadir PSA <0.03 and a median 8.8 (range 2.2-125.9) months in patients with nadir PSA ≥0.03 and this time was statistically significant (p<0.0001).

The relationship between time from surgery to BCR and SM status, preop PSA level, GS, T stage, postoperative nadir PSA level, PSA level at the time of RT, age, PSA level at last control were analyzed and shown in Table 2.

Analysis after salvage RT

In the follow-up, recurrence was detected in 7 (9.3%) of the patients who received local RT, and no recurrence was observed in any of the patients who received local + pelvic RT (p=0.33). 20.3% of patients had PSA ≥ 0.2 ng/ml at the last control in those receiving local RT, compared to 6.3% in those receiving local+pelvic RT (p=0.51). Subsequently, recurrence developed in 7 (8.3%) patients. The median time between surgery and BCR was 12.1 (3.0-45.3) months in patients with recurrence, and 14.8 (2.2-125.9) months in patients without recurrence (p=0.54).

Discussion

In this study, the median follow-up period from diagnosis was 6.5 years, and the median BCR after RP was 14.8 months. Factors that affect BCR significantly after surgery are; Gleason score, T stage, and PSA nadir level below 0.03 ng/dL. After the SRT, recurrence developed in 7 (8.3%) patients. All patients with recurrence were in the local RT arm. There was no recurrence in the local + pelvic RT arm during the follow-up period.

Studies have shown that 50-75% of patients with T3 disease develop BCR after RP [9,10]. There are also differences in the T3 stage itself in terms of BCR. In T3A disease, local control becomes difficult in the case of positive SM; In T3B stage, there may be an increased risk of recurrence independent of the SM status [11]. After RP, seminal vesicle invasion (SVI) (T3B disease) is an indicator of poor prognosis in general and increases the risk of BCR by 2.3 times [12]. Cancer-related death rates are higher in T3B stage and a worse prognosis has been reported compared to T3A [13,14]. Adjuvant RT (ART) is recommended in these patients due to reducing the risk of biochemical recurrence [15]. The main indications of ART are T3 disease, positive SM or the presence of other high-risk factors [16]. Close follow-up is required for patients who do not receive ART after the operation, and SRT is recommended in case of BCR positivity [17]. Although those with T3B disease are at higher risk and have worse outcomes, some authors have found a good prognostic subset of patients with SVI. Negative SM, negative LN, low GS, and PSA with isolated SVI represents a better prognosis [18,19]. According to our results, BCR duration was considerably shorter in T3B patients compared to other T stages, and this difference was statistically significant.

Primary and secondary Gleason scores are associated with higher BCR rates. They are also important predictors of metastatic disease and cancer-related mortality [20,21,22]. In previous studies, patients with GS ≥8 were associated with a BCR 3.3 times higher than GS = 6 [13,14]. In our study, there was a significant difference in BCR recurrence times between GS ≤8 and GS>8 groups, which was consistent with the literature.

Freedland et al. investigated the optimal cut-off level for BCR after RP. In patients with a postoperative PSA level >0.1ng/ml, the risk of PSA progression at 1 year and 3 years was 36% and 67%, respectively; For PSA > 0.2ng/ml, they found these rates to be 86% and 100%, respectively. According to the results of studies on the subject, PSA > 0.2ng/ml was taken as the threshold to define PSA recurrence after RP [20].

The risk of BCR is higher in patients with multiple and wide SM positivity compared to those with single and focal positivity [23]. The position of the positive SM also influences the BCR; bladder neck involvement carries a higher risk of BCR compared to other regions [24]. However, positive SM alone is not associated with a higher risk of prostate cancer mortality [25]. In a meta-analysis of 74 studies that included 11,521 patients with radical prostatectomy, the risk of recurrence increased with positive surgical margins in univariate analyzes, whereas seminal vesicle involvement, GS, post-operative RT, and SM positivity didn't show a significant contribution to recurrence in multivariate analyzes [26,27]. In the EORTC 22911 study, ART was compared with follow-up in positive SM or T3 patients, and a decrease in local recurrence rate and an increase in progression-free survival were observed in the ART group [28]. In our study, there was no statistically significant difference between positive SM and BCR times. It would be useful to evaluate the localization of CS positivity by performing subgroup analysis, but it could not be analyzed due to a lack of data.

PSA nadir is an important predictor of BCR after RT and brachytherapy [29,30]. Similarly, the relationship between PSA nadir levels and BCR after RP is significant [31].

The time to nadir PSA after radical prostatectomy is another risk factor for BCR [32]. The duration of PSA nadir was not evaluated in this study. However, in accordance

with the literature, BCR duration was significantly longer in patients with nadir PSA level was below 0.03 after surgery.

Conclusion

BCR time is shorter in patients with high GS, advanced T stage, and high postoperative PSA nadir. The increased risk of BCR is associated with increased prostate cancer-specific mortality and metastatic disease. Therefore, it is important to detect BCR early and not delay SRT in patients with these risk factors and not receiving adjuvant RT.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ankara Atatürk Education Hospital with the decision number E1/1535/2021 on 17/02/2021.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 ;71:209-49.
2. Incrocci L. Radiotherapy for prostate cancer and sexual health. Transl Androl Urol. 2015;4:124-30.
3. De Sousa A, Sonavane S, Mehta J. Psychological aspects of prostate cancer: a clinical review. Prostate Cancer Prostatic Dis. 2012 ;15:120-7.
4. Brandeis J, Pashos CL, Henning JM, Litwin MS. A nationwide charge comparison of the principal treatments for early stage prostate carcinoma, Cancer, 2000;89:1792–9.
5. Stephenson AJ, Scardino PT, Eastham JA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst. 2006;98:715-7. Erratum in: J Natl Cancer Inst. 2012;104:423.
6. Westesson KE, Stephenson AJ. Salvage Therapy for Prostate Cancer, Oncology & Hematology Review, 2013;9(1):21–5.
7. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol. 2014;66:243–50.
8. Toussi A, Stewart-Merrill SB, Boorjian SA, et al. Standardizing the Definition of Biochemical Recurrence after Radical Prostatectomy-What Prostate Specific Antigen Cut Point Best Predicts a Durable Increase and Subsequent Systemic Progression? J Urol. 2016;195:1754-9.
9. Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubicprostatectomy. The 15-year Johns Hopkins experience. Urol Clin North Am. 2001 Aug;28(3):555-65.
10. Han M, Partin AW, Zahurak M, et al. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol. 2003 Feb;169(2):517-23.
11. Kasibhatla M, Peterson B, Anscher MS. What is the best postoperative treatment for patients with pT3bN0M0 adenocarcinoma of the prostate? Prostate Cancer Prostatic Dis. 2005;8(2):167.
12. Eggener SE, Scardino PT, Walsh PC, et al. Predicting 15- year prostate cancer specific mortality after radical prostatectomy. J Urol. 2011;185:869-75.
13. Stephenson AJ, Scardino PT, Eastham JA, et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol. 2005;23:7005-12.
14. Cooperberg MR, Hilton JF, Carroll PR. The CAPRA-S score: A straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer. 2011;117:5039-46.
15. Patel AR, Stephenson AJ. Radiation therapy for prostate cancer after prostatectomy: adjuvant or salvage? Nat Rev Urol. 2011 Jun 14;8(7):385-92.
16. Boorjian SA, Karnes RJ, Viterbo R, et al. Long-term survival after radical prostatectomy versus external-beam radiotherapy for patients with high-risk prostate cancer. Cancer. 2011 Jul 1;117(13):2883-91.
17. Freedland SJ, Rumble RB, Finelli A, et al. Adjuvant and Salvage Radiotherapy After Prostatectomy: American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol. 2014 Nov 3. pii: JCO.2014.58.8525.
18. Freedland SJ, Aronson WJ, Presti JC Jr, et al. Predictors of prostate-specific antigen progression among men with seminal vesicle invasion at the time of radical prostatectomy. Cancer. 2004;100:1633-8.
19. Salomon L, Anastasiadis AG, Johnson CW, et al. Seminal vesicle involvement after radical prostatectomy: predicting risk factors for progression. Urology. 2003;62:304-9.
20. Freedland SJ, Sutter ME, Dorey F, Aronson WJ. Defining the ideal cutpoint for determining PSA recurrence after radical prostatectomy. Prostate-specific antigen. Urology. 2003;61:365-9.
21. Stephenson AJ, Kattan MW, Eastham JA, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. J Clin Oncol. 2006;24:3973-8.
22. Boorjian SA, Thompson RH, Tollefson MK, et al. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. Eur Urol. 2011;59:893-9.
23. Stephenson AJ, Wood DP, Kattan MW, et al. Location, extent and number of positive surgical margins do not improve accuracy of predicting prostate cancer recurrence after radical prostatectomy. J Urol. 2009;182:1357-63.
24. O'Neil LM, Walsh S, Cohen RJ, Lee S. Prostate carcinoma with positive margins at radical prostatectomy: role of tumour zonal origin in biochemical recurrence. BJU Int. 2015;116 (Suppl 3):42-8.
25. Stephenson AJ, Eggener SE, Hernandez AV, et al. Do margins matter? The influence of positive surgical margins on prostate cancer-specific mortality. Eur Urol. 2014;65:675-80.
26. Alkhateeb S, Alibhai S, Fleshner N, et al. Impact of positive surgical margins after radical prostatectomy differs by disease risk group. J Urol 2010; 183:145.
27. Yossepowitch O, Briganti A, Eastham JA, et al. Positive surgical margins after radical prostatectomy: a systematic review and contemporary update. Eur Urol. 2014 Feb;65(2):303-13.
28. Bolla M, Van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012; 380:2018.
29. Nishimura S, Ohashi T, Momma T, et al. Prostate-specific antigen nadir within 12 months as an early surrogate marker of biochemical failure and distant metastasis after low-dose-rate brachytherapy or external beam radiotherapy for localized prostate cancer. Cancer Med. 2018 May;7(5):1794-1801. doi: 10.1002/cam4.1443. Epub 2018 Mar 25. PMID: 29577651; PMCID: PMC5943430.
30. Alcantara P, Hanlon A, Buyyounouski MK, et al. Prostate-specific antigen nadir within 12 months of prostate cancer radiotherapy predicts metastasis and death. Cancer. 2007 Jan 1;109(1):41-7. doi: 10.1002/cncr.22341. PMID: 17133416; PMCID: PMC1892752.
31. Chung JH, Jeong JY, Lee JY, et al. Biochemical recurrence after radical prostatectomy according to nadir prostate specific antigen value. PLoS One. 2021 May 3;16(5):e0249709. doi: 10.1371/journal.pone.0249709. PMID: 33939714; PMCID: PMC8092790.
32. Skove SL, Howard LE, Aronson WJ, et al. Timing of Prostate-specific Antigen Nadir After Radical Prostatectomy and Risk of Biochemical Recurrence. Urology. 2017 Oct;108:129-134. doi: 10.1016/j.urology.2017.07.009. Epub 2017 Jul 19. PMID: 28735016; PMCID: PMC6150912.