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Original Article

Factors determining biochemical recurrence in low-risk prostate cancer patients who underwent radical prostatectomy

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ABSTRACT

Objective: This study was conducted to research the factors determining biochemical recurrence (BCR) in low-risk localized prostate cancer patients who underwent radical prostatectomy (RP).

Material and methods: We retrospectively analyzed the data of 504 patients who had undergone RP between 2003 and 2013 at our clinic. One hundred and fifty-two patients who underwent RP for low-risk prostate cancer were included in the study.

Results: The mean follow-up period for patients was 58.7 (21–229) months. The mean age of the patients was 63.7±7.2 years (49–79). The mean prostate specific antigen (PSA) value was 5.25±4.22 ng/mL (3.58–9.45). The BCR rate after the operation was 25% (38/152). In the univariate analysis, recurrence determining factors were shown to include extracapsular involvement (ECI) (p=0.004), capsular invasion (CI) (p=0.001), age (p=0.014), and tumor size (p=0.006). However, only CI was found to be significant in multivariate analysis (p=0.001).

Conclusion: Capsular invasion is an independent risk factor in low-risk prostate cancer patients who underwent RP for BCR.

Keywords: Biochemical recurrence; low-risk; radical prostatectomy.

Introduction

Prostate cancers (PC) are the most frequently diagnosed solid tumors in European males.[1] It is also reported to be the second reason for cancer-related deaths in males according to a study conducted in USA.[2] Radical prostatectomy (RP) is the standard form of treatment in low-risk localized PC patients. The patients who benefit the most from radical surgery are the patients within low-risk group.[3] The most important advantage of RP is the potential of cure without damaging the surrounding tissues and a better chance of tumor staging because the organ is completely removed. However, not all RP patients are completely cured. Biochemical recurrence (BCR) is diagnosed in 22% of follow-up low-risk patients[4] who require additional treatments. Therefore, determining BCR is important in treatment and follow-up plans. In our study, our main purpose was to review the low-risk localized PC patients that developed BCR after RP and to define the factors that determine the recurrence.

Material and methods

We retrospectively analyzed the data of 504 patients who had undergone RP between 2003 and 2013 at our clinic. All surgeries were performed by two surgeons who were experienced in RP. One hundred and fifty-two patients who underwent RP for low-risk PC were included in the study. Patients with clinical term ≤T2a, Gleason score ≤6, and prostate-specific antigen (PSA) ≤10 were defined as low-risk localized PC patients. All patients' ages, preoperative prostate-specific antigen (PSA) values, RP specimen pathology data, Gleason

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score (GS), perineural invasion (PNI), capsule invasion (CI), extracapsular extension (ECE), seminal vesicle invasion (SVI), positive surgical margins (PSM), and postoperative PSA values were recorded. All patients were followed with 3-month visits in the first, 6-month visits in the second and third, and yearly visits after the third year of operation. BCR was defined as a single PSA value over 0.2 ng/mL or high PSA values during the postoperative period.[5]

Statistical analysis

All statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 15.0 for Windows. Chi-square test was used to group and to define clinical parameter importance. Independent risk factors were determined by employing univariate and multivariate Cox regression analysis. P values below 0.05 were considered statistically significant.

Results

The patients' mean follow-up period was 58.7 (21–229) months, mean age was 63.7±7.2 years (49–79), and mean PSA value was 5.25±4.22 ng/mL (3.58–9.45). Thirty-eight (25%) patients were diagnosed with BCR. The average recurrence period was 22.5 months. When RP specimen pathological results were reviewed, 18 (11.8%) patients had PSM, 20 (13.2%) had CI, 30 (19.7%) had ECE, 18 (11.8%) had SVI, and 50 (32.9%) had PNI. Table 1 summarizes the clinical and pathological properties of the patients.

In univariate analysis, there was a significant relationship between BCR and ECE (p=0.004), age (p=0.014), tumor volume (p=0.006), and CI (p=0.001). There was no relation between recurrence and PNI (p=0.548), SVI (p=0.118), and PSM (p=0.086). In multivariate analysis, the only significant relationship was found between CI and BCR (p=0.001). Table 2 summarizes the values.

Discussion

Prostate cancer is a disease that requires long-term treatment and a good follow-up plan. Regardless of the first curative therapy administered, 16%–35% of the patients require a secondary treatment within 5 years after the initial treatment.[6-10] RP is one of the most commonly used treatments for PC and allows very good cancer control. The main goal in RP is to remove the cancer completely while it is still limited to the prostate gland. However, because of errors in clinical staging, specimens of 30%–40% of localized prostate patients who underwent RP showed extraprostatic involvement.[11,12] In addition, 35% patients develop BCR within 10 years following the operation.[13-15] Because of the superior sensitivity of PSA, recurrence of the disease can be diagnosed during the early term. There is a long time between BCR and localized relapse or far metastases for the previous reason. During this period, patients may require additional secondary treatments. There is still a contro-

Table 1. Clinical and pathological properties of RP patients

Patients (n)	**152**
Age	63.7±7.2 years
PSA	5.25±4.22 ng/mL
Tumor volume	14.4±12.9 mL
PNI	32.9% (50/152)
SVI	11.8% (18/152)
ECE	19.7% (30/152)
CI	13.2% (20/152)
PSM	11.8% (18/152)
BCR	25% (38/152)

PSA: prostate-specific antigen; PNI: perineural invasion; SVI: seminal vesicle invasion; ECE: extracapsular extension; CI: capsule invasion; PSM: positive surgical margins; BCR: biochemical recurrence

Table 2. Factors affecting biochemical recurrence

	Biochemical recurrence (+)	**Biochemical recurrence (-)**	**Univariate analysis p values**	**Multivariate analysis p values**
Mean age (years)	67.2±8.5	62.5±6.4	0.014	0.154
Mean tumor volume (mL)	21.4±15.3	12.0±11.2	0.006	0.496
ECE	16/38 (42.1%)	14/114 (12.3%)	0.004	0.574
PNI	12/38 (31.6%)	38/114 (33.3%)	0.548	-
CI	16/38 (42.1%)	4/114 (3.5%)	0.001	0.001
PSM	8/38 (21.0%)	10/114 (8.4%)	0.086	-
SVI	7/38 (18.4%)	11/114 (9.6%)	0.118	-

ECE: extracapsular extension; PNI: perineural invasion; CI: capsule invasion; PSM: positive surgical margins; SVI: seminal vesicle invasion

versy about which treatments should be administered to which patients. Considering this fact, determining BCR factors following the operation is very important. Many factors were found to affect the post-RP results.

One of the most known factors is the PSA value during initial diagnosis. Many authors who published predictor studies for BCR following RP reported PSA as a strong preoperative indicator in both univariate and multivariate analysis.[16-20] In addition, GS of the RP specimen is also an independent strong predictor for BCR in univariate and multivariate analysis.[16-20] Because we included only low-risk localized PC patients in our study, we disregarded those parameters.

Seminal vesicle invasion is a bad prognostic parameter with 5%–60% biochemical progression-free rates.[21,22] In our study, we did not find a relationship between SVI and BCR in univariate analysis. We think that because we worked with low-risk patients, SVI patient numbers were lower than those in the literature.

The effect of age on recurrence after RP is still debated. Poor prognosis is reported with advanced age.[23,24] However, some studies did not find any effect at all.[25,26] In another meta-analysis study, age was not found to be a prognostic factor.[27] In our study, age was significant in univariate (p=0.014) but insignificant in multivariate (p=0.154) analysis.

The relationship between tumor volume in RP specimens and recurrence is not clear. However, most studies did not find a relationship between them.[28,29] Our study results were also similar. Although it was significant in univariate (p=0.006) analysis, it was insignificant in multivariate (p=0.496) analysis.

Positive surgical margins are observed in 6%–41% of the RP cases.[30] The main reason for the difference between those values is the surgical experience. With the increasing surgical experience, those rates decrease.[31,32] In our study, this rate was 11.8%. Because we included only low-risk cases in our study, those rates were low. PSM is an unwanted and worrying situation for surgeons that perform oncological surgeries including RP. Although this term means that there are still live cancer cells within the patients' body, the prognostic importance of PSM in PC is still debated. Although some studies reported that PSM was related to higher BCR rates,[33-35] some did not show such a relationship.[36,37] On the other hand, Stephenson et al's[38] multivariate analysis showed that PSM number (≥1) and widespread PSM were significant in predicting BCR. In addition, Ahyai et al's[39] study on 932 RP patients showed that only 20% of the patients with PSM developed BCR, and adjuvant treatments administered to selected patients would decrease the overtreatment risk. BCR risk of PSM changes between 20% and 47% in a mean 5-year follow-up period.[40,41] In our study, this value was found to be 21.0%. BCR rate in patients with negative SM was 7% in our study. Although recurrence is more frequent in PSM patients, it was not found to be statistically significant (p=0.086).

The relationship between the tumor and prostate capsule is also an important factor affecting prognosis. Epstein et al's[42] 1993 study reported the importance of capsular invasion and the degree of capsular invasion in prognosis. Moreover, Wheeler et al's[43] 688 patient series study reviewed the relationship between cancer prognosis and CI grade and level using multivariate analysis. According to this study, patients with only CI had a 13% BCR rate, whereas patients with localized ECE had a 27% BCR rate in a 5-year follow-up after RP. The same study reported the BCR rate of widespread ECE patients to be 58%, stating that widespread ECE was an independent predictor for BCR. Theiss et al's[44] study showed a 10-year BCR rate in patients without CI as 21%, patients with CI as 35.3%, and 61.5% in ECE patients. The authors recommended that CI should be differentiated from ECE. In our study, BCR rate in patients without CI was 3.5% and 42.1% in CI patients. Those rates were found to be 42.1% in ECE and 12.3% in non-ECE patients. In univariate analysis, CI and ECE were found to be significant factors (p=0.001-0.004); however, in multivariate analysis, only CI was found to be an independent risk factor (p=0.001).

The clinical importance of PNI found in RP specimens is still questionable. D'Amico et al.[45] reported PNI as an independent prognostic factor in BCR. However, the studies that show no correlation between PNI and BCR are more common.[46-48] Jeon et al.[49] also reported that patients with PNI have higher GS, ECI, SVI, and PSM. Lee et al's[50] 2010 study showed that PNI presence was related to lymph node invasion, higher GS, PSM, higher tumor volume, and late-term PC; however, PNI was not an independent risk factor for BCR in multivariate analysis. Our study results were similar to the ones in the literature that show no relation between PNI and BCR (p=0.548).

One must not forget while reviewing all those studies that, as previously mentioned, PC manifestations vary greatly from geographical and racial factors. The effect of dietary customs as well as African race present with a higher risk of more aggressive PC may help explain these different results. A study conducted in Turkey also clearly showed that patients who underwent RP have higher grade tumors.[51]

One of the weak points in our study is its retrospective nature and limited patient numbers. In addition, more detailed patho-

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logical results could have been obtained, such as the extent and number of positive surgical margins, whether extracapsular involvement is focal or extended, which could have been added to the variables, thereby producing better results.

In our study, 25% of patients who underwent RP for localized PC developed BCR in an average follow-up period of 58.7 months. In univariate analysis, age, average tumor volume, capsule invasion, and extracapsular involvement were all significant for BCR. PNI and PSM were not statistically significant. In multivariate analysis, the only independent predictor for BCR was found to be CI. In these times where the adjuvant therapies administered to the patients during the period between BCR after RP and metastatic disease is still controversial, CI presence may show us a way for treatment. Although ECE and PSM were not found to be independent predictors in this study, wider series with longer follow-up periods and more detailed pathological data may solve the dilemmas in those areas.

Ethics Committee Approval: Due to the retrospective study design, ethics committee approval was not necessary.

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References

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe 2004. Ann Oncol 2005;16:481-8.
2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statics, 2006. CA Cancer J Clin 2006;56:106-30. [CrossRef]
3. Grossfeld GD, Chang JJ, Broering JM, Miller DP, Yu J, Flanders SC, et al. Impact of positive surgical margins on prostate cancer recurrence and the use of secondary cancer treatment: data from the CaPSURE database. J Urol 2000;163:1171-7. [CrossRef]
4. Zanatta DA, Andrade RJ, Pacagnan EF, München LW, Assumpção RA, Mercante VC, et al. Early stage prostate cancer: biochemical recurrenc eafter treatment. Int Braz J Urol 2014;40:137-45. [CrossRef]
5. Boccon-Gibod L, Djavan WB, Hammerer P, Hoeltl W, Kattan MW, Prayer-Galetti T, et al. Management of prostate-specific antigen relapse in prostate cancer: a European Consensus. Int J Clin Pract 2004;58:382-90. [CrossRef]
6. Grossfeld GD, Latini DM, Lubeck DP, Mehta SS, Carroll PR. Predicting recurrence after radical prostatectomy for patients with high risk prostate cancer. J Urol 2003;169:157-63. [CrossRef]
7. Lu-Yao GL, Albertsen PC, Li H, Moore DF, Shih W, Lin Y, et al. Does primary androgen-deprivation therapy delay the receipt of secondary cancer therapy for localized prostate cancer? Eur Urol 2012;62:966-72. [CrossRef]
8. Barry MJ, Gallagher PM, Skinner JS, Fowler FJ Jr. Adverse effects of robotic-assisted laparoscopic versus open retropubic radical prostatectomy among a nation wide random sample of medicare-age men. J ClinOncol 2012;30:513-8. [CrossRef]
9. Han M, Pound CR, Potter SR, Partin AW, Epstein JI, Walsh PC. Isolated local recurrence is rare after radical prostatectomy in men with Gleason 7 prostate cancer and positive surgical margins: therapeutic implications. J Urol 2001;165:864-6. [CrossRef]
10. Bott SR. Management of recurrent disease after radical prostatectomy. Prostate Cancer Prostatic Dis 2004;7:211-6. [CrossRef]
11. Powell IJ, Tangen CM, Miller GJ, Lowe BA, Haas G, Carroll PR, et al. Neoadjuvant therapy before radical prostatectomy for clinical T3/T4 carcinoma of the prostate: 5-year follow up, Phase II Southwest Oncology Group Study 9109. J Urol 2002;168:2016-9. [CrossRef]
12. Ward JF, Blute ML, Slezak J, Bergstralh EJ, Zincke H. The long-term clinical impact of biochemical recurrence of prostate cancer 5 or more years after radicalprostatectomy. J Urol 2003;170:1872-6. [CrossRef]
13. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3478 consecutive patients: long-term results. J Urol 2004;172:910-4. [CrossRef]
14. Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, Scardino PT. Cancer control with radical prostatectomy alone in 1000 consecutive patients. J Urol 2002;167:528-34. [CrossRef]
15. Amling CL, Blute ML, Bergstralh EJ, Seay TM, Slezak J, Zincke H. Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. J Urol 2000;164:101-5. [CrossRef]
16. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol 2003;169:517-23. [CrossRef]
17. Bostwick DG, Grignon DJ, Hammond ME, Amin MB, Cohen M, Crawford D, et al. Prognostic factors in prostate cancer. College of American Pathologists consensus statement 1999. Arch Pathol Lab Med 2000;124:995-1000.
18. Budäus L, Isbarn H, Eichelberg C, Lughezzani G, Sun M, Perrotte P, et al. Biochemical recurrence after radical prostatectomy: multiplicative interaction between surgical magrin status and pathological stage. J Urol 2010;184:1341-6. [CrossRef]

19. D'Amico AV, Whittington R, Malkowicz SB, Cote K, Loffredo M, Schultz D, et al. Biochemical outcome after radical prostatectomy or external beam radiation therapy for patients with clinically localized prostate carcinoma in the prostate specific antigen era. Cancer 2002;95:281-6. [CrossRef]
20. Stephenson AJ, Kattan MW, Eastham JA, Dotan ZA, Bianco FJ Jr, Lilja H, et al. Defining biochemica lrecurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. J Clin Oncol 2006;24:3973-8. [CrossRef]
21. Johnson CW, Anastasiadis AG, McKiernan JM, Salomon L, Eaton S, Goluboff ET, et al. Prognostic indicators for long term outcome following radical retropubic prostatectomy for prostate cancer involving the seminal vesicles. Urol Oncol 2004;22:107-11. [CrossRef]
22. Salomon L, Anastasiadis AG, Johnson CW, McKiernan JM, Goluboff ET, Abbou CC, et al. Seminal vesicle involvement after radical prostatectomy: predicting risk factors for progression. Urology 2003;62:304-9. [CrossRef]
23. Hong SK, Nam JS, Na W, Oh JJ, Yoon CY, Jeong CW, et al. Younger patients have poorer biochemical outcome after radical prostatectomy in high-risk prostate cancer. Asian J Androl 2011;13:719-23. [CrossRef]
24. Aleman M, Karakiewicz PI, Kupelian P, Kattan MW, Graefen M, Cagiannos I, et al. Age and PSA predict likelihood of organ-confined disease in men presenting with PSA less than 10 ng/mL: implications for screening. Urology 2003;62:70-4. [CrossRef]
25. Magheli A, Rais-Bahrami S, Humphreys EB, Peck HJ, Trock BJ, Gonzalgo ML. Impact of patient age on biochemical recurrence rates following radical prostatectomy. J Urol 2007;178:1933-7. [CrossRef]
26. Catalona WJ, Smith DS. Cancer recurrence and survival rates after anatomic radical retropubic prostatectomy for prostate cancer: intermediate-term results. J Urol 1998;160:2428-34. [CrossRef]
27. Parker CC, Gospodarowicz M, Warde P. Does age influence the behaviour of localized prostate cancer? BJU Int 2001;87:629-37. [CrossRef]
28. Noronha MR, Quintal MM, Magna LA, Reis LO, Billis A, Meirelles LR. Controversial predictors of biochemical recurrence after radical prostatectomy: a study from a Latin American (Brazilian) institution. Int Braz J Urol 2013;39:779-92. [CrossRef]
29. Salomon L, Levrel O, Anastasiadis AG, Irani J, De La Taille A, Saint F, et al. Prognostic significance of tumor volume after radical prostatectomy: a multivariate analysis of pathological prognostic factors. Eur Urol 2003;43:39-44. [CrossRef]
30. Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy: the 15-year Johns Hopkins experience. Urol Clin North Am 2001;28:555-65. [CrossRef]
31. Swindle P, Eastham JA, Ohori M, Kattan MW, Wheeler T, Maru N, et al. Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol 2008;179:47-51. [CrossRef]
32. Orvieto MA, Alsikafi NF, Shalhav AL, Laven BA, Steinberg GD, Zagaja GP, et al. Impact of surgical margin status on long-term cancer control after radical prostatectomy. BJU Int 2006;98:1199-203. [CrossRef]
33. Vis AN, Schroder FH, van der Kwast TH. The actual value of the surgical margin status as a predictor of disease progression in men with early prostate cancer. Eur Urol 2006;50:258-65. [CrossRef]
34. Karakiewicz PI, Eastham JA, Graefen M, Cagiannos I, Stricker PD, Klein E et al. Prognostic impact of positive surgical margins in surgically treated prostate cancer: multi-institutional assessment of 5831 patients. Urology 2005;66:1245-50. [CrossRef]
35. Pfitzenmaier J, Pahernik S, Tremmel T, Haferkamp A, Buse S, Hohenfellner M. Positive surgical margins after radical prostatectomy: do they have an impact on biochemical or clinical progression? BJU Int 2008;102:1413-8.
36. Patel DA, Presti JC Jr, McNeal JE, Gill H, Brooks JD, King CR. Preoperative PSA velocity is an independent prognostic factor for relapse after radical prostatectomy. J Clin Oncol 2005;23:6157-62. [CrossRef]
37. De La Roca RL, Da Cunha IW, Bezerra SM, Da Fonseca FP. Radical prostatectomy and positive surgical margins: relationship with prostate cancer outcome. Int Braz J Urol 2014;40:306-15. [CrossRef]
38. Stephenson AJ, Wood DP, Kattan MW, Klein EA, Scardino PT, Eastham JA, et al. Location, extent an dnumber of positive surgical margins do not improve accuracy of predcting prostate cancer recurrence after radicalp rostatectomy. J Urol 2009;182:1357-63. [CrossRef]
39. Ahyai SA, Zacharias M, Isbarn H, Steuber T, Eichelberg C, Köllermann J, et al. Prognostic significance of a positive surgical margin in pathologically organ confined prostate cancer. BJU Int 2010;106:478-83. [CrossRef]
40. Blute ML, Bostwick DG, Seay TM, Martin SK, Slezak JM, Bergstralh EJ, et al. Pathologic classification of prostate carcinoma: the impact of margin status. Cancer 1998;82:902-8. [CrossRef]
41. Kausik SJ, Blute ML, Sebo TJ, Leibovich BC, Bergstralh EJ, Slezak J, et al. Prognostic significance of positive surgical margins in patients with extraprostatic carcinoma after radical prostatectomy. Cancer 2002;95:1215-9. [CrossRef]
42. Epstein JI, Carmichael M, Walsh PC. Adenocarcinoma of the prostate invading the seminal vesicle: definition and relation of tumour volume, grade and margins of resection to prognosis. J Urol 1993;149:1040-5.
43. Wheeler TM, Dillioglugil O, Kattan MW, Arakawa A, Soh S, Suyama K, et al. Clinical and pathological significance of the level and extent of capsula rinvasion in clinical stage T1-2 prostate cancer. Hum Pathol 1998;29:856-62. [CrossRef]
44. Theiss M, Wirth MP, Manseck A, Frohmuller HG. Prognostic significance of capsular invasion and capsular penetration in patients with clinically localized prostate cancer under going radical prostatectomy. Prostate 1995;27:13-7. [CrossRef]
45. D'Amico AV, Wu Y, Chen MH, Nash M, Renshaw AA, Richie JP. Perineural invasion as a predictor of biochemical outcome

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following radical prostatectomy for select men with clinically localized prostate cancer. J Urol 2001;165:126-9. [CrossRef]
46. Freedland SJ, Csathy GS, Dorey F, Aronson WJ. Percent prostate needle biopsy tissue with cancer is more predictive of biochemical failure or adverse pathology after radical prostatectomy than prostate specific antigen or Gleasonscore. J Urol 2002;167: 516-20. [CrossRef]
47. Miyake H, Sakai I, Harada K, Eto H, Hara I. Limited value of perineural invasion in radical prostatectomy specimens as a predictor of biochemical recurrence in Japanese men with clinically localized prostate cancer. Hinyokika Kiyo 2005;51: 241-6.
48. Merrilees AD, Bethwaite PB, Russell GL, Robinson RG, Delahunt B. Parameters of perineural invasion in radical prostatectomy specimens lack prognostic significance. Mod Pathol 2008;21:1095-100. [CrossRef]
49. Jeon HG, Bae J, Yi JS, Hwang IS, Lee SE, Lee E. Perineural invasion is a prognostic factor for biochemical failure after radical prostatectomy. Int J Urol 2009;16: 682-6. [CrossRef]
50. Lee JT, Lee S, Yun CJ, Jeon BJ, Kim JM, Ha HK, et al. Prediction of perineural invasion and its prognostic value in patients with prostate cancer. Korean J Urol 2010;51:745-51. [CrossRef]
51. Eskicorapci SY, Türkeri L, Karabulut E, Cal C, Akpinar H, Baltaci S, et al. Validation of two preoperative Kattan nomograms predicting recurrence after radical prostatectomy for localized 74 prostate cancer in Turkey: a multicenter study of the Urooncollogy Society. Urology 2009;74:1289-95. [CrossRef]