Predictive values for extracapsular extension in prostate cancer patients with PSA values below 10 ng/mL

Zülfü Sertkaya, Metin İshak Öztürk, Orhan Koca, Mustafa Güneş, Muhammet İhsan Karaman

ABSTRACT

Objective: We aimed to determine predictive values of extracapsular extension (ECE) in patients who had undergone radical retropubic prostatectomy (RRP) with prostate-specific antigen (PSA) values below 10 ng/mL.

Material and methods: We retrospectively scanned data of 167 patients with PSA values below 10 ng/mL who had undergone radical retropubic prostatectomy (RRP) between April 2004 and August 2011 in our clinic. Age, PSA, PSA ratio, PSA density, digital rectal examination (DRE) findings, biopsy total Gleason score, perineural invasion (PNI), and lymphovascular invasion (LVI) were analyzed. Parameters of the groups with or without extracapsular extension in RRP pathology specimens were compared.

Results: The mean age of patients was 66.4±12.3 years. According to histopathological analysis of the specimens of RRP of 167 patients, 45 (26.9%) had extracapsular extension (pT3-4) (Group 1); 122 (73.1%) were confined to the prostate (pT2) (Group 2). The mean PSA level was high in Group 1 (p=0.114), PSA ratio was higher in Group 2 (p=0.09). PSA density was 0.17 in Group 1 and 0.24 in Group 2 (p=0.03). DRE positivity was 53.3% and 57.1%, respectively (p=0.71). Biopsy total Gleason score was higher in Group 1 than Group 2 with a statistically significant difference (p=0.04). A statistically significant difference was found between the rates of PNI and LVI (28.9% and 1.63%, respectively) (p=0.002). There was no statistically significant difference between both groups as for surgical margin positivity (p=0.18).

Conclusion: In PCa patients with PSA values below 10 ng/mL, PSA density, lymphovascular invasion and biopsy Gleason total score were statistically significant in predicting extracapsular invasion. Therefore, these results must be considered in preoperative evaluation.

Key words: Extracapsular invasion; Gleason score; prostate cancer; PSA density.

Introduction

Prostate cancer (PCa) is the most frequently seen tumor type in men.^[1] In the USA, 217.730 newly diagnosed prostate cancer, and more than 32.000 cases of prostate cancer-specific deaths were seen in the year 2010.^[2] In autopsy studies, histological PCa was detected at an incidence of 30% within the age group of 40-80 years.^[3] In prostate cancer screening studies, most frequently prostate-specific antigen (PSA) values, and digital rectal examination (DRE) are used. However in screening tests, PSA levels are found below 4 ng/mL in 85-92% of the patients.^[4,5] Thus screening tests result in early detection, and increase in the incidence of PCa.^[6]

Radical prostatectomy is the most frequently applied treatment modality in organ-confined cases with PCa. However, in nearly one-third of the patients surgical margin positivity

(24-42%), and seminal vesicle invasion (33%) have been detected.^[7] Surgical margin positivity increases local and/or systemic invasion of cancer in patients who had been surgically treated for curative therapy. Preoperative evaluation of organ confinement in patients will be helpful in the realization of nerve-sparing approach, and lymphadenectomy. This assessment can be achieved using the nomograms by Partin et al.^[8] which evaluate postoperative histopathological result, preoperative Gleason score (GS), PSA, and clinical stage of PCa. Besides, in many studies number of tumor positive biopsy cores, and GS were considered to be important in the prediction of postoperative histopathology.^[9]

In this study we aimed to determine parameters in the prediction of extracapsular extension (ECE) in patients with PSA values below 10 ng/mL who had undergone radical retropubic prostatectomy (RRP).

Clinic of Urology, Haydarpaşa
Numune Training and Research
Hospital, İstanbul, Turkey

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Correspondence:
Zülfü Sertkaya,
Clinic of Urology, Haydarpaşa
Numune Training and Research
Hospital, İstanbul, Turkey
Phone: +90 533 257 20 50
E-mail: zlfsertkaya@gmail.com

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Material and methods

Data of 167 patients with PSA values below 10 ng/mL who had undergone RRP between April 2004, and August 2011 were retrospectively reviewed.

The patients were divided in two groups as those with (Group 1: pT3-4) or without (Group 2) extracapsular extension based on their postoperative results of histopathological analyses of the specimens.

The patients whose preoperative data could not be obtained during screening of medical files were not included in the study.

Preoperative information about patients' age, PSA (ng/mL), free/total PSA ratio, PSA density (PSAD) (ng/mL/cc), DRE, biopsy GS, PNI, and LVI was retrieved. Postoperative data about prostatectomy specimen GS, ECE, PNI, and LVI were obtained. Total PSA value (ng/mL) was divided by prostate volume (cc) to estimate PSAD value. Prostate biopsy specimens were obtained under the guidance of transrectal ultrasound using 20-25 cm long 18 G biopsy needles.

Since this is a retrospective screening study of medical files, ethics committee approval, and completion of informed patient consent forms were not required.

Statistical analysis

For statistical evaluation SPSS (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) 15.0 for Windows was used. In statistical evaluation of intergroup comparisons of parameters, Mann-Whitney U, and chi-square tests were used. P values below 0.05 were considered to be statistically significant.

Results

Mean age of 167 patients who had undergone radical retro-pubic prostatectomy was 66.4 ± 12.3 years. In 45 (26.9%) of 167 patients, extracapsular extension was present (Group 1) [(incl. invasion of seminal vesicle(s)), and adjacent organ (s)]. However in 122 (73.1%) patients extracapsular extension was not observed (Group 2). Mean ages of both groups were comparable ($p=0.92$) (Table 1).

Median number of 11.4 (8-26) cores were retrieved from biopsy specimens.

Preoperative mean PSA value was 6.68 ± 3.12 (0.15-9.97). Median PSA values of Groups 1, and 2 were 7.4, and 6.3 ng/mL, respectively without statistically significant difference between groups ($p=0.114$) (Table 1).

Free/total PSA ratios were 0.124, and 0.161 in the groups with (Group 1), and without (Group 2) extracapsular extension, respectively. However intergroup difference was not statistically significant ($p=0.09$) (Table 1).

In Group 1 with extracapsular extension, PSA density was 0.24 ng/mL/cc, while in Group 2, it was 0.17 ng/mL/cc. In the group with extracapsular extension PSA density was markedly, and significantly elevated ($p=0.03$) (Table 1).

Mean prostate biopsy total Gleason score was 7.12 ± 2.12 in the group with extracapsular extension, while in Group 2, it was 5.95 ± 1.86 . Mean prostate biopsy total Gleason score was statistically significantly higher in Group 1 ($p=0.04$) (Table 1).

A significant difference was not found between groups as for perineural invasion ($p=0.083$), however in Group 1 with lymphovascular invasion, and extracapsular extension perineural invasion was seen at a significantly (28.9%) higher frequency ($p=0.002$) (Table 1).

Rates of surgical margin positivity were similar between groups ($p=0.18$) (Table 1).

Discussion

Prostate cancer (PCa) ranks second among cancer-specific causes of death in men.^[1] Thanks to its higher success rates, and lower morbidity, radical prostatectomy is a preferred mode of therapy in clinically localized prostate cancer patients with a life expectancy of ≥ 10 years.^[10] In patients with established PCa, preoperatively many parameters are evaluated, and used

Table 1. Evaluation of parameters between groups
(* $p < 0.05$)

	Extracapsular invasion (pT3-4) (Group 1)	Confined to prostate (pT2) (Group 2)	p value
Patients (n)	45	122	
Age (years)	65.6 ± 12.1	67.1 ± 12.9	0.92
DRM positive (%)	53.3	57.1	0.71
PSA (ng/mL)	7.4 ± 1.8	6.3 ± 1.4	0.114
PSA ratio (%)	12.4 ± 2.9	16.1 ± 3.2	0.09
PSA density (ng/mL/cc)	0.23 ± 0.07	0.17 ± 0.04	0.03*
Total Gleason score	7.12 ± 2.12	5.95 ± 1.86	0.04*
PNI positive (%)	93.3	63.9	0.083
LVI positive (%)	28.9	1.63	0.002*
Surgical margin positive (%)	8.9	7.4	0.18
DRE: digital rectal examination; PSA: prostate-specific antigen; PNI: perineural invasion; LVI: lymphovascular invasion			

in the prediction of postoperative condition of the patient. As predictive factors for postoperative pathology, and survival, preoperatively many parameters including PSA, DRE, PSA ratio, PSA density, biopsy Gleason score, PNI, and LVI can be used.^[2] Prediction of extracapsular extension will aid the surgeon to evaluate survival and/or requirement for additional treatment. Especially patients can be informed with the aid of this information.

Many studies performed related to prostate-specific antigen density (PSAD) have shown that PSAD was valuable in predicting pathologic outcomes, and extracapsular extension. Seaman et al.^[11] found that PSA density is more valuable than PSA value, and Gleason score in the prediction of postoperative pathology results. They advocated that patients with lower PSA densities are more amenable to radical prostatectomy. In our study, in the group with extracapsular extension prominently higher PSAD values were demonstrated. During preoperative evaluation this difference should be considered. However, Chang et al.^[12] detected that PSAD combined with magnetic resonance imaging (MRI) findings would be more valuable in the prediction of extracapsular invasion, and surgical margin positivity.^[12,13] Ishida et al.^[13] suggested inadequacy of DRE in predicting pathological stage, and extracapsular invasion, and potential predictive value of PSA density combined with MRI. It has been reported that multiparametric MRI evaluation might aid in the decision-making process between active surveillance and surgical treatment.^[14] In our study MRI evaluation of the patients was not performed.

Gleason score has been frequently used in the prediction of postoperative outcomes. Though biopsy Gleason score is one of the most frequently used parameters, studies performed have demonstrated inadequacy of biopsy Gleason score in the prediction of postoperative pathology specimen Gleason score.^[15] Therefore, Gleason score per se fails to predict pathologic stage of the disease. Similar outcomes were reported in our study.

In patients who had undergone prostate biopsy because of higher prostate-specific antigen levels, detection of prostate cancer was directly correlated with age, but inversely related to the prostate size. In young patients with higher PSA values, detection rate of prostate cancer was relatively lower.^[16] Noldus et al.^[17] evaluated 70 patients preoperatively, and determined close relationship between PSA values, and tumor size in the surgical specimen, however in subsequently performed large series such correlations were refuted. Extracapsular invasion has been seen in 24, and 46% of the patients with PSA levels between 2-6 ng/mL, and 7-10 ng/mL, respectively.^[15] However, in our study, in 26.9% of the patients with PSA levels below 10 ng/mL, extracapsular invasion was detected. We have shown

the inadequacy of PSA values in the prediction of pathological stage, and extracapsular invasion.

In the preoperative evaluation of the prostate cancer patients, diversities between the reported histopathological results of the preoperative biopsy specimen, and intraoperatively excised specimen, inadequacy of histopathological analysis of the biopsy material in predicting postoperative pathology, all reveal that this evaluation is not very successful with this respect. Among parameters used during evaluation, differences between the results of DRE-biopsy, and biopsy-surgical specimen demonstrate that these preoperative parameters fail to assess clearly postoperative pathology.^[18,19] DRE is not sufficiently enlightening in the prediction of extracapsular invasion. In support of the literature findings, in our study DRE findings of both groups were nearly similar.

In a study which investigated the predictive value of prostate-specific antigen ratio in the foresight of pathological outcomes, Masieri et al.^[20] demonstrated the association between lower PSA ratio with extracapsular extension.^[20] In our study, in patients with extracapsular extension, lower PSA ratios were found with statistically significant intergroup difference.

Limitations of our study can include its retrospective, and single-centered design, and inclusion of the operations performed more than one surgeon in the analysis. Scarce number of patients can be seen as another deficiency of our study.

In conclusion, it has been demonstrated that in prostate cancer patients with PSA values below 10 ng/mL, during preoperative evaluations, age, DRM, PSA value, and PSA ratio have no value in the prediction of extracapsular extension, and their use fails to predict postoperative pathology.

Prostate-specific antigen density, increased Gleason score, and presence of LVI were significant parameters in the prediction of extracapsular extension. In preoperative evaluations, extracapsular extension can be predicted based on these parameters. With these available information, patients can be informed about their medical prognosis beforehand, and postoperative requirement for additional therapy can be determined.

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References

1. Parker SL, Tong T, Bolden SL. Cancer statistics. *Cancer J Clin* 1997;47:5.
2. Andriole GL, Crawford ED, Grubb III RL, Buys SS, Chia D, Church TR. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310-9.
3. Silverberg E, Boring CC, Squires TS. Cancer statistic. *Cancer* 1990;40:9-26.
4. Catalona WS, Smiths DS, Ratliff TL. Detection of organ-confined prostate cancer is increased through prostate-specific antigen based screening. *JAMA* 1993;270:948-54.
5. Mettlin C, Lee F, Drago J. Findings on the detection of early prostate cancer in 2425 men. *Cancer* 1991;67:2949-58.
6. Bensalah K, Lotan J, Karam JA, Sheriat SF. New circulating biomarkers for prostate cancer. *Prostate Cancer Prostatic Dis* 2008;11:112-20.
7. D'amico AV, Whittington R, Malkowicz SB. Clinical Utility of the percentage of positive prostate biopsies in defining biochemical outcome after radical prostatectomy for patients with clinically localized prostate cancer. *J Clin Oncol* 2000;18:1164-72.
8. Partin AW, Kattan MW, Subong EN. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. *J Am Med Assoc* 1997;277:1445-51.
9. Grossklau DJ, Coffey CS, Shappell SB. Percent of cancer in biopsies predicts pathological findings after prostatectomy. *J Urol* 2002;167:2032-6.
10. Walsh PC. Anatomic radical retropubic prostatectomy; in Walsh PC, Retik AB, Vaughan ED Jr., Wein AJ (eds): *Campbell's Urology* 1998, ed 7, Philadelphia, vol 3, 2565-88.
11. Seaman EK, Whang IS, Cooner W, Olsson CA, Benson MC. Predictive value of prostate-specific antigen density for the presence of micrometastatic carcinoma of the prostate. *Urology* 1994;43:645-8.
12. Chang JS, Choi H, Chang YS, Kim JB, Oh MM, Moon DG, et al. Prostate-specific antigen density as a powerful predictor of extracapsular extension and positive surgical margin in radical prostatectomy patients with prostate-specific antigen levels of less than 10 ng/mL. *Korean J Urol* 2011;52:809-14.
13. Ishida M, Nakashima J, Hashiguchi A, Mizuno R, Shinoda K, Kikuchi E, et al. Are predictive models for cancer volume clinically useful in localized prostate cancer? *Int J Urol* 2009;16:936-40.
14. Stamatakis L, Siddiqui MM, Nix JW, Logan J, Rais-Bahrami S, Walton-Diaz A, et al. Accuracy of multiparametric magnetic resonance imaging in confirming eligibility for active surveillance for men with prostate cancer. *Cancer* 2013;119:3359-66.
15. Perrotti M, Pantuck A, Rabbani F. Review of staging modalities in clinically localized prostate cancer. *Urology* 1999;54:208-14.
16. Görgel SN, Şefik E, Balcı U, Girgin MC, Dinçel Ç. The relationship between prostate size, patient age and prognostic factors in patients with prostate biopsy cancer detected. *Turkish Journal of Urology* 2012;38:121-5.
17. Noldus J, Stamey TA. Limitations of serum prostate specific antigen in predicting peripheral and transition zone cancer volumes as measured by correlation coefficients. *J Urol* 1996;155:232-7.
18. Bostwick DG. Staging prostate cancer: Current methods and limitations. *Eur Urol* 1997;32:2-14.
19. Günlüsoy B, Zeyrek N, Arslan M, Değirmenci T, Minareci S, Ayder AR. Preoperative prediction of surgical margin status in patients with localized prostate cancer treated by radical prostatectomy. *Turkish Journal of Urology* 2006;32:30-6.
20. Masieri L, Minervini A, Vittori G, Lanciotti M, Lanzi F, Lapini A, et al. The role of free to total PSA ratio in prediction of extracapsular tumor extension and biochemical recurrence after radical prostatectomy in patients with PSA between 4 and 10 ng/mL. *Int Urol and Neph* 2012;44:1031-8.