Ekvivalent: Vrijednosti prostata specifičnog antigena (PSA) u bolesnika s adenokarcinomom prostate niskog i visokog rizika

Mašić, Silvija

SVEUČILIŠTE U ZAGREBU
MEDICINSKI FAKULTET

Silvija Mašić

Vrijednosti prostata specifičnog antigena (PSA) u bolesnika s adenokarcinomom prostate niskog i visokog rizika

Završni specijalistički rad

Zagreb, 2024. godine

Ovaj rad načinjen je u Kliničkom zavodu za patologiju i citologiju Ljudevit Jurak, Kliničkog bolničkog centra Sestre milosrdnice u Zagrebu.

Rad je objavljen u časopisu Acta Clinica Croatica: Acta Clin Croat (Suppl 1) 2019;58:12-5. doi: 10.20471/acc.2019.58. s2.02.

Navedeni rad je ekvivalent završnog specijalističkog rada.

Voditelj rada: **Prof. dr. sc. Božo Krušlin, dr. med**

Acta Clin Croat (Suppl. 1) 2019; 58:12-15 Original Scientific Paper

doi: 10.20471/acc.2019.58.s2.02

PROSTATE-SPECIFIC ANTIGEN (PSA) VALUES IN PATIENTS WITH LOW-AND HIGH-RISK PROSTATIC ADENOCARCINOMA

Silvija Mašić[1], Ivan Pezelj[2] and Božo Krušlin[1,3]

[1]Ljudevit Jurak Department of Pathology and Cytology, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia; [2]Department of Urology, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia; [3]Department of Pathology, School of Medicine, University of Zagreb, Zagreb, Croatia

Summary – Prostatic adenocarcinoma (PC) comprises around 19% of malignancies in Croatian male population. On the basis of PSA value, Gleason score, grading group and clinical stage, PC can be classified into low- and high-risk groups which is significant for different therapeutic regimens and prognostic outcomes. In this retrospective study, we analyzed the difference in preoperative PSA value in a group of 272 patients who underwent radical prostatectomy and were diagnosed with PC adenocarcinoma in our institution in a period from January 1st, 2018 untill December 31st, 2018. Subsequently, they were divided into low- and high- risk prostatic adenocarcinoma groups. Our results demonstrated positive correlation in preoperative PSA values between the groups and therefore support the use of PSA as one of the parameters in defining low- and high-risk prostatic adenocarcinoma categories.

key words: *Prostatic Adenocarcinoma, PSA, Gleason Grade, Low-risk, High-risk*

Introduction

Adenocarcinoma of the prostate (PC) is considered to be one of the most common malignancies in male population of Western society[1,2]. In developed countries, the percentage of men suffering from this cancer rises up to 15.3 %, while in underdeveloped ones, that percentage is much lower[3,4]. In most cases prostate cancer can be considered low-risk and treated successfully with therapeutic approaches including active surveillance of the patient, surgery and radiation[5]. Still, cases that can be characterized as a high-risk disease should be recognized, since it implies larger mortality risk and the possibility of resistance to treatment when compared to low-risk cases[5,6]. Gleason score, grade groupings, clinical stage and preoperative PSA value are important factors in defining these two groups of patients suffering from prostate adenocarcinoma. The aim of this study was to analyze the correlation in preoperative PSA value between low- and high-risk group patients diagnosed with prostatic adenocarcinoma.

Patients and methods

The study included 272 patients, median age of 64.7 years (range 40 - 78 years), treated with radical retropubic prostatectomy for prostatic adenocarcinoma at the Department of Urology in Sestre milosrdnice University Hospital Centre in Zagreb, Croatia. The diagnosis of prostatic adenocarcinoma was established on needle core biopsies and confirmed by HE slides examination of radical prostatectomy specimens in all cases. Data on PSA preoperative values, Gleason score and clinical stage were collected from database of Ljudevit Jurak Department of Pathology and Cytology, and Dpt of Urology, Sestre milosrdnice University

Corresponding to: *Božo Krušlin, MD, PhD, Professor of Pathology,* Ljudevit Jurak Department of Cytology and Pathology, Sestre milosrdnice University Hospital Centre, Vinogradska 29, Zagreb, Croatia
e-mail: bozo.kruslin@gmail.com

Table 1. Gleason score and clinical stage T of evaluated patients

Gleason score	Number of patients
<7	10 (3.7 %)
7	230 (84.6%)
8	14 (5.1 %)
9	18 (6.6%)
Clinical stage T	
T2a	16
T2b	0
T2c	206
T3	50

Table 2. Number of patients and median value of preoperative PSA value in low- and high-risk group of patients with prostatic adenocarcinoma

	Low- risk group	High- risk group	P value
number of patients	183 (67.3%)	89 (32.7%)	
Preoperative PSA (median value)	14.7 ng/ml	25.5 ng/ml	P < 0.01

Hospital Centre, Zagreb, Croatia. Patients were divided into low- and high- risk prostatic adenocarcinoma category based on National Comprehensive Cancer Network (NCCN) criteria for definition of high- grade prostatic adenocarcinoma (PSA ≥ 20 ng/ml or biopsy Gleason sum 8-10 or clinical stage ≥ T3 or any 2 of the following: T2b/c, biopsy Gleason sum 7, PSA 10-20 ng/ml) [6].

Statistical analysis was performed using Mann-Whitney U test. Results were considered statistically significant in cases of p value < 0.05.

Results

Gleason score was under 7 in 10 (3,7%) patients, while 230 (84,6%) patients had a score 7, yet 169 (62,1%) patients had a score 7 (3+4), while 61 (22,4%) had a score 7 (4+3). Gleason score 8 was recorded in 14 (5,1%) patients with 4 (1,5%) of them having 4+4, 7 (2,6%) having a score 3+5 and 3 (1%) had a score 5+3. Eighteen patients had a score 9 (6.6%), with 15 (5.5%) having a score 4+5, and 3 (1,1%) a score 5+4. in stage t2 were 222 patients, with 16 of them in stage 2a, and 206 in T2c, while 50 patients were in T3 clinical stage (table 1). Low-risk group consisted of 183 (67.3%) patients, while high-risk group had 89 (32.7%) patients. Range of PSA was 0.79- 92.6 ng/ml, in low-risk group 0.79- 19.22 ng/ ml, median value 14.7 ng/ ml and in high-risk group 3.4 - 92.6 ng/ml, with a median value of 25.5 ng/ml. We demonstrated positive correlation of preoperative PSA value between low- and high-risk group; patients with low-risk prostatic adenocarcinoma had smaller values of preoperative PSA than patients in the high-risk group ($p < 0.01$, $p < 0.05$) (table 2).

Discussion

Prostatic cancer is among the most common visceral malignancies in male population, including Croatia[1,7]. Men with family history of prostate carcinoma, those with inherited BRCA1 and 2 mutations and men of black race are considered to be more susceptible to development of this disease[2]. It can demonstrate heterogeneity in its clinical behavior, ranging from indolent to aggressive disease characterized by metastatic and potentially lethal disease resistant to therapy[8]. Therefore, risk stratification of patients with this malignancy is necessary for the right therapeutic approach to be applied[8]. Currently, different criteria for risk stratification are used[8]. Most patients are diagnosed with low-risk disease, however, up to 15% of diagnosed cases are high-risk[9]. Determining a patient's disease risk is important when choosing adequate treatment option and therefore achieve best prognostic outcome possible[9,10].

Current definitions regarding risk assessment involve Gleason grading as an important factor that has over the years become relevant in determining high-risk disease, which has great significance in clinical settings for predicting prognosis of the disease. In addition, Gleason score has important impact on therapeutic approach to the patient, assisting in deciding whether radical method or just active surveillance of the patient should be applied[11,12]. Study of Berney et al.[10] demonstrated that patients with Gleason score 6 (3+3) require only surveillance, but also that patients with a score 7 (3+4) and minimal percentage of pattern 4 have a good prognosis. The same authors emphasized the importance of pattern 4 and 5 percentage affecting therapeutic measures, since their presence implicates

worse prognosis[10]. Kamel et al showed that patients with Gleason score 7 (4+3) prostate cancers have higher PSA levels at diagnosis than those with 7 (3+4).[13]

PSA still holds an important place in risk assessment and prostate carcinoma management considering its role in the process of disease screening, estimation of future disease appearance, recurrent disease or occult metastatic disease detection and in the process of disease management[2]. PSA is commonly detected in blood as total prostate specific antigen (tPSA) and usually increases in the presence of prostatic malignant disease[3]. However, PSA level increase is not specific for prostatic carcinoma, since it can occur due to prostatitis and benign prostatic hyperplasia, which are benign conditions by nature[3]. Increase in PSA is according to International Society of Urological Pathology an important point in diagnosis of prostate carcinoma, yet not solely suficient for prognosis and estimation of disease progression[14]. Currently, the value of PSA 20 ng/ml or more has been used as a cut-off for defining high-risk category patients, yet, its value cannot be used as the only factor in risk assessment due to lack of specificity. However, in combination with other parameters such as Gleason score and clinical stage, it has great value in prostate cancer risk assessment[15]. Our study also demonstrated the importance of pretreatment PSA value, since levels were significantly higher in high-risk than in low-risk patient groups.

Another important factor for defining risk groups of prostatic carcinoma is the clinical stage. Contemporary definitions for high-risk cancer include clinical stage T2b or higher in combination withpretreatment PSA and Gleason score; however, standardized definition has still not been established[15].

Definitions of high-risk disease are not only heterogeneous, but also associated with differences in prognostic outcome[8]. Mossanen et al. demonstrated significant differences in the outcome in patients depending which criteria for high-risk disease were applied before treatment[5]. In case of patients with high-risk disease, optimal treatment is still debatable, but the options currently include radical prostatectomy, androgen deprivation therapy combined with external beam radiotherapy or a combination of androgen deprivation therapy with external beam radiotherapy and brachytherapy[6]. As for the low-risk group, Roy et al. demonstrated no significant difference in survival among patients with low-risk cancer when compared to those treated with active surveillance and those undergoing active treatment[16].

In conclusion, we emphasize the importance of risk assessment in prostate adenocarcinoma patients. In addition, our study demonstrated positive correlation of pretreatment PSA value with the high-risk group as defined by National Comprehensive Cancer Network (NCCN) criteria, therefore supports its use as one of the parameters in the estimation of risk. Further studies with correlation of grade groups and preoperative PSA values may also be informative.

References

1. Moch H, Humphrey PA, Ulbright TM, Reuter VE (Ed.).WHO Classification of Tumours of the Urinary System and Male Genital Organs WHO/IARC Classification of Tumours, 4th Edition, Volume 8, Lyon 2016.
2. Pezaro C, Woo HH, Davis ID. Prostate cancer: measuring PSA. Intern Med J. 2014; 44:433-40. doi: 10.1111/imj.12407.
3. Janbaziroudsari H, Mirzaei A, Maleki N. Association of serum prostate-specific antigen levels with the results of the prostate needle biopsy. Bull Cancer. 2016;103: 730–4.doi: 10.1016/j. bulcan.2016.05.006.
4. Ghodoussipour S, Cacciamani GE, de Castro Abreu AL. Radical prostatectomy for high-risk prostate cancer. IntBraz JUrol.2019;45:42834.doi:10.1590/S16775538.iBJu.2019.03.03.
5. Mossanen M, Nepple KG, Grubb RL 3rd, Androile GL, Kallogjeri D, Klein EA. Heterogeneity in definitions of high-risk prostate cancer and varying impact on mortality rates after radical prostatectomy. Eur Urol Oncol. 2018;1:143-8. doi: 10.1016/j.euo.2018.02.004.
6. Zumsteg ZS, Zelefsky MJ, Woo KM, Spratt DE, Kollmeier MA, McBride S. Unification of favourable intermediate-, unfavourable intermediate-, and very high-risk stratification criteria for prostate cancer. BJUInt.2017;120:E87–E95. doi:10.1111/ bju.13903.
7. Hrvatski zavod za javno zdravstvo, Registar za rak Republike Hrvatske. Incidencija raka u Hrvatskoj 2016., Bilten 41, Zagreb, 2019.
8. Mossanen M, Krasnow RE, Nguyen PL,Trinh QD, Preston M, Kibel AS. Approach to the patient with high-risk prostate cancer. Urol Clin North Am. 2017;44: 635–45.doi: 10.1016/j. ucl.2017.07.009.
9. Mason RJ, Joniau S, Karnes RJ. Defining "high risk" for men with localized prostate cancer: how close can clinical parameters get us? Eur Urol Oncol. 2018;1:149-50. doi: 10.1016/j. euo.2018.04.009.
10. Berney DM, Beltran L, Sandu H, Soosay G, Møller H, Scardino P et al. The percentage of high-grade prostatic adenocarcinoma in prostate biopsies significantly improves on Grade

Groups in the prediction of prostate cancer death. Histopathology. 2019;75:589-57. doi: 10.1111/his.13888.

11. Solarić M, Grgić M, Omrčen T, Petković M, Frobe A, Belaj N et al. Kliničke upute za dijagnostiku, liječenje i praćenje bolesnika oboljelih od raka prostate Hrvatskog onkološkog društva i urološkog društva Hrvatskog liječničkog zbora. Liječ Vjesn. 2013;135:298-305.
12. Tomašković I, Bulimbašić S, Čustović Z, Reljić A, Krušlin B, Kraus O. Correlation of Gleason grade in preoperative prostate biopsy and prostatectomy specimens. Acta Clin Croat. 2003; 42:225-7.
13. Kamel MH, Khalil MI, Alobuia WM, Su J, Davis R. Incidence of metastasis and prostate-specific antigen levels at diagnosis in Gleason 3+4 versus 4+3 prostate cancer. Urol Ann. 2018;10: 203–8. doi: 10.4103/uA.uA_124_17.
14. Kato M, Kimura K, Hirakawa A, Kobayashi Y, Ishida R, Kami-hira O. Prognostic parameter for high risk prostate cancer patients at initial presentation. Prostate. 2018; 78:11-16. doi: 10.1002/pros.23438.
15. Goldberg H, Baniel J, Yossepowitch O. Defining high-risk prostate cancer. CurrOpin Urol. 2013;23:337-41. doi: 10.1097/ mOu.0b013e328361dba6.
16. Roy S, Hyndman ME, Danielson B, Fairey A, Lee-Ying R., Cheung WY. Active treatment in low-risk prostate cancer: a population-based study. Curr Oncol. 2019;26:e535-e40. doi: 10.3747/co.26.4953.

Sažetak

VRIJEDNOSTI PROSTATA SPECIFIČNOG ANTIGENA (PSA) U BOLESNIKA S ADENOKARCINOMOM PROSTATE NISKOG I VISOKOG RIZIKA

S. Mašić, I. Pezelj i *B. Krušlin*

Adenokarcinom prostate čini oko 19% malignideta u muškoj populaciji hrvata. Svi dijagnosticirani adenokarcinomi prostate se s obzirom na vrijednost PSA, Gleason zbroj i klinički stadij mogu svrstati u skupine niskog i visokog rizika. U ovoj retrospektivnoj studiji analizirali smo razliku u vrijednostima preoperativnog PSA u skupini od 272 pacijenta kojima je dijagnosticiran adenokarcinom prostate nakon radikalne prostatektomije učinjene u našoj ustanovi u razdoblju od jedne godine (01. siječnja do 31. prosinca 2018.), a koji su podijeljeni u skupine adenokarcinoma prostate niskog i visokog rizika. Rezultati naše studije pokazuju pozitivnu korelaciju u vrijednostima preoperativnog PSA između grupa. Nadalje, rezultati naše analize podupiru upotrebu PSA kao jednog od parametara u definiranju kategorija niskog i visokog rizika karcinoma prostate.

ključne riječi: *PSA, Gleason zbroj, adenokarcinom prostate visokog rizika*

ŽIVOTOPIS

Dr.sc. Silvija Mašić, dr. med, specijalistica je patologije i citologije u Kliničkom zavodu za patologiju i citologiju, Kliničkog bolničkog centra Sestre milosrdnice.

Rođena je 20. travnja 1984. godine u Varaždinu. Srednjoškolsko obrazovanje u vidu opće gimnazije završava u Varaždinu 2002. godine.

Medicinski fakultet u Zagrebu upisala je 2002. godine i na istom je diplomirala 2008. godine. Nakon završetka studija odradila je obavezni liječnički staž u trajanju od godinu dana (od studenog 2008. do studenog 2009. godine) u Općoj bolnici Varaždin nakon čega je položila državni ispit u siječnju 2010. godine te stekla odobrenje za samostalan rad.

Od veljače 2010. do rujna 2011. godine bila je zaposlena u svojstvu liječnika hitne medicine u Zavodu za hitnu medicinu Varaždinske županije te od listopada 2012. godine do veljače 2017. godine u istom svojstvu u Nastavnom zavodu za hitnu medicinu grada Zagreba.

Specijalizaciju iz patologije i citologije na Kliničkom zavodu za patologiju i citologiju „Ljudevit Jurak“ Kliničkog bolničkog centra Sestre milosrdnice započela je u veljači 2017. godine te istu završila u lipnju 2022. godine stekavši naslov specijalista patologije i citologije.

Od 2011. do 2018. godine pohađala je Poslijediplomski znanstveni studij „Biomedicina i zdravstvo“, a disertaciju pod naslovom „Ekspresija plakofilina 3 u difuznom malignom pleuralnom mezoteliomu“ pod mentorstvom prof. dr. sc. Svena Seiwertha obranila je 14.ožujka 2018. godine te je za istu dobila nagradu Sergej Saltykow za najbolju disertaciju iz područja patologije u prosincu 2018. godine.

Poslijediplomski specijalistički studij Patologija i citologija pohađala je u akademskoj godini 2019/2020.

U 2021. godini postaje znanstveni suradnik na Medicinskom fakultetu Sveučilišta u Zagrebu te od iste sudjeluje u izvođenju nastave kolegija Patologija na Medicinskom fakultetu Sveučilišta u Zagrebu kao vanjski suradnik.

Aktivno je sudjelovala na brojnim domaćim i međunarodnim kongresima te na više tečajeva trajnog medicinskog usavršavanja iz područja patologije.

Autorica je i koautorica više znanstvenih članaka kao i kongresnih sažetaka prezentiranih na domaćim i stranim znanstvenim skupovima. Također je recenzirala više znanstvenih članaka za međunarodne znanstvene časopise.

Članica je Hrvatske liječničke komore, Hrvatskog liječničkog zbora, Hrvatskog društva patologa i sudskih medicinara te Europskog društva patologa.

Aktivno se služi engleskim, španjolskim, njemačkim i slovenskim jezikom.