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Biopsy Quantitative Patohistology and Seral Values of Prostate Specific Antigen-Alpha (1) Antichymotrypsine Complex in Prediction of Adverse Pathology Findings after Radical Prostatectomy

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ABSTRACT

In this prospective study we examined the utility of parameters obtained on prostate needle biopsy and prostate specific antigen-alpha(1)-antichymotripsine complex (PSA-ACT) to predict adverse pathologic findings after radical prostatectomy. 45 consecutive patients assigned for radical prostatectomy due to clinically localized prostate cancer were included in the study. Prostate biopsy parameters such as number of positive cores, the greatest percentage of tumor in the positive cores, Gleason score, perineural invasion, unilaterality or bilaterality of the tumor were recorded. PSA-ACT was determined using sandwich immunoassay chemiluminiscent method (Bayer, Tarrytown, New York). We analyzed relationship of preoperative PSA, PSA-ACT and quantitative biopsy parameters with final pathology after prostatectomy. Adverse findings were considered when extracapsular extension of cancer (pT3) was noted. Postoperatively, 29 (64.4%) patients were diagnosed with pT2 disease and 16 (35.6%) with pT3 disease. There was a significant difference in localized vs. locally advanced disease in number of positive biopsy cores ($p<0.001$), greatest percentage of tumor in the core ($p=0.008$), localization of the tumor ($p=0.003$) and perineural invasion ($p=0.004$). Logistic regression was used to develop a model on the multivariate level. It included number of positive cores and PSA-ACT and was significant on our cohort with the reliability of 82.22%. The combination of PSA-ACT and a large scale of biopsy parameters could be used in prediction of adverse pathologic findings after radical prostatectomy. Clinical decisions and patients counselling could be influenced by these predictors but further confirmation on a larger population is necessary.

Key words: *prostate cancer, PSA, PSA-ACT, prostate cancer staging, extraprostatic extension, perineural invasion, positive surgical margins, prostate biopsy*

Introduction

Quantitative pathohistology relates to a number of biopsy parameters that can be obtained on prostate biopsy specimen and could provide additional information in patient assessment regarding type and aggressiveness of the cancer as well as tumor volume or extent. These include number of biopsy positive cores, tumor percentage in a positive core, unilaterality or bilaterality of positive cores, biopsy Gleason score, perineural invasion and a number of molecular markers. Although radical prostatectomy provides excellent control of prostate cancer, about one third of men will develop biochemical recurrence (BCR) within 10 years of surgery. Additionally, men with adverse pathological features including extraprostatic extension, positive margins and seminal vesicle invasion have as high as 60% risk of BCR within 3 years, leading to increased risk of prostate cancer death[1]. There is a certain diversity among practicing urologists in preoperative utility of biopsy parameters in tailoring treatment of prostate cancer patients and contradictory results were found by studies investigating the relationship among the prostate biopsy findings (such as number of positive cores, percent-

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age of positive cores (PPCs), and cancer length in a positive biopsy core), postoperative pathological stage, and biochemical failure[2].

Prostate specific antigen complexed with alpha (1)-antichymotripsin is predominant form of circulating PSA and its fraction is higher in cancer patients than in those with benign hyperplasia[3]. Due to its stability and minimal variability comparing to other forms of PSA, PSA-ACT is a potential marker for prediction of adverse pathology findings after radical prostatectomy[4].

In this prospective study we examined the utility of parameters obtained on prostate needle biopsy and prostate specific antigen-alpha(1)-antichymotripsine complex (PSA-ACT) to predict adverse pathological findings, namely, organ confined *vs.* non-organ confined disease, on a univariate and multivariate level.

Patients and Methods

45 consecutive patients assigned for radical prostatectomy due to clinically localized prostate cancer were included in the study. All patients underwent sextant biopsy with 18 gauge needle under transrectal ultrasound (Siemens SI 400, biplanar 5.0/7.0 Hz sound) control. Digitorectal examination, transrectal ultrasound and PSA measurement were used in staging. We excluded those who were on neoadjuvant hormonal therapy or any other medications for prostate diseases, who had previous prostate surgery, who had PSA>20 ng/mL, older than 75 yrs, biopsy Gleason sum greater than 7. Preoperatively, a blood sample was taken from each of them to measure level of PSA and PSA-ACT. PSA-ACT was determined using sandwich immunoassay chemiluminiscent method (Bayer, Tarrytown, New York). PSA analysis was done on automatic analyzer ACS: 180+ (Bayer). We also recorded prostate biopsy parameters: number of positive cores, the greatest percentage of tumor in the positive cores, Gleason score (primary and secondary pattern), perineural invasion, unilaterality or bilaterality of the tumor. The prostatectomy specimen were fixed in buffered formaldehyde, and entirely included in whole mounting sections after inking surgical margins which helped determining relationship of cancer with inked margin. pTNM classification (2002. revision) was used for tumor staging.

We analyzed relationship of PSA, PSA-ACT and quantitative biopsy parameters and final pathology after prostatectomy (pT stage).

Statistics

Quantitative parameters were described by mean, median, range and standard deviation. For comparison of these parameters between two final pT stage groups (pT2 and pT3) Mann-Whitney nonparametric test was used. Qualitative parameters were described in frequency tables. Fisher´ s exact test was used for comparison of these parameters between two final pT stage groups (pT2 and pT3). $p<0.05$ was considered significant. Logistic regression model was developed to predict final stage of the disease.

TABLE 1
QUANTITATIVE PARAMETERS AND THEIR COMPARISON WITH RESPECT TO FINAL PATHOLOGIC STAGE. ASTERISK SHOWS STATISTICAL SIGNIFICANCE ($p<0.05$)

	pT stage	$\overline{X}$	Median	Standard deviation	Minimum	Maximum	p value
Age	pT2	64.40	65.00	4.66	55.00	72.00	0.167
	pT3	66.50	66.50	2.82	61.00	71.00	
Volume	pT2	33.70	32.00	12.89	17.00	77.00	0.123
	pT3	39.44	34.50	12.90	20.00	69.00	
PSA	pT2	8.22	7.50	3.81	3.71	18.20	0.188
	pT3	9.93	10.15	4.63	2.57	18.82	
PSA-ACT	pT2	7.58	7.03	3.61	3.32	17.43	0.209
	pT3	9.31	9.38	4.41	2.36	18.37	
Number of positive biopsy cores	pT2	2.10	2.00	1.11	1.00	5.00	<0.001*
	pT3	4.31	4.50	1.45	1.00	6.00	
Greatest percentage of tumor in core	pT2	32.76	30.00	23.05	5.00	80.00	0.008*
	pT3	57.81	75.00	31.57	5.00	90.00	
Gleason score	pT2	5.89	6.00	0.90	4.00	7.00	0.135
	pT3	6.31	6.50	0.79	5.00	7.00	

PSA - prostate specific antigen, PSA-ACT – prostate specific antigen-alpha(1)-antichymotripsine complex

Results

Out of 45 patients with clinically localized prostate cancer, 29 (64.4%) had organ confined disease, and 16 (35.6%) had extracapsular extension on final pathology after radical prostatectomy. 270 biopsy cores were analyzed.

Quantitative parameters: age, PSA-ACT, PSA, prostate volume, number of positive biopsy cores, greatest percentage of tumor in the core, Gleason score on biopsy are presented in Table 1. (pts. with organ confined *vs.* non-organ confined disease).

Comparison of quantitative parameters between pts. with organ confined *vs.* pts. with non-organ confined disease (Table 1) showed no difference in age (p=0.167) and prostate volume (p=0.123). Number of positive biopsy cores is different among patients in those groups (mean 2.10 *vs.* 4.31; p<0.001). Greatest percentage of tumor in the core was also different among pts in organ confined *vs.* locally advanced disease ($\overline{X}$ 32.76 *vs.* 57.81%; p=0.008). No difference was observed in seral values of TPSA and PSA-ACT (p=0.188 and p=0.209) among groups on the univariate level.

Qualitative parameters: digitorectal examination (DRE), transrectal ultrasound (TRUS), presence of tumor unilaterally or bilaterally (UNI-BI), perineural invasion (PNI), presence of Gleason grade 4 (GS-4) on biopsy are presented in frequency Table 2. Significant difference was observed with respect to perineural invasion (PNI; p=0.004) and laterality of tumor (UNI-BI; p=0.003). There was no difference with respect to DRE, TRUS and presence of Gleason grade 4 in biopsy Gleason score (p values in Table 2).

Logistic regression was used for analysis of given parameters on a mulitivariate level.

Initial model predicts final stage with 64.44% accuracy with initial –2 Log Likelihood = 58.57. This model basically represents accuracy of the clinical assessment of the stage. In stepward forward fashion number of positive cores was added and the reliability of the model improved to 80% with –2 Log Likelihood = 36.46 which was significant compared to the initial model (hi-square=22.1; p<0.001). In the second step PSA-ACT was chosen as next parameter in the model and reliability of the model reached 82.22% (Table 3) with –2 Log Likelihood = 32.08 which was significant compared to both the initial model (hi-square =26.5 ; p<0.001), and first step of logistic regression (χ^2 =4.4 ; p=0.04). Further adding of parameters in the logistic regression did not improve the model. Therefore from given parameters: age, PSA-ACT, TPSA, prostate volume, number of positive biopsy cores, greatest percentage of tumor in the core, Gleason score, presence of Gleason grade 4 on biopsy, digitorectal examination (DRE), transrectal ultrasound (TRUS), presence of tumor unilaterally or bilaterally (UNI-BI), perineural invasion (PNI), only number of positive biopsy cores and PSA-ACT were chosen in the model as the most appropriate. They were strong predictors of the cancer stage.

TABLE 2
QUALITATIVE PARAMETERS AND THEIR COMPARISON WITH RESPECT TO FINAL PATHOLOGIC STAGE. ASTERISK SHOWS STATISTICAL SIGNIFICANCE (p<0.05)

		pT2	pT3	p value
DRE	–	15	7	0.758
	+	14	9	
TRUS	–	16	6	0.353
	+	13	10	
Unilateral- bilateral	UNI	24	6	0.003*
	BI	5	10	
Perineural invasion	YES	0	5	0.004*
	NO	29	11	
Gleason grade 4	YES	21	7	0.107
	NO	8	9	

DRE – digitorectal examination, TRUS – transrectal ultrasound

Discussion

Predicting prostate cancer extent has immense value, dictating choice of treatment; surveillance, surgical, radiation or palliative and affecting the patient counselling. But in spite of all technological advances preoperative staging is still much or less inaccurate. DRE and additional tests such as transrectal ultrasound, CT or MR have been used in assessment of local stage but their positive predictive value varies between 57-92%[5–8]. There is a number of molecular staging methods emerging but their utility in everyday practice is still limited due to high coasts[9,10]. Besides imaging techniques, there are various multimodel staging tools[11,12]. However, even the best statistical model does not accurately predict prostate cancer stage[13].

Almost one third of patients undergoing radical prostatectomy in present series have extraprostatic disease[14]. So, there is a pressing need to develop indirect means for predicting the pathology stage. Although not perfect, PSA remains a cornerstone in everyday practice and its com-

TABLE 3
LOGISTIC REGRESION: SECOND STEP; INCLUSION OF PSA-ACT IN THE PREDICTION MODEL. DIFFERENCE COMPARED TO BASIC MODEL AND COMPARED TO FIRST STEP OF LOGISTIC REGRESION (p<0.001, p=0.04) WAS STATED. OVERALL RELIABILITY OF THE MODEL INCREASED TO 82.22%

Step 2: PSA-ACT	Predicted localized	Predicted advanced	Percent correct (%)
Observed localized	26	3	89.66
Observed advanced	5	11	68.75
χ^2=26.5; p<0.001		Total: 82.22%	
χ^2=4.4; p=0.04			

bining with other parameters is still the most convenient option.

PSA-ACT has been reported to be more relevant in prostate cancer patients comparing to total PSA, having in mind that its´ proportion rises in these patients to a greater extent than in BPH patients[3,4]. The goal of radical prostatectomy for the treatment of localized prostate cancer is to cure the disease while restoring quality of life. Nerve sparing and possibly seminal vesicle sparing techniques increase the likelihood of preserving erectile function. It is conceivable that in higher risk cases of clinically localized prostate cancer, preserving these structures may compromise local disease control[15].

In the present study we tried to evaluate the importance of broader spectrum of biopsy parameters and their combination with PSA-ACT in tumor stage prediction on the univariate and multivariate level. PSA-ACT has been found by some authors to be more accurate in cancer diagnosis which was the reason to include this form of PSA in the evaluation of stage[4]. In our material 64.4% of patients were organ confined, and 35.6% had extracapsular extension after radical prostatectomy. Mean age between pT2 and pT3 group was not different (64.4 *vs.* 66.5 yr). On the univariate level number of positive biopsy cores and percentage of positive biopsy cores were significantly different among quantitative parameters ($p<0.001$ and $p=0.008$ respectively) while perineural invasion and tumor localization in one or both lobes were different in pT2 and pT3 group among quantitative parameters ($p=0.004$ and $p=0.003$). Different biopsy parameters have been studied in this context. Sankin et al. found, using a univariate analysis, age, serum prostate-specific antigen (PSA), prostate volume, clinical stage, Gleason score, number of positive biopsies, percent positive biopsy cores, percent volume of prostate cancer in cores and perineural invasion all to be significant predictors of both ECE and seminal vesicle invasion (SVI). A multivariate analysis was performed to determine the independent predictors of ECE and SVI. Serum PSA, biopsy Gleason score, percent volume of biopsy cores with cancer and perineural invasion were found independent predictors of side-specific ECE. Age, serum PSA, Gleason score and prostate volume were independent predictors of side-specific SVI[15].

Sebo and coworkers determined important role of PSA, percentage of tumor in positive biopsy core, perineural invasion and Gleason score in prediction of tumor extent[16]. Number of cores and PSA-ACT were not analyzed. Rubin and all. found age, number of positive cores, tumor percentage, perineural invasion, PSA and Gleason score to be predictive of stage on a cohort of 632 patients[17]. Their study did not include tumor location nor PSA-ACT. In the study of Villamón-Fort et al. the multivariate analysis for organ-confined disease, the total percentage of biopsy tissue with cancer, the preoperative PSA level, the Gleason score and the clinical stage were the most accurate predictive factors of pathological stage. The multivariate analysis for the study of biochemical failure indicated that only the total percentage of biopsy tissue with cancer, the preoperative PSA level and the Gleason score were independent predictive factors. According to the logistic regression analysis for disease recurrence, 3 risk groups could be identified: low risk (less than 10% probability of disease progression), intermediate risk (30%) and high risk (more than 70%)[18]. Gancarczyk stated Gleason sum, PSA and tumor percentage to correlate with stage and a nomogram was proposed[19]. Number of positive cores was not analyzed. A systematic review of the literature was performed recently to assess the relationship between the presence of perineural invasion (PNI) at prostate biopsy and extraprostatic extension (EPE) of prostate cancer. In univariate analysis, PNI showed a statistically significant association with pT3 tumours ($p<0.00001$), which could be observed for both pT3a ($p<0.0001$) and pT3b ($p<0.0001$). In conclusion, the cumulative analysis shows a statistically significant higher incidence of EPE in patients who had PNI at needle biopsy[20].

Miyake and Hara group were the first to propose PSA-ACT use in the prediction of prostate cancer extent[21,22] and they came to conclusion that it could be used as useful predictor of stage especially in the setting of some biopsy parameters (percentage of positive biopsy core and tumor location only). However, on a multivariate level they failed to show that PSA-ACT and biopsy parameters analyzed were statistically better than combination of PSA and biopsy parameters. In our study on the multivariate level logistic regression developed a model that included PSA-ACT and the number of positive cores as the strongest predictors of cancer stage with a 82.22% reliability.

Conclusion

Although our study is limited by a small study population, our results and the review of the literature show that these parameters could be useful in predicting extraprostatic disease while conflicting data on some items necessitate further investigation in this area.

REFERENCES

1. SIMON RM, HOWARD LE, FREEDLAND SJ, ARONSON WJ, TERRIS MK, KANE CJ, AMLING CL, COOPERBERG MR, VIDAL AC, Adverse pathology and undetectable ultrasensitive prostate-specific antigen after radical prostatectomy: is adjuvant radiation warranted?, BJU Int, accessed 28.06.2015. Available from: URL: http://www.ncbi.nlm.nih.gov/pubmed. DOI: 10.1111/bju.13182. — 2. SUEKANE S, NOGUCHI M, NAKASHIMA O, YAMADA S, KOJIRO M, MATSUOKA K, Int J Urol, 14 (2007) 713. — 3. ZHU L, JÄÄMAA S, AF HÄLLSTRÖM TM, LAIHO M, SANKILA A, NORDLING S, STENMAN UH, KOISTINEN H, Prostate, 73 (2013) 219. — 4. ČUSTOVIĆ Z, KRAUS O, TOMAŠKOVIĆ I, TARLE M, Anticancer Res, 27 (2007) 2817. — 5. PORTALEZ D, MALAVAUD B, Nature Reviews Urology, 12 (2015) 310. — 6. THOMPSON J, LAWRENTSCHUK N, FRYDENBERG M, THOMPSON L, STRICKER P, BJU Int, 112 (2013) 6. — 7. ROSENKRANTZ AB,

CHANDARANA H, GILET A, DENG FM, BABB JS, MELAMED J, TANEJA SS, J. Magn Reson Imaging, 38 (2013) 312. — 8. MARIČIĆ A, VALENCIĆ M, SOTOŠEK S, OGUIĆ R, IVANCIĆ A, AHEL J, Coll Antropol, 34 (2010) 239. — 9. CALABRIA F, CHIARAVALLOTI A, TAVOLOZZA M, RAGANO-CARACCIOLO C, SCHILLACI O, Nucl Med Commun, 34 (2013) 733. — 10. UMBEHR MH, MÜNTENER M, HANY T, SULSER T, BACHMANN LM, Eur Urol, 64 (2013) 106. — 11. VICKERS AJ, CA Cancer J Clin, 61 (2011) 315. — 12. XIAO WJ, YE DW, YAO XD, ZHANG SL, DAI B, WANG CF, WANG J, ZHANG HL, SHEN YJ, ZHU Y, ZHU YP, SHI GH, MA CG, QIN XJ, LIN GW, Can J Urol, 18 (2011) 5619. — 13. BOYCE S, FAN Y, WATSON R, MURPHY T, BMC Med Inform Decis Mak, 13 **(**2013) 126. — 14. MAKAROV DV, TROCK BJ, HUMPHREYS EB, MANGOLD LA, WALSH PC, EPSTEIN JI, PARTIN AW, Urology, 69 (2007) 1095. — 15. SANKIN A, TAREEN B, LEPOR H, Prostate Cancer Prostatic Dis 12 (2009) 204. — 16. SEBO TJ, CHEVILLE JC, RIEHLE DL, LOHSE CM, PANKRATZ VS, MYERS RP, BLUTE ML, ZINCKE H, Cancer, 91 (2001) 2196. — 17. RUBIN MA, BASSIY N, SANDA M, MONTIE J, STRAWDERMN MS, WOJNO K, Am J Surg Pathol, 24 (2000) 183. — 18. VILLAMÓN-FORT R, MARTÍNEZ-JABALOYAS JM, SORIANO-SARRIÁ P, RAMOS-SOLER D, PASTOR-HERNÁNDEZ F, GIL-SALOM M, Urol Int, 78 (2007) 328. — 19. GANCARCZYK KJ, WU H, MCLEOD DG, KANE C, KUSUDA L, LANCE R, HERRING J, FOLEY J, BALDWIN D, BISHOFF JT, SODERDAHL D, MOUL JW, Urology, 61 (2003) 589. — 20. COZZI G, MARIA ROCCO B, GRASSO A, ROSSO M, ABED EL RAHMAN D, OLIVA I, TALSO M, Scand J Urol Nephrol, 47 (2013) 443. — 21. MIYAKE H, HARA S, YAMANAKA N, ONO Y, ETO H, YAMADA Y, TAKECHI Y, ARAKAWA S, KAMIDONO S, HARA I, Urol Int, 68 (2002) 232. — 22. HARA I, MIYAKE H, HARA S, YAMANAKA N, ONO Y, ETO H, TAKECHI Y, ARAKAWA S, KAMIDONO S, BJU Int, 88 (2001) 53.

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BIOPSIJSKA KVANTITATIVNA PATOHISTOLOGIJA I SERUMSKE VRIJEDNOSTI PSA-ACT U PREDVIĐANJU NEPOVOLJNOG PATOLOŠKOG NALAZA NAKON RADIKALNE PROSTATEKTOMIJE

S A Ž E T A K

U ovoj prospektivnoj studiji ispitali smo korisnost parametara dobivenih na iglenoj biopsiji prostate i prostata specifičnog antigena-alfa (1) -antichymotripsin kompleksa (PSA-ACT) u predviđanju nepovoljnog patološkog nalaza nakon radikalne prostatektomije. 45 uzastopnih pacijenata podvrgnutih radikalnoj prostatektomiji zbog klinički lokaliziranog karcinoma prostate bili su uključeni u istraživanje. Zabilježeni su biopsijski parametri kao što je broj pozitivnih cilindara, najveći postotak tumora u pozitivnom cilindru, Gleason zbroj, perineuralna invazija, unilateralnost ili bilateralnost tumora. PSA-ACT određena je pomoću sendvič »immunoassay chemiluminiscent« metode (Bayer, Tarrytown, New York). Analizirali smo odnos preoperativnog PSA, PSA-ACT i kvantitativnih parametara biopsije s konačnim nalazom patološke dijagnoze nakon prostatektomije. Nepovoljnim patohistološkim nalazom smatrana je prisutnost proširenja raka prostate izvan kapsule prostate (pT3). Postoperativno, 29 (64,4%) bolesnika je imalo pT2 bolest i 16 (35,6%) pT3 bolest. Postojala je značajna razlika u odnosu lokalizirane vs. lokalno uznapredovale bolesti u broju pozitivnih biopsijskih cilindara ($p<0,001$), najvećeg postotka tumora u cilindru ($p=0,008$), lokalizacije tumora ($p=0,003$) i perineuralne invazije ($p=0,004$). Logistička regresija korištena je razvijanje prediktivnog modela na multivarijatnoj razini. Model uključuje broj pozitivnih cilindara i PSA-ACT i bio je značajan na našoj skupini s pouzdanosti 82.22%. Kombinacija PSA-ACT i biopsijski parametri mogu se koristiti u predviđanju negativnih patoloških nalaza nakon radikalne prostatektomije. Klinička odluka i savjetovanje pacijenata mogli bi biti pod utjecajem tih prediktora, ali je potrebno potvrda na većoj populaciji ispitanika.