Transperineal Ultrasound Guided-Template Biopsy of Prostate as First Means of Diagnosis of Prostate Cancer

One single's centre experience on 405 cases

IOAN SCARNECIU[1,2], CAMELIA CORNELIA SCARNECIU[1,2], ALEXANDRU BANUTA[2], COSTIN VLAD ANASTASIU[1], CIPRIAN TODEA-MOGA[3,4], ORSOLYA MARTHA[3,4], VERONICA GHIRCA[3,4], DANIEL PORAV-HODADE[3,4], LAURIAN MAXIM[2*]

[1]University of Medicine and Pharmacy Transilvania, 56 Nicolae Balcescu Str., 500019, Brasov, Romania
[2]Clinical Emergency County Hospital, 25-27 Bucuresti Road, 500326, Brasov, Romania
[3]Urology Clinic, Mures County Hospital, 50 Dr. Gheorghe Marinescu Str., 540136, Targu Mures, Romania
[4]University of Medicine, Pharmacy, Science and Technology, 38 Gheorghe Marinescu Str., 540139, Targu Mures, Romania

Even if today's standard procedure for diagnosis of prostate cancer is transrectal ultrasound guided prostate biopsy (TRB), transperineal ultrasound -guided template biopsy (TPTB) is a safe procedure because the infectious complication have been increasing, with a detection ratio even better than TRB. We consider that TPTB can be the gold standard biopsy. To assess the efficiency and safety of transperineal ultrasound-guided template biopsy of prostate (TPTB). We studied prospectively a number of 405 patients who underwent TPTB of prostate as first means of diagnosis from September 2015 to August 2017.The procedure was performed in the surgery room, in lithotomy positon, under local anesthesia, by means of standard freehand method sampling of at least 12 fragments,based on predetermined mapping. The data base included the age of the patient, the PSA level, the prostatic volume, the presence of clinical suspicion at digital rectal examination, the histopathological data and immediate and late post-surgery complications. Prostate cancer was diagnosed in 68.6 % of men (median PSA level was 11 ng/mL). A higher detection ratio within patients with prostate volume < 60 mL can be noticed.The average Gleason score was of 7.6. No patient developed any feverish symptom or urosepsis. Given the increasing trend of sepsis ratio as a result of transrectal biopsy of prostate, as well as the increased ratio of antibiotic resistance, we appreciate that the benefit of transperineal approach is important enough in order to perform TPTB as first means as well as routine for all patients. In this report we looked to assess the efficiency and the safety of TPTB as first mean of diagnosis. None of the patients had a previous biopsy by transrectal or transperineal method.

Keywords: prostate cancer, biopsy, transperineal approach,detection, prostate specific-antigen, complication

Prostate cancer is the most diagnosed cancer and the second cause of death by cancer in males. Transrectal ultrasound has been introduced in 1968 as an instrument for detection of prostate cancer [1,2].

Even if at global level the first biopsy of prostate was transperineal, while transrectal biopsy (TRTB) came 125 years later, today's standard procedure for diagnosis of prostate cancer is transrectal ultrasound guided prostate biopsy, by means of sampling 12 fragments.

Within the past years an increase of infection ratio and urinary sepsis after transrectal biopsy of prostate has been observed, which can be connected to the increase of prevalence of multiresistant bacteria [3,4]. The first study that evaluated infectious complications corelated with prostate biopsy was published in 1971 [5].

Transperineal ultrasound-guided template biopsy of prostate (TPTB) has the advantage that it avoids penetration of rectal mucosa and it minimizes inoculation of rectal flora in prostate.

Experimental part
Patients and methods

The objectives were to assess the efficiency and safety of transperineal ultrasound-guided template biopsy of prostate (TPTB).

We studied prospectively a number of 405 patients who underwent transperineal ultrasound-guided template biopsy of prostate as first means of diagnosis, within the Urology Clinic of Brasov County Clinical Emergency Hospital, Romania, from September 2015 to August 2017. The database included the age of the patient, the PSA level, the prostatic volume, the presence of clinical suspicion at digital rectal examination, the histopathological data, as well as the immediate and late post-surgery complications of the procedure.

None of the patients had a previous prostate biopsy by transrectal or transperineal method. All patients received preprocedural injectable antibiotic prophylaxis and their digestive tract was prepared by enema.

Patients underwent transperineal ultrasound-guided biopsies using a linear transducer. The procedure was performed in the surgery room, in lithotomy positon, under local lidocaine 1% anesthesia (ultrasound guided pudendal and periprostatic nerve block), by means of standard freehand method sampling of at least 12 fragments. From each prostatic lobe 6 fragments were sampled, based on predetermined mapping, from the base of the prostate, mid-gland and apex level.

Before performing biopsy, the prostate was scanned from the level of seminal vesicles to the level of apex and the prostatic volume was calculated.

The biopsy procedure was performed by means of a single incision along the median line above the anus,the fragments were collected using an automated Magnum biopsy gun with a 22 mm cutting length and Tru-cut 18 G needles.

The patients included within the study had increased PSA level, digital rectal examination with or without clinical suspicion and suspicion on imaging investigations (RMN pelvis, transrectal ultrasound with elastography).

Patients with acute urinary infections, acute prostatitis or histopathologically confirmed prostate cancer were not included in the study.

All patients undersigned consent documents prior to initiating the procedure.

Patients were discharged the day after surgery, being prescribed a 3 days treatment with levofloxacin 500 mg.

All biopsies were analized by the hospital's Pathological department.

The statistic analysis of all the patients was performed using SPSS Statistics v23.

Results and discussions

A total number of 405 patients underwent consecutively transperineal ultrasound-guided template biopsy of prostate, along with analyzing following data: age, PSA level prior to biopsy, number of sampled biopsies, prostate volume, Gleason score.

The average age of the group of biopsied patients was of 70.7 years (minimum age 43 years and maximum age 90 years), whereas the average age of patients from this group diagnosed with prostate cancer was of 71.7 years. Biopsy indication included increased PSA (99.9 %), abnormal digital rectal examination at 289 patients (71.3 %), increased PSA and abnormal digital rectal examination or suspicion on imaging investigations.

The global prostate cancer detection ratio was of 68.6%. Refering to patients who were submitted to a first transperineal biopsy and to those for whom biopsy was repeated by means of transperineal method, detection ratio increased from 68.6% to 70.4%.

An average number of 14.7 fragments (from 12 to 26 fragments) was obtained from each patient.

In a number of 18 (4.4%) patients we performed saturation transperineal biopsy (24 fragments), as initial transperineal biopsy was negative and clinical suspicion or by means of increased PSA maintained, whereas from a number of 112 patients (27.6%), for whom clinical or imaging suspicion of prostate cancer existed, there were sampled 12 standard fragments plus 2 fragments from the level of lesion.

The average prostatic volume was of 56 mL. The average time of the surgery perfomed under local anesthesia was of 21 min.

We established that there are significant statistic differences when using the t test (9.31) for independent samples, between patients diagnosed with prostate cancer and patients without prostate cancer, with regard to prostate volume. ($p < .001$, d Cohen=1.07).

Detection ratio based on prostate volume varies. We analized 2 grups, based on prostate dimensions. The first group is the one of patients with small prostate volume (< 60 mL) and it includes 259 patients, while the second group is the one of patients with large prostate volume (> 60 mL) and it includes 146 patients. A higher detection ratio within patients with prostate volume < 60 mL can be noticed. (83% vs 43.2%). χ^2 test has a value of 68,92 and is statistically significant ($p < .001$).

PSA values distributions are abnormal, with very high values for some of the patients with cancer (positive assymetric distribution Skewness = 9.06 and high Kurtosis = 103.24), in order to compare PSA values for patients diagnosed with cancer and those with no cancer, we used the non-parametric Mann-Whitney test, the resulted difference between the two groups being statistically significant: $Z = -8.91$, $p < .001$ (table 1).

Presence of cancer		No.	Minimum	Maximum	Mean	Median	Std. Deviation	Skewness	Kurtosis
No Cancer	PSA	127	4.06	108	14.76	9.6	17.21	3.75	15.03
With cancer	PSA	278	.16	8920	165.99	11	681.20	9.06	103.24

Table 1

		Gleason Score		Gleason Score categories	
		Frequency	Percent	Frequency	Percent
Gleason Score	4	10	3.6%	10	3,6%
	5	2	0.7%	116	41,7%
	6	37	13.3%		
	7	77	27.7%		
	8	80	28.8%	152	54,7%
	9	54	19.4%		
	10	18	6,5%		
	Total	278	100.0%		

Table 2

			Gleason Score	PSA
Spearman's rho	Gleason Score	Correlation Coefficient	1.000	.210**
		Sig. (2-tailed)	.	.000
		N	278	278
	PSA	Correlation Coefficient	.210**	1.000
		Sig. (2-tailed)	.000	.
		N	278	278
**. Correlation is significant at the 0.01 level (2-tailed).				

Table 3

By splitting total serum PSA on categories, we notice that within the largest number of patients, 124 (30.6%), 105 (25.9%) respectively, were diagnosed within categories 4.01-10 and 10.01-20. The average PSA for the entire group was of 118,5 ng/mL.

The average Gleason score was of 7.6. By splitting Gleason score on categories, we notice that the most important percentage of 54.7% refers to patients with Gleason score higher than 8.

The Spearman correlation coefficient obtained between numerical Gleason score and PSA is weak positive but statistically significant $\rho= .215$, $p < .001$, which means that high Gleason score patients have high PSA values (table 3)

With regard to adverse events (table 4), a number of 208 patients presented minor adverse events immediately after surgery of a few days after surgery. Adverse events which did not need hospitalization of patients in order to manage complications.

Table 4

Hematuria	44 (10.8%)
Fever >38,5	0 (0%)
Urethroragy	96 (23.7%)
Hematospermia	21 (5.18%)
Rectal bleeding	2 (0.49%)
Sepsis	0 (0%)
Dysuria	42 (10.3%)
Acute urine retention	3 (0.74%)

From a historical point of view, transperineal prostate biopsy were performed under general anesthesia, but recent studies have proven that combined anesthesia (pudendal and periprostatic nerve block), is well tolerated, the majority of patients tolerating the procedure at a reduced level of discomfort during the procedure [6,7].

Detection ratio was of 66.41%, close to the one described within other published studies regarding transperineal prostate biopsy [8-10].

There are a few studies which notice the relationship between prostate cancer detection and prostate volume [11-13]. The conclusion of these studies is close to the one of our study and it notices a superior and statistically significant detection ratio in case of small prostate volume (< 60 mL), compared to large prostate volume > 60 mL [14-17].

The most frequent Gleason score was 8, the majority of patients being part of the group with high-risc prostate cancer (Gleason 8-10). A significant statistical correlation between Gleason score and total serum PSA can be revealed. Patients diagnosed by means of increased or very increased PSA, also show a higher Gleason score ($\rho=.215$) [18,19].

Transperineal approach also highlights the easy access at the level of anterior zone of prostate, as well as a very low risk (in our study 0) of serious infectious complications, the risk of such infectious complication in case of TRB being of 1-2%.

Given our experience, complications, such as rectal bleeding, urethroragy [20] or serious infectious complications [21,22], can be largely avoided by means of performing TPTB. We have not faced any case of sepsis, maybe also due to the fact that within our facility biopsy puncture of prostate has become a standard procedure, being performed during continuous 2 days hospitalization, with both prior and postprocedural antibiotic prophylaxis. In the largest series of patients (3000 patients), Pepe and Aragona report fever in 17 cases (0.5%) and lower urinary tract infections which in 21 cases (0.7%) need hospitalization [13].

Acute urine retention was of 0.74% in our study, Guy's Hospital series with 634 patients reported an acute urine retention of 1.7% [23]. Comparing our study with other series, acute urine retention appeared in very few cases [24-29].

Cardiovascular comorbidities and related disorders must be diagnosed before the procedure and treated in order to avoid complications [30-33].

Conclusions

Since 2015, our department has set the goal of performing all prostate biopsies template transperineal ultrasound-guided, in order to benefit from the superior diagnosis accuracy, as well as from the lower risc of complications. Even if in time the learning curve for the procedure is longer compared to transrectal prostate biopsy, involving technical qualities, especially in case of large prostates, the final results minimize complication ratio.

Increased the ability to diagnose prostate cancer for apical and anterior zones has implications for patients

undergoing active surveillance and for patients who are considering minimally invasive treatment options.

In conclusion, given the increasing trend of sepsis ratio as a result of transrectal biopsy of prostate, as well as the increased ratio of antibiotic resistance [34], we appreciate that the benefit of transperineal approach is important enough in order to perform TPTB as first means, as well as routine for all patients.

References

1.BARENTSZ, J. O., FRAUSCHER, F., HEIJMINK, WITJES, J. A., VAN MOERKERK, H., KIEMENEY, L. A. L. M., Eur Radiol, **16**, no. 4, 2006, p. 927.

2.RADAVOI, G.D., PRICOP, C., JINGA, V., MATES, D., RADOI, V.E., JINGA, M., URSU, R.I., BRATU, O.G., MISCHIANU, D.L., IORDACHE, P., Rom J Morphol Embryol., **57**, no. 2, 2016, p. 467.

3.NAM, R. K., SASKIN, R., LEE, Y., LIU, Y., LAW, C., KLOTZ, L. H., NAROD, S. A., J. Urol., **189**, 1 Suppl, 2013, S12.

4.WEIDNER, W., PEREPANOVA, T., PILATZ, A., WULLT, B., WAGENLEHNER, F. M. E., BJERKLUND JOHANSEN, T., NABER, K., Eur. Urol., **63**, no. 3, 2012, p. 521.

5.DAVIDSON, P., MALAMENT, M., J. Urol., **105**, no. 4, 1971, p. 545.

6.TIGLIS, M., NEAGU, T.P., ELFARA, M., DIACONU, C.C., BRATU, O.G., VACAROIU, I.A., GRINTESCU, I.M., Rev Chim (Bucharest), **69**, no. 10, 2018, p. 2877.

7.CIUHU, A.N., RAHNEA NITA, R.A., POPESCU, M., DUMITRU BADIU, C.D., PANTEA STOIAN, A.M., LUPULIASA, D., GHERGHICEANU, F., DIACONU, C.C., RAHNEA NITA, G. Farmacia, **65**, no. 2, 2017, pp. 173-178.

8.GALFANO, A., NOVARA, G., IAFRATE, M., COSENTINO, M., CAVALLERI, S., ARTIBANI, W., FICARRA, V., EAU-EBU Update Series, **5**, no. 6, 2007, p. 241.

9.DEMURA, T., HIOKA, T., FURUNO, T., KANETA, T., GOTODA, H., MURAOKA, S., SATO, T., MOCHIZUKI, T., NAGAMORI, S., SHINOHARA, N., Cancer, **103**, no. 9, 2005, p. 1826.

10.FURUNO, T., DEMURA, T., KANETA, T., GOTODA, H., MURAOKA, S., SATO, T., NAGAMORI, S., SHINOHARA, N., KOYANAGI, T., Prostate, **58**, no. 1, 2004, p. 76.

11.AL-KHALIL, S., BOOTHE, D., DURDIN, T., SUNKARA, S., WATKINS, P., YANG, S., HAYNES, A., DE RIESE, W., Int Urol Nephrol, **48**, no. 1, 2016, p. 91.

12.KIM, J.S., RYU, J.G., KIM, J.W., HWANG, E.C., JUNG, S.I., KANG, T.W., KWON, D., PARK, K., Int Braz J Urol, **41**, no. 2, 2015, p. 258.

13.PEPE, P., ARAGONA, F., Urology, **81**, no. 6, 2013, p. 1142.

14.SPINU, D., BRATU, O., MARCU, D., MISCHIANU, D., HUICA, R., SURCEL, M., MUNTEANU, A., SOCEA, B., BODEAN, O., URSACIUC, C., Rev. Chim. (Bucharest), **69**, no. 3, 2018, p. 645.

15.MARCU, D., SPINU, D., MISCHIANU, D. , SOCEA, B., OPREA, I., BRATU, O., Romanian Journal of Military Medicine, **120**, no. 3, 2017, p. 39.

16.POPESCU, R., BRATU, O., SPINU, D., MARCU, D., FARCAS, C., DINU, M., MISCHIANU, D., Romanian Journal of Military Medicine, **118**, no. 3, 2015, p. 16.

17.BRATU, O., SPINU, D., OPREA, I, POPESCU, R., MARCU, D., FARCAS, C., DINU, M., MISCHIANU, D., Romanian Journal of Military Medicine, **118**, no. 3, 2015, p. 23.

18.BRATU, O., MISCHIANU, D., CONSTANTINOIU, S., Chirurgia (Bucur)., **108**, no. 2, 2013, p. 250.

19.SCARNECIU, I., ANDREI, C., SCARNECIU, C., LUPU, A.M., BRATU, O.G., LUPU, S., Urology Journal, **15**, no. 5, 2018, p. 297.

20.TICA, O.A., TICA, O., ANTAL, L., HATOS, A., POPESCU, M.I., PANTEA STOIAN, A., BRATU, O.G., GAMAN, M.A., PITURU, S.M., DIACONU, C.C., Farmacia, **66**, no. 6, 2018, p. 972.

21.RADULESCU, A., MADAN, V., AUNGURENCI, A., BRATU, O., FARCAS, C., DINU, M., MISCHIANU, D., Romanian Journal of Military Medicine, **118**, no. 3, 2015, p. 20

22.SPINU, D., BRATU, O., POPESCU, R., MARCU, D., RADULESCU, A., MISCHIANU, D., Romanian Journal of Military Medicine, **118**, no. 3, 2015, p. 12.

23.VYAS, L., ACHER, P., CHALLACOMBE, B., CHANG, R.T., STURCH, P., CAHIL, D., CHANDRA, A., POPERT, R., BJU Int., **114**, no.1, 2014, p. 32.

24.AYALA, A.G., RO, J.Y., BABAIAN, R., TRONCOSO, P., GRIGNON, D.J., Am. J. Surg. Pathol., **13**, no. 1, 1989, p. 21.

25.PINKSTAFF, D.M., IGEL, T.C., PETROU, S.P., BRODERICK, G.A., WEHLE, M.J., YOUNG, P.R., Urology, **65**, no. 4, 2005, p. 735.

26.SATOH, T., MATSUMOTO, K., FUJITA, T., TABATA, K., OKUSA, H., TSUBOI, T., ARAKAWA, T., IRIE, A., EGAWA, S., BABA, S., Urology, **66**, no. 1, 2005, p. 114.

27.BOTT, S.R., HENDERSON, A., HALLS, J.E., MONTGOMERY, B.S., LAING, R., LANGLEY, S.E., Urology, **68**, no. 5, 2006, p. 1037

28.MORAN, B.J., BRACCIOFORTE, M.H., CONTERATO, D.J., J. Urol., **176**, 4 Pt 1, 2006, p. 1376.

29.BARZELL, W.E., WHITMORE, W.F., Urol Times, **31**, 2003, p. 31.

30.DIACONU, C.C., DRAGOI, C.M., BRATU, O.G., NEAGU, T.P., PANTEA STOIAN, A., COBELSCHI, P.C., NICOLAE, A.C., IANCU, M.A., HAINAROSIE, R., STANESCU, A.M.A., SOCEA, B., Farmacia, **66**, no. 3, 2018, p. 408

31.DIACONU, C.C., STANESCU, A.M.A., PANTEA STOIAN, A., TINCU, R.C., COBILINSCHI, C., DRAGOMIRESCU, R.I.F., SOCEA, B., SPINU, D.A., MARCU, D., SOCEA, L.I., BRATU, O.G., Rev Chim (Bucharest), **69**, no. 6, 2018, p. 1367

32.DIACONU, C.C., MANEA, M., IANCU, M.A., STANESCU, A.M.A., SOCEA, B., SPINU, D.A., MARCU, D., BRATU, O.G., Rev Chim (Bucharest), **69**, no. 5, 2018, p. 1071.

33.MANEA, M., MARCU, D., PANTEA STOIAN, A., GAMAN, M.A., GAMAN, A.M., SOCEA, B., NEAGU, T.P., STANESCU, A.M.A., BRATU, O.G., DIACONU, C.C., Rev Chim (Bucharest), **69**, no. 11, 2018, p. 4180.

34.DIACONU, C., BALACEANU, A., MOROSAN, E. Farmacia, **63**, no. 6, 2015, pp. 811-815.