Palestinian Medical and Pharmaceutical Journal

Volume 5 | Issue 2 Article 6

2-7-2020

Transperineal saturation prostate biopsy in treated and untreated patients

Mahmoud Mustafa
mah1969mah@hotmail.com

John Ward

John W Davis

Currtis Pettaway

Louis Pisters

Recommended Citation

Mustafa, Mahmoud; Ward, John; W Davis, John; Pettaway, Currtis; and Pisters, Louis (2020) "Transperineal saturation prostate biopsy in treated and untreated patients," *Palestinian Medical and Pharmaceutical Journal*: Vol. 5 : Iss. 2 , Article 6.
Available at: https://doi.org/10.59049/2790-0231.1076

Transperineal saturation prostate biopsy in treated and untreated patients

Abstract

The purpose of the current study was to assess the diagnostic value of transperineal saturation prostate biopsy in diagnosing false-negative cases by transrectal ultrasound-guided biopsies (TRUSG) in treated and untreated patients. Forty-eight patients with median age 62.5 years (range: 44-85) who underwent transperineal saturation biopsy after previous negative TRUSG biopsies between July 2002 and March 2011 were included. Thirty-one were primary cases (untreated) and 17 patients (treated) have received radiotherapy or cryotherapy. The median values of prostate-specific antigens before saturation biopsy were 5 ng/ml and 9 ng/ml for treated and untreated patients respectively (p=0.01). The median number of cores at saturation biopsy in treated and untreated patients was 60 (range: 22-104) and 54 (range: 24-110) respectively (p=0.22). Results of transperineal biopsy with respect to diagnostic value, Gleason score, number of positive cores, and volume of cancer, location of positive cores, pathologic stage and morbidity of saturation biopsy were evaluated. Twenty three patients (47.92%) were positive for prostate cancer; 10 (58.82%) in treated and 13 (41.93%) from untreated patients (p=0.26). Gleason scores were ,â• 7 in 19 patients (82.60%). Eleven patients (47.82%) underwent radical prostatectomy. The pathological stages at pathologic specimens were T2b in 6 patients, T2a in 2, T3a in 2 and T3b in 1. Three patients (6.25%) had complications in terms of urinary retention and urosepsis. In conclusion, transperineal saturation biopsy is a useful diagnostic tool in treated and untreated patients with persistent suspicious of prostate cancer after previous negative transrectal biopsies. Transperineal saturation prostate biopsy detected clinically significant cancer with modest complication rate.

Keywords

Saturation Biopsy, Prostate, Prostate Cancer.

Palestinian Medical and Pharmaceutical Journal (PMPJ). 2020; 5(2): 117-124

Transperineal saturation prostate biopsy in treated and untreated patients

Mahmoud Mustafa[1], John Ward[2], John W Davis[2], Currtis Pettaway[2] & Louis Pisters[2]*

[1]Urology Department, Faculty of Medicine & Health Science, An-Najah National University, Nablus, Palestine. [1]Visiting Scientist, MD Anderson Cancer Center, Urology Department, University of Texas, Houston, Texas, United States. [2]MD Anderson Cancer Center, Urology Department, University of Texas, Houston, Texas, United States.

*Corresponding author: dr_mahmoud681@yahoo.com

Received: (27/9/2019), Accepted: (7/2/2020)

ABSTRACT

The purpose of the current study was to assess the diagnostic value of transperineal saturation prostate biopsy in diagnosing false-negative cases by transrectal ultrasound-guided biopsies (TRUSG) in treated and untreated patients. Forty-eight patients with median age 62.5 years (range: 44-85) who underwent transperineal saturation biopsy after previous negative TRUSG biopsies between July 2002 and March 2011 were included. Thirty-one were primary cases (untreated) and 17 patients (treated) have received radiotherapy or cryotherapy. The median values of prostate-specific antigens before saturation biopsy were 5 ng/ml and 9 ng/ml for treated and untreated patients respectively (p=0.01). The median number of cores at saturation biopsy in treated and untreated patients was 60 (range: 22-104) and 54 (range: 24-110) respectively (p=0.22). Results of transperineal biopsy with respect to diagnostic value, Gleason score, number of positive cores, and volume of cancer, location of positive cores, pathologic stage and morbidity of saturation biopsy were evaluated. Twenty three patients (47.92%) were positive for prostate cancer; 10 (58.82%) in treated and 13 (41.93%) from untreated patients (p=0.26). Gleason scores were ≥ 7 in 19 patients (82.60%). Eleven patients (47.82%) underwent radical prostatectomy. The pathological stages at pathologic specimens were T2b in 6 patients, T2a in 2, T3a in 2 and T3b in 1. Three patients (6.25%) had complications in terms of urinary retention and urosepsis. In conclusion, transperineal saturation biopsy is a useful diagnostic tool in treated and untreated patients with persistent suspicious of prostate cancer after previous negative transrectal biopsies. Transperineal saturation prostate biopsy detected clinically significant cancer with modest complication rate.

Keywords: Prostate, Saturation Biopsy, Prostate Cancer.

INTRODUCTION

Advances in prostate cancer screening have lead to an increase in the number of patients undergoing prostate biopsy. Transrectal ultrasound-guided prostate biopsy (TRUSG) has become the standard for the histologic diagnosis of prostate cancer. Transperineal prostate biopsy is not as common as transrectal prostate biopsy, however it has the advantages of fewer complications and greater prostate cancer detection rate [1,2]. An extended prostate biopsy with at least 10 cores is considered the standard scheme in men undergoing initial biopsy [3,4]. In repeated biopsy set, several studies have reported an improvement in prostate cancer detection rate when saturation biopsy is used [5-7]. Accordingly, several authors have recommended the use of saturation biopsy with at least 20 cores as a standard in patients undergoing re-biopsy [3,4]. There is no consensus on the ideal number of cores of the saturation biopsy, and there is no study reported on the diagnostic value of saturation biopsy after failure of initial therapy for prostate cancer. Herein we evaluated the diagnostic value of extensive transperineal prostate biopsy in patients, treated with radiotherapy, brachiotherapy or cryotherapy, and in untreated patients after prior negative extended TRUSG guided biopsies. Up to our knowledge we are the first who reported on the diagnostic value of saturation biopsy after failure of initial therapy of prostate cancer.

MATERIALS AND METHODS

The study cohort consisted of 48 consecutive patients who had extensive TRUSG biopsy in MD Anderson Cancer Center from

July 2002 to March 2011. The median age of the patients was 62.5 years (range: 44-85). All patients had at least one negative extended TRUSG biopsy, persisted high level of serum prostate-specific antigens (PSA), highly suspicious for carcinoma of prostate, or failure of initial therapy of prostate cancer. All patients had T1c clinical stage except two patients who had T3a and T3c respectively. Thirty-one patients (64.58%) were primary cases (untreated) and 17 treated patients (35.41%) who have failed initial therapy; among them 7 patients underwent cryotherapy and 10 received radiotherapy or brachytherapy with/without cryotherapy. The perineal biopsy was conducted as a day-care procedure in the operating room under general/spinal anesthesia and TRUSG guidance. One dose of antibiotics for prophylaxis was given. The patient positioned in dorsal lithotomy position, then the patient prepared and draped in sterile fashion. Transrectal ultrasound probe placed and the prostate volume is estimated. The brachytherapy template was placed in positioned and systematic saturation biopsy were performed taken from right and left upper base, right and left lower base and from right and left apex of the prostate. The pathological outcomes of saturation biopsy were evaluated in terms of Gleason score, number of positive cores, volume of cancer at positive cores, location of positive cores as well as perioperative complications.

Statistical analysis

The SPSS ver. 10.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A p-value of greater than 0.05 was accepted as insignificant. A comparison between the parameters of subgroups was calculated by use of Student t-test, the Mann Whitney U test, and chi-square tests.

RESULTS

The overall detection rate of prostate cancer at transperineal saturation biopsy in treated and untreated patients was 47.92% (23/48). The detection rate in treated patients was 58.85% (10/17) and in untreated patients the detection rate was 44.70% (13/31) (p=0.26). Gleason scores were 7 in 14 patients (60.86%), 8 or 9 in 5 patients (21.73%) and 6 in 4 patients (17.39%). The demographic characteristics for treated and untreated patients are summarized in table 1. The initial median values of PSA was 7.5ng/ml for treated and untreated patients (p=0.55). The median values of PSA before saturation biopsy were 5 ng/ml (range: 1.2-13) for treated patients and 9ng/ml (range: 2.3-44.4) for untreated patients (p=0.01). The median values of cores at saturation biopsies for treated and untreated patients were 60 (range: 22-104) and 54 (range: 24-110) respectively (p=0.22). The number of previous negative biopsies before trasperineal saturation biopsy in the study group was 1 biopsy in 14 patients (29.19%), 2 biopsies in 16 patients (33.33%), 3 biopsies in 11 patients (22.91%) and 4 biopsies or more in 7 patients (14.59%). The median numbers of cores in negative TRUSG biopsies were 10 for the first biopsy and 11 cores for the remaining negative biopsies.

Table (1): The median values of the clinical variables for the treated and untreated patients.

Variable	Treated	Untreated	Total	P
Patients number n(%)	17(35.41)	31(64.58)	48(100)	
Initial PSA, ng/ml, (median, range)	7.5(3.7-18)	7.5(2.6-21)	7.5(2.6-21)	0.55
Age, year (median, range)	71(58-85)	57(44-70)	62.5(44-85)	<0.01
Prostate volume cc (median, range)	22(12-46)	39(16-130)	33(12-130)	<0.01
Pre saturation PSA ng/ml (median, range)	5(1.2-13)	9(2.3-44.4)	7.6(1.2-44.4)	<0.01
Number of negative biopsy (median, range)	1(1-3)	3(1-6)	2(1-6)	
Patients with positive saturation biopsy (n,%)	10(58.82)	13(41.93)	23(47.92)	0.26
Numbers of cores at saturation biopsy (median, range)	60(22-104)	54(24-110)	59(22-110)	0.22
Number of positive cores at saturation biopsy (median, range)	5(1-12)	7(2-25)	6(1-32)	0.26

Variable	Treated	Untreated	Total	P
Percentage of positive cores at saturation biopsy (median, range)	9(0.96-20)	15(2.66-50)	13.63(0.96-50)	0.036
Location of positive cores at anterior prostate (n,%)	5(50)	10(76.92)	15(65.21)	
length of cancer at saturation biopsy mm (median, range)	13.25(1-53.5)	19(1-176)	17(1-176)	
Gleason score				
6 (n,%)	1(10)	3(23.07)	4(17.39)	
7 (n,%)	6(60)	8(61.53)	14(60.86)	
8 (n,%)	3(30)	0	3(13.04)	
9 (n,%)	0	2(15.38)	2(8.69)	
Radical prostatectomy (n,%)	3(30)	8(61.53)	11/23(47.82)	

N; the number of the patients, **PSA**; prostate-specific antigens

The characteristics of patients who were diagnosed with or without cancer are listed in Table 2. The median numbers of cores at transperienal saturation biopsy were 59 for patients with positive or negative biopsies (p=0.84). The numbers of negative TRUSG biopsies were 2 for patients with positive or negative saturation biopsy. The median values of PSA for patients with or without prostate cancer were 7.7 ng/dl and 7.2 ng/dl (p=0.13). The median volume of prostate was 33 cc in patients with positive biopsy and 35 cc in patents with negative biopsy (p=0.035). A comparison between the biopsy findings of treated and untreated patients are summarized in Table 1. The median number of positive cores for treated and untreated patients was 5 (range, 1-12) and 7 (range: 2-25) respectively (p=0.26). The accumulative cancer length at saturation biopsies was 13.25 mm (range: 1-53.5) in treated patients and 19 mm (range, 1-176) in untreated patients. The prostate cancer was detected in the anterior portion of the prostate (apex or/ and upper base) in 15 patients (65.21%) of the study group. In the treated patients who received cryotherapy before saturation biopsy, cancer was detected in 6 patients and 4 of them (66.66%) had cancer at the apex of the prostate. The clinical variables before and after saturation biopsy for each treated patient were summarized in Table 3. In relation to the number of previous negative biopsies sets; prostate cancer was found in 9 patients (39.13%) after single negative biopsy, in 3 (13.04%) after 2 sets of previous negative biopsies, in 6 (26.23%) after 3 sets of previous negative biopsies and in 5 (21.73%) after 4 or more sets. The mean follow-up periods for patients with positive or negative saturation biopsies were 22 months (range: 3-99) and 24 months (range: 3-74) respectively.

Table (2): Comparison between the median values of patients with positive or negative saturation biopsy.

Variable	Positive saturation biopsy	Negative saturation biopsy	P
Patients (n,%))	23(47.92)	25(52.1)	
Age year(range)	65(49-85)	59(44-76)	0.025
Volume of prostate cc (range)	33(16-130)	35.5(12-102)	0.035
PSA ng/ml (range)	7.7(2.6-44.4)	7.2(1-37.3)	0.13
Treated patients (n)	10	7	
Untreated patients (n)	13	18	
Core number (n,range)	59(49-104)	59(36-110)	0.84
negative biopsy (n, range)	2(1-6)	2(1-4)	
PIN (n,%)	6(26.1%)	7(28)	
Follow up months (range)	22(3-99)	24(3-74)	0.73

N; number of patients, **PSA;** prostate specific antigens, **PIN;** prostate intraepithelial neoplasia.

Table (3): The clinical characteristics of treated patients before and after a saturation biopsy.

Initial therapy	Age Year	Gleason score before saturation biopsy	Pre-saturation biopsy PSA ng/ml	No. of negative biopsies	Saturation biopsy result	No of cores	No. of positive cores(n, %)	Location of cancer	Gleason Score at saturation biopsy
RT	39	8	8.3	1	0	50	0	0	
RT	64	7	3.5	1	0	37	0		
RT+BT	63	7	4.7	1	0	50	0	0	
RT+CA	72	7	2.5	1	1	92	3(3.26)	SV	8
BT	75	6	5	2	0	72	0	0	
BT	64	6	2.6	1	0	67	0	0	
BT	74	7	6.2	1	1	71	8(11.26)	Base	8
BT	63	6	6.7	2	0	49	0	0	
BT	58	7	9.5	1	1	60	12(20%)	Base,SV	8
BT	71	6	5	1	1	22	3(13.6)	Base	6
CA	71	7	1.7	3	1	104	1(1)	Base	7
CA	78	7	4	2	1	57	10(17.5)	Base,apex	7
CA	64	7	13	1	1	60	4(6.6)	Base	8
CA	85	7	3.6	1	1	61	10(16.4)	Base,apex	8
CA	59	7	3	1	1	87	6(6.8)	Base,apex	7
CA	71	6	1.2	1	1	58	3(5.2)	Base,apex	7
CA	76	8	5.6	3	0	72	0	0	

RT; radiotherapy, **BT;** brachytherapy, **CA;** cryotherapy, **PSA;** prostate-specific antigens, **SV;** seminal vesicle

DISCUSSION

Negative systematic biopsies do not exclude clinically significant cancer, and several authors modify the technique in attempt to increase sensitivity. Nonetheless, urologists are still facing the problem with patients who had persistently elevated levels of PSA after negative prostate biopsy. An extended biopsy scheme failed to detect up to 20% of significant cancers detected by pathologic evaluation at prostatectomy specimens [8,9]. Saturation biopsy was coined by Stewart *et al.* in 2001, to describe a technique of extensive prostate sampling to be used on a repeat biopsy, including up to 22 cores, which diagnosed prostate cancer in 30% of the patients [6]. In our study cancer detection rates were the same in treated and in untreated patients with overall detection rate of 47.92% (p=26). Our detection rate was similar to the reported rates in the literature. Most published papers on saturation biopsy reported data using the transrectal approach, with detection rates of 14-45% [6,7, 10-12]. Conversely, only a few studies were reported of saturation prostate biopsy using the transperineal route, showing detection rates of 22.7-42.2% [9, 13-15]. Moran *et al.* reported detection rate of 38% in 180 patients who underwent transperineal biopsy after previous negative TRUSG biopsy [14]**.** Merrick *et al.* reported an overall detection rate that was as high as 42.2% in a series of 102 patients undergoing as transperineal template-guided saturation biopsy, sampling a median of 50 cores [9]. Satoh *et*

al. [15] reported a 22.7% detection rate in a series of 128 patients where 22 cores were sampled. The majority of the studies which have similar sampled cores to that of Satoh *et al.* reported identical detection rates and significantly lower than that of those who used larger sampled cores [15,16]. Simon J *et al.* reported the highest number of core at extensive saturation biopsy (64 cores), and the detection rate was 45% [12]. It is clear that the detection rate is higher in those with extensive numbers of cores. Our results of detection rate in treated and untreated patients are identical to that of Merrick *et al.* and Simon *et al.* who used similar number of cores at saturation biopsy [9,12] (table 4). We believe that extensive saturation biopsy with high number of cores improves the detection rate of prostate cancer. Also we concluded that saturation biopsy has a good diagnostic value in treated patients, although the architecture of the prostate tissue is lost and changed due to the initial therapy of cancer. Recent studies suggest the incorporating of transperineal and magnetic resonance imaging(MRI)-transrectal ultrasound fusion techniques as it improves the detection rate of prostate cancer [17]. Three-Tesla MRI guided prostate biopsy had prostate cancer detection rate of about 41% and the majority of detected cancer was clinically significant (87%) [18]. It is clear that the detection rate of prostate cancer in systematic saturation biopsy and MRI-targeted biopsy are almost similar. But there may be patients that worrisome PSA profiles and no lesion on the MRI, these patients may be good candidates for a saturation biopsy. We consider saturation biopsy as useful diagnostic tool, especially in the treated patients where detection of viable cancer at prostate biopsy after radiotherapy or brachytherapy represents a dilemma for oncologist. Taking into account that biochemical recurrence after primary therapy for localized prostate cancer occurs in 40-50% of treated patients and 72% of patients with an increasing serum PSA level after radiation therapy have local recurrence of 72% as evidenced by a positive prostate biopsy [19]. Thus it is of utmost important to detect the early recurrence of prostate cancer thus the appropriate therapy could be given early.

The majority of the patients with positive saturation biopsies had their cancer at the anterior part of the prostate especially in untreated patients or in patients treated with cryotherapy before saturation biopsy (Table 4). This may be due to the superiority of transperineal biopsy in detection prostate cancer located at the apex and upper part of the base as it gives easy access to these regions. A lot of studies demonstrated that apical region and in particular apex had a significantly higher incidence of cancer than the rest of the prostate gland [9,14]. Both of these facts showed the importance of transperineal saturation biopsy in diagnosing prostate cancer in treated and untreated patients. The oncologic features of detectable cancer at saturation biopsy showed clinically significant tumors. Seventeen patients (82%) had Gleason score more than or equal to 7. All patients except 1 had ≥ 3 positive cores at saturation biopsy. The length of cancer at saturation biopsy was ≥ 5 mm for all patients except for 2. The oncological findings at pathological specimens showed clinically significant tumor in patients who underwent radical prostatectomy (RP); 8 patients had cancer confined to prostate and 3 patients had cancer outside the capsular with right seminal vesicle involvement in one of them. The Gleason score at the pathologic specimen was similar to Gleason score found at saturation biopsy except in one patient who's Gleason score increased from 8 at biopsy to 9 at specimen. Ploussard *et al.* have shown that a considerable proportion of patients considered for an active surveillance program based on the preoperative parameters, e.g Gleason score less than or equal 6 had significant cancer based on the histopathology report [20]. Accordingly we suggest that patients with previously negative transrectal biopsies and elevated PSA levels or underactive surveillance to have extensive saturation biopsy to have accurate oncologic mapping for prostate cancer. Thompson *et al.* emphasis on the superiority of transperineal prostate biopsy in active surveillance for prostate cancer as it reduces the likelihood of unfavorable disease at RP, possibly due to earlier detection of anterior tumor [21]. The oncologic outcomes after appropriate treatment were promising. The last PSA value for those who had positive transperienal satura-

tion biopsies was undetectable in 90.9% from those who underwent RP also the last PSA value was undetectable in 40% from those who had cryotherapy. Seven patients (30.43%) from those who had positive saturation biopsy have detectable PSA level. Fifteen patients out of 25 who had negative saturation biopsies and received no further therapies after biopsy showed median value of PSA 7.65 ng/ml at the last follow up period which is similar to the value of PSA before saturation biopsy. We may conclude that patients, who were negative for cancer at saturation biopsy, seem to be free malignancy as there was no progress in their PSA level. These findings show that extensive saturation biopsies detect clinically significant cancer with low rate of false-negative results and favorable oncologic outcomes after appropriate therapy.

Table (4): Extensive saturation biopsy of the prostate in previous reports.

References	Patients (n)	Route	Volume cc	No. of negative biopsy(range)	PSA ng/ml	No. of cores(range)	Detection rate (%)
Merrick [9]	102	Transperineal	63	2.1±1.1	9.1	50(24-66)	42.2
Simon [12]	40	Transrectal	NR	2(1-8)	12.2	64(39-139)	45
Present	48	Transperineal	33	2(1-6)	7.5	59(22-110)	47.92

NR; nor reported, **PSA;** prostate-specific antigen.

Complications of transperineal biopsy have received little attention in the literature as pointed by Takenaka *et al.* [22]. In our study 3 patients (6.25%) had complications after saturation biopsy where urinary catheterization and appropriate medication were enough to resolve the complications. The complication rates in the present study were similar to the reported rates in the literature. Simon at al who had extensive saturation biopsy reported hematuria in 16 patients (40%) [12]. The majority of the studies reported lower rates of complications after saturation biopsy; Walz *et al.* reported urinary retention in 2 patients (1.24%) and morbidity rate of 2.48%. [7]. Moran *et al.* reported urinary retention in 18 patients 10% after repeat transperineal prostate biopsy [14]. These findings showed that saturation had clinically moderate complications which can be managed successfully.

CONCLUSION

Transperineal saturation biopsy using a scheme with median core number of 59 cores results in a higher detection rate of prostate cancer for patients with previous negative TRUSG guided biopsy. Transperineal saturation biopsy is feasible and safe tool that detect clinically significant prostate cancer with low rate of complication.

We have no conflict of interest to declare

REFERENCES

1) Emiliozzi P, Corsetti A, Tassi B, Federico G, Martini M, Pansadoro V. Best approach for prostate cancer detection: a prospective study on transperineal versus transrectal six-core prostate biopsy. Urology 2003; 61: 961–6.

2) Vis AN, Boerma MO, Ciatto S, Hoedemaeker RF, Schröder FH, van der Kwast TH. Detection of prostate cancer: a comparative study of the diagnostic efficacy of sextant transrectal versus sextant transperineal biopsy. Urology 2000; 56: 617–21.

3) Patel AR, Jones JS. Optimal biopsy strategies for the diagnosis and staging of prostate cancer. Curr Opin Urol. 2009; 19:232-7.

4) Scattoni V, Zlotta A, Montironi R, Schulman C, Rigatti P, Montorsi F. Extended and saturation prostatic biopsy in the diagnosis and characterisation of prostate cancer: a critical analysis of the literature. *Eur Urol*. 2007; 52: 1309- 22.

5) de La Taille A, Antiphon P, Salomon L, Cherfan M, Porcher R, Hoznek A *et al.*. Prospective evaluation of a 21-sample

needle biopsy procedure designed to improve the prostate cancer detection rate. *Urology*. 2003; 61: 1181-6.

6) Stewart CS, Leibovich BC, Weaver AL, Lieber MM. . Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies. *J Urol*. 2001;166: 86-91.

7) Walz J, Graefen M, Chun FK, Erbersdobler A, Haese A, Steuber T *et al.*. High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series. *Eur Urol*. 2006; 50: 498-505.

8) King CR, McNeal JE, Gill H, Presti JC Jr. Extended prostate biopsy scheme improves reliability of Gleason grading: implications for radiotherapy patients. Int J Radiat Oncol Biol Phys. 2004 (1); 59(2):386-91.

9) Merrick GS, Gutman S, Andreini H, Taubenslag W, Lindert DL, Curtis R *et al.*. Prostate cancer distribution in patients diagnosed by transperineal template guided saturation biopsy. *Eur Urol* 2007; 52: 715–23.

10) Ficarra V, Novella G, Novara G, Galfano A, Pea M, Martignoni G*et al.*. The potential impact of prostate volume in the planning of optimal number of cores in the systematic transperineal prostate biopsy. *Eur Urol* 2005; 48: 932–7.

11) Fleshner N, Klotz L. Role of 'saturation biopsy' in the detection of prostate cancer among difficult diagnostic cases.*Urology* 2002; 60: 93–7.

12) Simon J, Kuefer R, Bartsch G Jr, Volkmer BG, Hautmann RE, Gottfried HW. Intensifying the saturation biopsy technique for detecting prostate cancer after previous negative biopsies: a step in the wrong direction. *BJU Int* 2009; 102: 459–62.

13) Bott SR, Henderson A, Halls JE, Montgomery BS, Laing R, Langley SE. Extensive transperineal template biopsies of prostate: modified technique and results. *Urology* 2006; 68: 1037–41.

14) Moran BJ, Braccioforte MH, Conterato DJ. Re-biopsy of the prostate using a stereotactic transperineal technique. *J Urol* 2006; 176: 1376–81.

15) Satoh T, Matsumoto K, Fujita T, Tabata K, Okusa H, Tsuboi T *et al.*. Cancer core distribution in patients diagnosed by extended transperineal prostate biopsy. *Urology* 2005; 66: 114–8.

16) Novara G, Boscolo-Berto R, Lamon C, Fracalanza S, Gardiman M, Artibani W *et al.* . Detection rate and factors predictive the presence of prostate cancer in patients undergoing ultrasonography-guided transperineal saturation biopsies of the prostate. BJU Int. 2010; 105(9):1242-6.

17) Kuru TH, Saeb-Parsy K, Cantiani A, Frey J, Lombardo R, Serrao E *et al.*. Evolution of repeat prostate biopsy strategies incorporating transperineal and MRI-TRUS fusion techniques. World J Urol. 2014;32(4):945-50.

18) Hoeks CM, Schouten MG, Bomers JG. Three-Tesla Magnetic resonance-guided prostate biopsy in men with increased prostate-specific antigen and repeated negative random, systematic, transrectal ultrasound biopsies: detection of clinically significant prostate cancer. Eur Urol 2012;62(5): 902-9.

19) Kuban DA, Thames HD, Levy LB, Horwitz EM, Kupelian PA, Martinez AA *et al.*. Long-term multi-institutional analysis of stage T1–T2 prostate cancer treated with radiotherapy in the PSA era. Int J Radiat Oncol Biol Phys 2003; 57: 915-28.

20) Ploussard G, Salomon L, Xylinas E, Allory Y, Vordos D, Hoznek A *et al.*. Pathological findings and prostate specific antigen outcomes after radical prostatectomy in men eligible for active surveillance--does the risk of misclassification vary according to biopsy criteria? J Urol. 2010; 183(2):539-44.

21) Thompson JE, Hayen A, Landau A, Haynes AM, Kalapara A, Ischia j. *et al.*. Medium-term oncological outcomes for extended vs saturation biopsy and

transrectal vs transperineal biopsy in active surveillance for prostate cancer. BJU Int. 2015 ;115(6):884-91.

22) Takenaka A, Hara R, Ishimura T, Fujii T, Jo Y, Nagai A *et al.*. A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. Prostate Cancer Prostatic Dis. 2008; 11(2):134-8.