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Research Article

Does General Anesthesia and Extended Prostate Biopsies Enhance Prostate Cancer Detection Rate?

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Abstract

Objectives: Negative prostate biopsies result in extra-expenditures. We explored if prostate biopsies done under general anesthesia may facilitate higher number of samples and better gland evaluation with better sampling and targeting.

Methods: 2,168 prostate biopsies (mean age: 59.2, SD:3.0) with at least 18 fragments undertaken under general anesthesia were studied. Narrow Prostate Specific Antigen (PSA) stratification, gland volume and number of fragments were analyzed according to presence of nodes and vascularity as for prostate cancer (CaP). p values were significant if <0.05.

Results: Overall, CaP detection rate was 35.8%. Patients showed the same diagnostic rate on 1st (35.7%), 2nd (33.9%), 3rd (35.7%) - $p > 0.05$; with diminished probability for the 4th (18.2%) biopsy- $p > 0.05$. PSA < 4.0 showed similar rate of CaP detection - 32.4% X 35.6%; and number of CaP (+) cores - 3.9 X 4.6; in comparison to those with higher PSA. Suspected node on US increased the rate of CaP diagnosis ($p = 0.001$) but node was not specific for CaP. Vascularity of the node was not related to CaP detection. PSA > 4.0 is more relevant for low volume gland than for larger glands.

Conclusions: Contrary to expectation use of general anesthesia did not improve the diagnostic detection rate for CaP on different sessions of biopsies except for small gland with PSA < 4 ng/dl where the detection rate improved with statistical significance.

Keywords: Analgesia; Prostate Biopsy; Prostate Cancer; Prostate Gland; Ultrasonography

Introduction

Although PSA is a potent indicator when to perform the biopsy, the via, number of fragments and even the PSA level leading to the decision to biopsy is a matter of debate. General anesthesia may potentially influence the quality of the sampling because pain may rush the examiner and limit the number of procured cores. Transrectal Ultrasound (TRUS) became the most popularized auxiliary image exam to perform prostate biopsy allowing direct morphological examination of the gland such as nodules and hyper vascularized areas but identification of potential areas of interest to be sampled demands time and expertise from the examiner to properly localize areas of interest and increase the number of cores [1-3] instead of standard template of the gland in order to avoid the dilemma of repeating the procedure in the future. The old concept of 6-core sampling was based on empirical experience and underperforms in diagnosing prostate cancer [4] when compared to any schemes with higher number of samples [1,2,5].

In contemporary series four forces play against sextant template: (1) CaP diagnosis has been shifted toward to smaller tumors after the spread use of PSA decreasing the chance of appropriate sampling for malignant tissue, (2) prostate biopsy represents a tiny sample of the gland - ~ 0.04% [6] (3) organ-confined disease presents better biochemical recurrent free-survival driving the tendency to lower the PSA value as an indication to biopsy [7] at the same time there is acknowledgement that the (4) higher number of cores may improve the diagnostic rates. We assumed that doing prostate biopsy under general anesthesia would enhance the diagnostic rate of CaP and improve the sampling of desired areas.

Methods

2,168 consecutive men (mean age: 59.2, SD:3.0) submitted to prostate biopsy were prospectively studied during 2008 to 2012 after consenting for the study and signing for it. 1,896 patients

had had his first biopsy, 168 his second biopsy, 56 his third, 44 his fourth and 4 cases had had his fifth biopsy. Patients were requested to have prostate biopsy due to clinical suspicion of prostate cancer on Digital Rectal Examination (DRE) - 87 cases (4%) or elevation of PSA (96%) - primary elevation, persistent elevation or trend of PSA increase. Patients received prophylactic fluoroquinolone for 5 days after the procedure. Additional antibiotics were added for those considered at risk for endocarditis or with implanted prosthetic devices. Patients received a fleet enema on admission to the outpatient surgical unit. All saturation biopsies were performed in the operating room under intravenous general anesthesia with propofol using transrectal-guided ultrasound to procure the prostate fragments. The prostate gland was imaged with the Acuson 128XP ultrasound machine (Acuson Computed Sonography, Mountain View, California) with an EC7 5 to 7 MHz endocavity 45-degree probe enabling proper visualization of the needle and the intended area. After examining the prostate with ultrasound and determining the echogenic characteristic of different areas Doppler evaluation was conducted in search for hyper or hypovascularized areas. Saturation biopsy was performed using the automatic MaxCore Disposable 18-gauge MC1820 Biopty gun (C. R. Bard, Inc., Covington, Georgia).

First cores were obtained at the most lateral border at the gland adding procured cores in the middle and apical zones of the gland. Next, biopsies were next directed slightly medial by rotating axially the probe 20 to 30 degrees from the outermost row and so on until the midline of the prostate was reached. This biopsy method ensured complete sampling of the whole prostate gland irrespective of its size. If present, at least 3 samples from hypoechoic or hyper vascularized lesions were also performed. The number of sample cores was no less than 18 and the gland was sampled according to radiological criteria for the presence of nodes, hypoechogenic areas or hyper vascularized areas, as the simultaneous Doppler was done. The relationship between PSA and the probability of CaP diagnosis were analyzed for each stratification of 1.0 ng/ml of PSA starting from 2.0 ng/ml and with larger interval until 20. PSA at saturation biopsy was also evaluated as a continuous variable using categories of <4.0, > 4.0, 4 to 10, 10 to < 20 and > 20 ng/ml. Associations were evaluated based on the chi-square test for nominal variables and the Wilcoxon´s rank sum test for continuous variables, such as PSA, number of CaP cores and number of saturation cores. The association of each nominal variable with a CaP diagnosis was calculated with 95% confidence interval. All calculated p values were 2-sided and p <0.05 was considered statistically significant. IBM-SPSS software was used. Different prostate volume intervals (< 20 g; 21 to 40g; 41 to 60 g; 61 to 80 g; 81 to 100 g and > 100 g), PSA, number of (+) cores and CaP detection rate were all also analyzed. The study was approved by Institutional Review Board of the involved hospitals which dispensed a protocol as the exam is part of the regular exams for CaP.

Results

Among the studied population 775 (35.8%) of 2,168 cases were diagnosed with CaP. Patients had a maximum of 38 and a minimum of 18 fragments. Non-cancer (median; 19.1 fragments) and the cancer group (median: 18.8 fragments - p > 0.05) had comparable amount of procured fragments. Except for the PSA interval 9.1 - 10 where the number of fragments were higher (mean: 27.5) the number of fragments remained stable (mean: 18.1) for the whole population. Patients showed the same probability of CaP diagnosis on biopsy despite they have had it as the one biopsy (36.2%), 2 biopsies (33.9%) or 3 biopsies (35.7%) (p > 0.05) with significant reduction of prostate cancer diagnosis after 4 biopsies (18.2%) (p < 0.05). A low number of patients with 5 biopsies did not allow comparative analysis. Analysis of the prevalence of prostate cancer diagnosis stratified by narrowed PSA intervals showed difference on the range of cancer detection in the 3.1 to 6.0 interval and 15.1 -17.0 - (Table 1).

PSA	Number of biopsied cases in this PSA interval	% of CaP diagnosed in this PSA range	% of the total cases (775) with CaP (n)	% of the total cases (1393) with non-malignant finding (n)	p
< 2,0	85	24.7%	2.7% (21)	2.9% (64)	0.083
2,0 - 3,0	136	32.3%	5.6% (44)	4.2% (92)	0.06
3,1 - 4,0	353	34.2%	15.6% (121)	10.7% (232)	0.048
4,1 - 5,0	402	36.3%	18.8% (146)	11.8% (256)	0.045
5,1 - 6,0	327	38.8%	16.3% (127)	9.2% (200)	0.045
6,1 - 7,0	255	30.1%	9.9% (77)	8.2 (178)	0.08
7,1 -8,0	124	22.5%	3.6% (28)	4.4% (96)	0.075

8,0 - 9,0	72	40.2%	3.7% (29)	2.0% (43)	0.055
9,1 -10,0	102	35.2%	4.6% (36)	3.0% (66)	0.06
10,0 - 12,0	101	38.6%	5.0% (39)	2.8% (62)	0.05
12,1 - 15,0	73	30.1%	2.8% (22)	2.3% (51)	0.068
15,1 - 17,0	23	65.2%	1.9% (15)	0.4% (8)	0.03
17,1 - 20,0	48	54.2%	3.3%(26)	1.0% (22)	0.05
> 20,1	67	65.7%	5.6% (44)	1.0% (23)	0.04
Total	2168		775	1393	
PSA- Prostate Specific Antigen CaP- Prostate cancer cases					

Table 1: Comparison of prostate cancer diagnostic rate on the studied population separated by PSA intervals.

Our data showed that 574 (26.4%) out of 2168 cases presented in the PSA range <4.0 ng/ml and they would not have been biopsied if PSA > 4.0 ng/ml would have been the adopted limit for cutoff. In the range with PSA < 4.0 ng/ml the amount of CaP diagnosis of was 32.4% (186 out of 574 cases) very similar to the amount rate of CaP in higher limit ranges (PSA: 4.1 to < 20.0) - mean: 35.6% (p <0.05); meaning that PSA was not discriminative when a large amount, of samples were procured. In the same manner, the number of positive biopsied cores remained constant along all PSA breakdowns intervals with an median of 4.5 positive cores amidst 18.8 procured fragments (Table 2).

PSA	Number of cases	Mean number of biopsied cores	Mean number of positive biopsied cores	% of cores with neoplasic findings from the total biopsied cores
< 2,0	21	18.8	3.2	17.1%
2,0 - 3,0	44	20.1	5,1	25.2%
3,1 - 4,0	121	17.9	3,5	19.8%
4,1 - 5,0	146	21.2	4.5	21.3%
5,1 - 6,0	127	17.5	5.5	31.4%
6,1 - 7,0	77	19.2	5	26.1%
7,1 -8,0	28	17.9	4.3	24.2%
8,0 - 9,0	29	18.6	1.8	9.4%
9,1 -10,0	36	27.8	2.9	10.2%
10,1 - 12,0	39	17.9	5.6	31.5%
12,1 - 15,0	22	20.1	2	9.9%
15,1 - 17,0	15	16.2	6	37.5%
17,1 - 20,0	26	16	5	31.2%
> 20,1	44	15.3	8.3	54.2%
Total average		18.8	4.48	24.9%

Table 2: Relationship between the number of cores procured and percent of positive cores for CaP according to different PSA breakdowns.

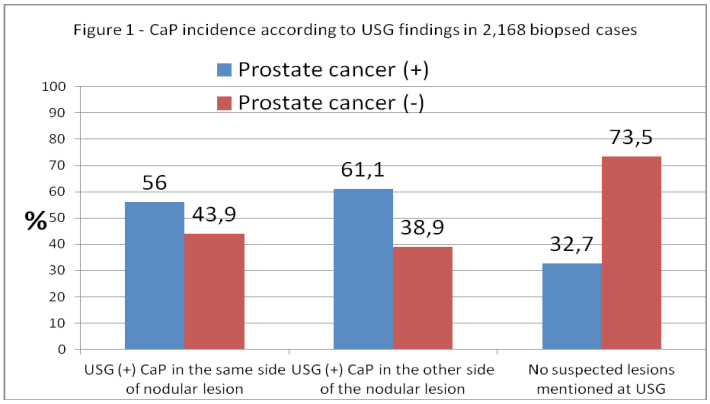
The number of positive cores for CaP stratified by PSA range did not differ according to PSA breakdowns except for the PSA > 20 ng/ml where the number of positive cores were higher (8.3) Even for those cases with PSA < 4.0 ng/ml the number of positive cores averaged 3.9 for an median of 18.9 procured cores in comparison to the PSA > 4.0 ng/ml where positive cores summed 4.6 in average in 18.9 sampled cores (p > 0.05). 890 (41.1%) of 2168 cases had nodular lesions visualized during transrectal evaluation. 521 of 890 (58.5%) cases with nodular lesions on TRUS were diagnosed with CaP while 254 of 1278 (19.8%) without nodular TRUS findings showed CaP diagnosis (p = 0.001). This meant that positive finding on TRUS enhances the chance of CaP on prostate biopsy. However, when the

subset of CaP cases where analyzed by laterality of the suspected lesion on US it was not related to the side of CaP localization, as 251 of 521 (48.2%) cases were diagnosed on the same side of the suspected lesion and 270 of 521 (51.8%) cases had CaP diagnosed on the contra-lateral side of the suspected lesion. Laterality on the identified node did not interfere with CaP diagnosis (p = 0.2) (Table 3).

	CaP (+) (775)	CaP (-) (1393)	p
US (+) and same side CaP	56% (251)	43.9% (197)	0.056
US (+) and contralateral CaP	61.1% (270)	38.9% (172)	0.03
US (-)	19.8% (254)	80.1% (1024)	< 0.001

Table 3: Relationship between CaP diagnosis, US finding of suspected lesion and laterality of the nodular formation.

Moreover, laterality of suspected lesion on US was not different in the group diagnosed with CaP (251 cases with cancer - right side: 134 cases; left side: 117 cases) or on the non-CaP groups (197 cases without cancer - right side: 104 cases; left side: 93 cases) (p = 0.4) (Figure 1).



USG- Ultrasonography

Figure 1: Prostate Cancer incidence according to USG findings in 2,168 biopsed cases.

On the other hand, the subset of patients diagnosed with CaP showed an unpredictable pattern on the laterality with only 32.8% of the total cases of diagnosed CaP in the same side of the identified node, with 34.8% of the cases showing neoplasia in the contra-lateral side of the suspected node and 32.7% of the neoplasic cases showing no suspected lesion (p = 0.9).

Interestingly, the vascular density of the nodular lesions detected by Doppler during the procedure showed that from 890 detected nodular formations only 195 cases (21.9%) showed hypervascularity pattern (right - 103; left - 92) with no CaP detected on the hyper vascularized lesions in the left side (0 in 92) and detection in 49% on the right hyper vascularized nodules (51 in 103) (p < 0.0001). Prostate volume showed a trend to increase PSA accordingly, but the CaP diagnostic rate decreased as the volume of the gland increased with no differences on cancer detection rate on different PSA breakdown for prostate volume larger than 21 g (Table 4).

	CaP (n)	Non-CaP	% of cancer
< 20 g (n=85)	49	36	57.6%
21 - 40 g (n=916)	378	538	41.3%
41 - 60 g (N=572)	194	378	33.9%
61 - 80 g (N=326)	67	259	20.5%
81 - 100 g (N=158)	54	104	34.2%
> 100 g (N=111)	33	78	29.7%
Total (N=2168)	775	1393	

Table 4: Percent of prostate cancer diagnosis on prostate biopsy according to the prostate gland volume (g).

As expected, as the mean number of cores were regular and comparable among the groups the rate of CaP diagnosis was higher in the lower volumes brakdwons (< 40 g) when compared to voluminous gland (> 40 g) (p < 0.03) with a trend to decrease the diagnostic rate for CaP as prostate volume enlarged (p<0.004) (Table 5).

	Median PSA level for the whole group	Median PSA for CaP patients	Median PSA for non-malignant patients	CaP X non-Cap cases
< 20 g	3.5	4.2	1,91	p < 0.05
21 - 40 g	4.75	4.57	4.2	p > 0.05
41 - 60 g	6.4	7.1	6.73	p > 0.05
61 - 80 g	7.01	8.2	7.4	p > 0.05
81 - 100 g	6.95	7.57	8.15	p < 0.05
> 100 g	7.93	4.05	10.4	p < 0.05
TRUS- Transrectal ultrasonography				

Table 5: Relationship between prostate gland volume (g) and PSA level in the rate of prostate cancer detection rate by TRUS guided biopsy.

PSA was determinant for the chance of CaP diagnosis in cases where prostate gland volume is < 20 g. Here, CaP cases showed a median PSA: 4.2 ng/ml whereas the non-CaP showed a median of PSA: 1.91 (p < 0.05). Likewise, prostate gland with volume larger than > 100 g also showed decreased rate of CaP if

PSA were < 10.0 ng/ml ($p < 0.05$).

Discussion

The indication to biopsy the prostate gland due to abnormal DRE in our study was 4% but it is still an absolute indication in the urological community [9]. However, the main reason prostate biopsy is nowadays indicated is the increase in PSA in combination or not with abnormal DRE. It is acknowledged that prostate with PSA between 4 and 10 ng/ml leads to 20 to 30% of false-negative CaP due to inappropriate sampling of the gland [9-11]. It is still not clear where is the best predictor to invasively investigate the prostate for a PSA elevation, but it can be claimed that lowering PSA bar will result in higher organ-confined disease detection rate and better cure rates [1,12] although an undesired effect of over detection cancer may follow with this recommendation. In that particular, our data reveals that 186 (32.4%) of the CaP cases were diagnosed with PSA < 4.0 ng/ml which is highly superior to Catalina's series [13] and others [1] where 22% of their series had CaP diagnosis with PSA levels of 2.6 to 4.0 ng/ml possibly reflecting the higher number of cores and the use of anesthesia allowing better sampling. Our rate was kept higher even in comparison to the 21 cores sampling from Guichard´s series done under local anesthesia where the diagnostic rate was only 25% on those with PSA < 4.0 ng/ml [3] which seems to be appealing since this sub-group of low PSA represent the more curable cases and more prone to false-negative first biopsy. As 65 to 90% of the patients claim discomfort during the procedure, some radiologists may feel pressed to end the exam not targeting specific or desired studied areas. Good sedation allied to higher number of cores seemed to be superior to sextant [14] and 12-cores [2,15]. Our studied population with a median 18.8 cores/patient revealed a total detection rate of 35.8% for CaP which is higher than that in the literature with 20 cores [3,15] possibly because of undisturbed time to examine and sample the gland. Our data was deeply studied and stratified by narrower intervals of PSA breakdown differentiating it from other studies in the literature where the PSA breakdown is analyzed into wider intervals (< 4.0; 4-10; > 10 and so on). Our routine use of at least 18 fragments did improve the detection rate to 35.8% but on the specific subgroups with prostate volume < 20 g and PSA < 4.0 where the gain on detection rate showed impressive improvement in comparison to the literature [16]. Our findings showed a plateau effect on the 18 cores for PSA > 4 with no gain on the diagnostic rate [1].

Stewart [17] pioneered the extended biopsy practice procuring a higher number of cores and increased the detection rate to 34% in patients with previous negative sextant biopsy similar to our 35.8% rate. Intuitively, adding more cores to the biopsied gland would enhance the detection rate of CaP but a plateau effect seemed to be evident at near the 20 procured cores as demonstrated in our study as well as in others [15,18,19]. Although many studies did show improvement on detection rate with more cores, the majority of those studies compared sextant to 10-cores or 12-cores templates in previously biopsied-negative patients [2]. Moreover, as at least 18-fragments were routinely used in our study it did not improve the detection rate on voluminous gland either probably meaning that if CaP is present a higher number of cores would be necessary in voluminous gland or the alteration in PSA is related to the volume and not to CaP itself. TRUS initially substituted the digitally oriented approach of areas to be biopsied because US seemed to identify more properly CaP areas. However, the acknowledgement of non-characteristic echogenic appearance of CaP led Hodges to adopt empirical sextant approach [4]. As also showed in our data, the identification of nodular formation or vascularity were not related to higher chance of CaP detection as only 28.2% of those with positive finding on TRUS was diagnosed with CaP similar to 19.8% of those with negative finding on TRUS. It is noteworthy that 34.8% of CaP cases were diagnosed on the opposite side of the lesion identified on TRUS contradicting the ordinary expectation. Moreover, 67.6% of the CaP cases did not show any suspicious lesion on US.

A more stringent analysis of US findings revealed that diagnosing CaP based on US lesions corresponded almost to toss a coin. Surprisingly, as our patients were under general anesthesia we expected a much higher detection rate for CaP as higher number of samples and better evaluation of the glandular areas were possible. However, when we looked up to additional parameters that could improve the detection rate such as nodular formation, hypervascularity, prostate volume and PSA, only PSA and gland volume influenced the rate of detection, meaning that high PSA with low prostate volume enhances the CaP detection rate in 18 cores scenario but not the additional findings obtained by US evaluation. Surprisingly, all other combinations of PSA breakdown did not predict higher chance to detect CaP. In conclusion, doing extended prostate biopsy under general anesthesia with at-least-18 fragments increased the detection rate for CaP in a large studied population of referred cases but it also showed that PSA level was not determinant on CaP diagnostic rate, except for cases with PSA < 4.0 ng/ml where higher number of cores enhanced the detection rate for CaP. Additionally, positive findings such as nodular formation or hypervascularized areas found on TRUS did not correlate to neoplasic areas.

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