

TWELVE CORE PROSTATE BIOPSY VERSUS SIX SYSTEMATIC SEXTANT BIOPSIES

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ABSTRACT

Objectives: We have studied patients submitted to twelve core prostate biopsy (Bx12C) to evaluate its sensitivity in the diagnosis of prostate cancer (PCa) as well as the addition of pathologic information when compared to those obtained by sextant prostate biopsy (Bx6C) guided by transrectal ultrasound.

Materials and Methods: Seventy-eight men underwent Bx12C. Transrectal ultrasound evaluated prostate volume and guided the biopsies to the 12 following areas: right and left apex, right and left mid prostate, right and left base, right and left transition zone, 1 and 2 right mid-lateral and 1 and 2 left mid-lateral. The efficiency of the Bx12C was compared to the 6 cores of the Bx6C in the same patients.

Results: Mean PSA was 17.3 ng/ml and 60 patients (77%) had abnormal digital rectal examination. The Bx12C diagnosed 28 prostate cancers (35%), adding 2 (8%) tumors ($p = 0.81$) and 2 (50%) cases of prostatic intraepithelial neoplasia (PIN) to the Bx6C. The Bx12C added 2 tumors to the 4 diagnosed by the Bx6C in the 6 patients with prostate cancer whose prostates weighed more than 40 grams. On the other hand, the Bx12C did not add any neoplasia ($p = 0.039$) in the 22 patients with prostate cancer whose prostates weighed less than 40 grams. In PCa cases, the additional cores increased the percentage of positive cores in 4 cases, diagnosed bilateral PCa in 1 case, increased Gleason's score in 1 case and added 2 cases of perineural infiltration.

Conclusions: The Bx12C does not increase prostate cancer detection when compared to the Bx6C among patients with high serum PSA and palpable nodule. In the patients subgroup with prostates > 40 g, Bx12C increased the number of PCa diagnosed.

Key words: prostate; prostatic neoplasms; diagnosis; biopsy; needle

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INTRODUCTION

Traditionally, the PCa diagnosis has been done through a transrectal ultrasound guided prostate biopsy with 6 standardized cores (1) associated to the biopsy of suspicious regions, such as palpable or ultrasound hypoecogenic nodules. Some recent studies have suggested that the standard sextant biopsy (Bx6C) lacks sensibility (2-4). Besides, prospective studies have demonstrated that the addition of lateral cores to the Bx6C significantly increases PCa detection (2,3).

Besides PCa diagnosis, the histopathologic data obtained in the biopsy, such as the Gleason's score, the presence of grades 4 and 5, the percentage of positive cores, and presence of perineural infiltration, are of prognostic value (5,6). The Gleason's score is included in category I of pathologic factors (6), considering its important prognostic value. The tumor volume can be estimated by the number of positive cores and by the higher percentage of tumor among the positive cores. From the tumors with at least 1 positive core in more than 80% of their extension, 73% are pT3, contrasting with the 18% of pT3 if the

extension is < 40% (5). The perineural via is one of the capsular infiltration routes. Patients with perineural infiltration in the biopsy are among the 50% of pT3 cases, versus the 25% of pT3 without this infiltration (5). However, despite the important information revealed by the biopsy, there are many discrepancies regarding the surgical specimen. This difference is probably the result of an insufficient tumor sample which does not represent the real neoplasia magnitude. It is likely that the information obtained in the biopsy with more cores better reflects the real tumor behavior.

We have studied patients submitted to 12-core prostate biopsy (Bx12C) to evaluate the Bx12C sensibility in the PCa diagnosis. We have also analyzed the addition of histopathologic prognostic parameters in patients with PCa submitted to the Bx12C when compared to the Bx6C.

MATERIALS AND METHODS

From March to October 2000, 78 men were submitted to prostate biopsies. The indication for the procedure was: PSA > 4 ng/ml and/or suspicious digital rectal examination (DRE) (nodule, hardened prostate). Patients were included in the study through a written consent and a protocol previously approved by Research Ethics Committee of our Institution. The transrectal ultra-sonography (TRUS) was performed with a transrectal transducer "endfire" 6.5 Mhz (Mitsubishi, Japan). The TRUS guided the biopsies and evaluated the prostate volume (volume = 0.52 x antero-posterior diameter x sagittal diameter x transverse diameter) and the presence of nodules. The patient was placed in lateral decubitus with inflected legs. A needle with automatic biopsy pistol angulated 30° of the prostatic surface was used. It was directed to the following 12 regions: right and left apex (RA and LA, respectively), right and left mid-prostate (RM and LM, respectively), right and left base (RB and LB, respectively) (longitudinal cut), right and left transition zone (RTZ and LTZ, respectively), right mid-lateral (RML1 and RML2 – 2 cores), and left mid-lateral (LML1 and LML2 – 2 cores) (transversal cut), Figure.

Specimens were fixed in 10% buffered formaldehyde. Later, the material was processed and stored in paraffin. Five-µm serial cuts were performed. The number of positive cores for neoplasia and perineural infiltration were verified.

The efficiency of the Bx6C and the Bx12C was compared in the same patients. Data were analyzed through the computer softwares Excel 97, Epi-info 5.0 and Statistica 5.0. The Student's t test was used to analyze parametric variables, the Mann-Whitney-U test to analyze non-parametric variables and the Fisher and chi-square tests were used to compare proportions.

RESULTS

Patients with PCa were significantly older (general mean age = 69 years; patients with PCa = 72 years and patients without PCa = 57 years; $p = 0.01$), with higher PSA (general mean PSA = 17.3 ng/ml; with PCa = 24.9 ng/ml; without PCa = 12.9 ng/ml; $p = 0.001$) and with smaller prostates when compared to those patients without PCa (general mean prostate volume = 35.4 g; with PCa = 29.3 g; without PCa = 38.8 g; $p = 0.002$). Regarding biopsy indication, 8 patients (10%) presented PSA < 4 ng/ml with abnormal DRE, 46 patients (60%) presented PSA > 10 ng/ml and abnormal DRE, and 24 patients (30%) presented PSA between 4 and 10 ng/ml, being 8 (10%) with normal DRE and 16 (20%) with abnormal DRE. In the 18 patients with normal DRE, the mean PSA was 15.6 ng/ml (6 - 55.2 ng/ml), being 8 (10%) with PSA < 10 ng/ml.

The Figure shows the location of the biopsies and the number of diagnosed PCa per each core of Bx12C. The Bx12C has diagnosed PCa in 28 patients (35%), 2 (8%) more than the Bx6C ($p = 0.81$), being 1 patient with PSA = 10.5 ng/ml, DRE unilaterally hardened, with 2 positive cores (RTZ and LTZ) and the other patient with PSA = 20.4 ng/ml, DRE unilaterally hardened, with 1 positive core (LTZ). Any of the lateral cores (RML1, RML2, LML1, LML2) exclusively diagnosed PCa. The perineural infiltration was evident in 6 patients in the Bx12C.

The prostate volume of the patients with PCa with exclusive diagnosis by the Bx12C was

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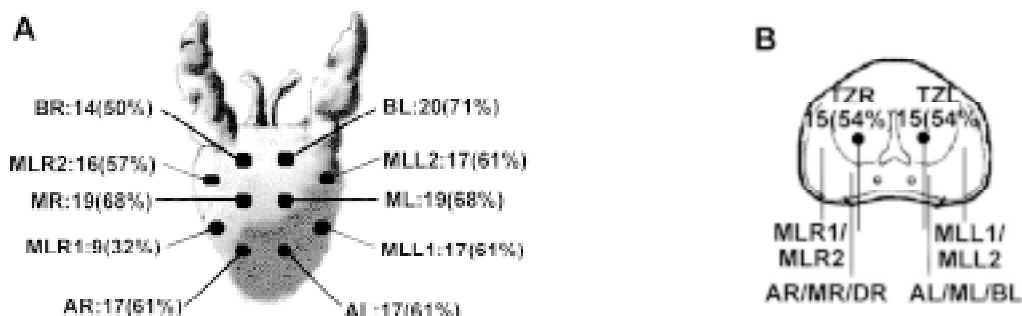


Figure - Biopsy site and sensitivity of each core among 28 prostate cancers detected. (A) posterior view, (B) transversal view. BR: base right; BL: base left; MLR1: mid – lateral right core, more distally located; MLL1: mid – lateral left core, more distally located; MLR2: mid – lateral right core, more proximally located; MLL2: mid – lateral left core, more proximally located; MR: mid right; ML: mid left; AR: apex right; AL: apex left; TZR: transition zone right; TZL: transition zone left.

significantly higher than the diagnosed by the Bx6C (58.5 g versus 27 g, $p = 0.01$). The Bx12C significantly diagnosed more tumors in the prostates with more than 40 g ($p = 0.039$), increasing the diagnostic sensibility in this subgroup in 50% when compared to the Bx6C (Table-1). The Bx12C was not more efficient than the Bx6C in the patients with lower PSA. When comparing the different biopsy strategies, there was no significant PCa diagnostic difference between the different models (Table-2).

Regarding the pathologic information, we have observed that in 5 (19%) of the 26 patients with PCa diagnosed by the Bx6C, the additional cores of the Bx12C added at least one histopathologic information. From the 6 cases with only prostatic intraepithelial neoplasia (PIN), 2 (33%) were only diagnosed by the Bx12C (Table-3).

DISCUSSION

The sextant transrectal prostatic biopsy (Bx6C) is the traditional method used in the PCa diagnosis. Until the end of the 80's, the biopsies were directed to the nodules of the digital rectal examination and, later, also to the ultrasound hypoecogenic nodules. In 1989, Hodge et al. (1) directed the biopsies to 6 standard quadrants and also to hypoecogenic areas (Bx6C). This standard identified PCa in 62% of 136 patients. In 1995, Stamey (7), after analyzing the histologic cuts of radical prostatectomies, observed that the higher tumor volume was in the peripheral zone more lateral to the Bx6C plane. Based on this, Eskew et al. (2) were the first to perform biopsies with more lateral cores. They performed biopsies in 5 regions, adding

Table 1 - Prostate volume of 28 prostatic carcinomas (PCa) detected through Bx6C or Bx12C.

| Diagnosis | Prostate Volume | |
|----------------------------|-----------------|--------|
| | > 40 g* | < 40 g |
| PCa detected only by Bx12C | 2 | 0 |
| PCa detected by Bx6C | 4 | 22 |

Bx6C: sextant biopsy; Bx12C: twelve core biopsy; * additional cores of Bx12C had a 50% sensitivity increase in prostate cancer detection among prostate volume greater than 40 g; $p = 0.039$, Fisher exact test.

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Table 2 - Sensitivity for prostate biopsy models, grouping different cores from Bx12C.

| Biopsy Model | Apex (right/left) | Mid (right/left) | Base (right/left) | TZ (right/left) | ML1 (right/left) | ML2 (right/left) | Sensitivity PCa detected (%) |
|---------------------|------------------------------|-----------------------------|------------------------------|----------------------------|-----------------------------|-----------------------------|---|
| Transition Zone | | | | X | | | 20 (71) |
| Additional cores | | | | X | X | X | 25 (89) |
| More lateral | X | | X | | | X | 25 (89) |
| Mid core | X | | X | | X | | 26 (92) |
| Bx6F | X | X | X | | | | 26 (92) |
| Bx12F | X | X | X | | X | X | 28 (100) |

TZ: transition zone; ML1: mid – lateral core, more distally located; ML2: mid – lateral core, more proximally located; PCa: prostate cancer; Bx6C: sextant biopsy; Bx12C: twelve core biopsy; X: biopsy sample taken.

3 planes to the Bx6C, being 2 lateral and 1 median, obtaining at least 13 cores per patient. In this study (2), the additional regions added 35% of PCa diagnosis. After that, many studies started to analyze the value of the lateral cores (4,8-10). Norberg et al. (8) included lateral and transitional zone cores, observing that the Bx6C did not diagnosed 15% of the 276 PCa. Chang et al. (9) also added lateral cores to the Bx6C, where the Bx6C and the additional cores diagnosed 76% and 80% of the 121 PCa, respectively. To compare the effect of the increase in the number

of cores without amplifying the biopsy regions, Ravery et al. (11) performed biopsies in intermediate regions to the Bx6C. They concluded that the 10-core biopsy sensibility does not surpass the Bx6C when the regions of the biopsy are not different. This way, the biopsy of additional regions promotes better prostate samples. Computer programs with prostatic biopsies simulations (4) have demonstrated that the Bx6C reaches only 65% to 72% of the PCa. On the other hand, Naughton et al. (10) have prospectively analyzed 244 patients submitted to 6 or 12-core

Table 3 - Pathological information added by twelve core biopsy (Bx12C).

| Patient | Increase in number of Positive Fragments (positive cores x 100 / cores obtained) | | Increase in Gleason score | Bilateral Tumor | Perineural Infiltration | PIN[Ⓞ] |
|-------------------|---|--------------------------|----------------------------------|------------------------|--------------------------------|------------------------|
| | Bx6F | Bx12F | | | | |
| # 10 [Ⓟ] | 1+/6 (16%) | 3+/12 (25%) [£] | MLR1* | | | |
| # 11 [Ⓟ] | | | | | MLL1 | |
| # 17 [Ⓟ] | 3+/6 (50%) | 7/12 (58%) [¥] | | TZR | | |
| # 21 [Ⓟ] | 2+/6 (33%) | 5/+12 (42%) [§] | | | MLR2 | |
| # 27 [Ⓟ] | 2+/6 (33%) | 6+/12 (50%) [¢] | | | | |
| # 45 [Ⓞ] | | | | | | MLL1 |
| # 60 [Ⓞ] | | | | | | MLR2 |

Bx6C: sextant biopsy; [£] core responsible for such increase: MLR1; [¥] core responsible for such increase: TZR, TZL, MLL1 and MLL2; [§] core responsible for such increase: MLR1, MLL1 and MLR2; [¢] core responsible for such increase: MLL1, MLR2 and MLL2; * Gleason score increased from 3 to 4; [Ⓟ] prostate cancer patients; [Ⓞ] PIN: prostatic intraepithelial neoplasia (no prostate cancer found).

prostate biopsies, observing a similar diagnostic sensibility in the 2 groups (26% and 27%, respectively). However, such study deserves two critics: it was designed to detect a difference of more than 10% between the 2 groups, being smaller differences not demonstrated with this number of patients, and the number of diagnosed PCa by the 6 standard cores in the 12-core group was significantly smaller than the PCa obtained in the 6-core group. The improvement in biopsy protocols suggests, therefore, that the addition of lateral cores adds tumors to the Bx6C in up to 35% of the cases.

In our study, even though the percentage of detected tumors (35%) is in accordance with the other series (2,3,10), the gain of 8% in Bx12C sensibility in relation to the Bx6C was small when compared to the other studies. Besides, any lateral fragment (RML1, LML1, RML2 and LML2) added neoplasia diagnosis, differently from most studies, where lateral cores to the Bx6C are the ones which add more tumor diagnosis (2,3,8). In our view, this difference is related to the amount of tumor per prostate volume and the growing pattern of the peripheral zone tumors: the bigger expansion of peripheral zone PCa occurs laterally, in transverse direction over the posterior capsule surface and, in smaller proportion, in the cephalocaudal direction (7). The higher the growth and the tumoral mass, the smaller the diagnostic complementation added to the Bx12C lateral cores. While analyzing the PCa staging in the studies of Eskew et al. (2) and Ravery et al. (3), we observe that at least half of them is T1c (79% and 50%, respectively), contrasting with our sampling, where 78% of the PCaP are higher than cT1c. The same occurred with the mean PSA in these studies (7.3 to 16.3 ng/ml) (2,3,9), where the values were below ours (24.9 ng/ml). Such information suggests that our sampling is composed of larger neoplasias. It is also known that the addition of lateral cores to the Bx6C has higher efficacy in the PCa diagnosis in subgroups with PSA < 10 ng/ml (2,3), which corresponds to only 21% of our cases of PCa. It is possible that the inexpressive increase in the Bx12C diagnostic sensibility of the present study has been a result of the larger tumor size of our patients.

As up to 25% of the prostates with cancer present tumors in the TZ (12), there has been an effort to systematically obtain cores from the TZ. Terris et al. (13) have demonstrated less than 5% of additional PCa diagnosis when compared to the Bx6C. In our casuistics, the TZ cores added a 8% sensibility, which is a value very close to the 10% obtained by Kojima et al. (14). Differently from most studies, the gain of diagnostic sensibility in our study was exclusively thanks to the TZ cores. This inversion can be explained by the natural history of primary neoplasias in the TZ. The extra-prostatic growth and expansion of the TZ tumors is different from PZ, once the first are generally limited by the compressed fibromuscular tissue of the benign prostatic hyperplasia (BPH) (7). The PZ and prostatic capsule are rarely affected, even in large TZ tumors (12) and high PSA. This way, the tumors located exclusively in the TZ of our study would benefit from the Bx12C, because they would not be included in the PZ cores even if more advanced, as supposed by our sampling. Therefore, TZ cores would be important in high PSA casuistics.

The relationship between the prostatic volume and PCa detection was initially studied by Uzzo et al. (15), who observed a higher PCa detection with Bx6C in prostates < 50 g. Karakiewicz et al. (16) evaluated the Bx6C ability to diagnose PCa in prostates of different volumes and obtained a 39.6% of PCa in prostatic volumes < 20 g and 10.1% of PCa in those between 80 and 90 g. In our study, we have also obtained a higher detection of PCa in small prostates. Besides, the Bx12C diagnosed additional PCa in prostatic volumes significantly higher. These findings are in accordance with Ravery et al. (3), who has obtained better PCa detection with the use of additional cores in prostates > 50 g. Even though Chen et al. (17) have observed two times the number of small volume tumors (< 0.5 ml) in prostates > 50 g when compared to the small ones, Eskew et al. (18) have not observed any difference in tumor volume or Gleason's score in tumors diagnosed by the Bx6C and their 5-region biopsy protocol. Thus, we believe that when we perform biopsies in more regions, the larger prostates are better evaluated, with higher chances of diagnosing an additional neoplasia with clinical relevance.

The PIN presence (high grade) in the absence of tumor is associated with prostate adenocarcinoma diagnosis in more than 30% of the re-biopsies (19). In our study, from the 50 patients without PCa, 6 (12%) presented PIN. The Bx6C diagnosed 4 cases and the Bx12C added 2 more (50%). This way, the increase in the number of cores in prostate biopsies has also an impact in the re-biopsy indication, because it allows a better PIN diagnosis.

The additional cores have been used for staging purposes (13). The percentage of positive cores in the biopsy is a predictor of extra-capsular extension, seminal vesicle infiltration and tumor volume (20), being included in prognostic factors category II (6). Rubin et al. (5) analyzed the presence of perineural infiltration and the percentage of core compromising in prostate biopsies of 632 patients submitted to radical prostatectomy. They observed that the high percentage of cancer in one core is intimately associated with the perineural infiltration, being both associated with the pT3 stage in univariate analysis. By applying multivariate analysis, only the percentage of core compromising in the biopsy remained a predictor of pT3 stage. However, when these authors (5) added pT2+ (pT2 with compromised margin) to pT3 stage, as the same adverse pathology stage, the perineural infiltration remained a predictor even in the multivariate analysis. This way, the perineural infiltration and the tumor volume estimation in prostate biopsies are associated with more advanced stages. In our study, the percentage of cores with PCa, a estimation of tumor volume, increased the additional cores in 4 cases, worsening its prognostic impression. The perineural infiltration, considered a prognostic factor category III (6), was observed in 6 of our cases. Two of them were evident only by the additional cores of the Bx12C. Besides this information, one patient who presented a unilateral tumor in the Bx6C presented, in fact, a bilateral one in the Bx12C. We believe that the real value of this additional information which is obtained by the more extensive biopsy should be re-evaluated with a larger group of patients and in a long-term follow-up.

CONCLUSIONS

The increase in the number of prostate biopsy cores of patients with high PSA and palpable nodule did not increase the PCa diagnostic sensibility. In patients with prostates > 40 g, the increase in the number of cores substantially increased the PCa diagnosis. A higher number of cores in previously determined sites added prognostic information which better define the real tumor biological behavior.

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