# Discontinuous Foci of Cancer in a Single Core of Prostatic Biopsy

## *When it Occurs and Performance of Quantification Methods in a Private-practice Setting*

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**Abstract:** In addition to clinical data, prostatic biopsy (Bx) reports orient urologists in outlining the patient's treatment options. Discontinuous involvement of a core by multiple foci of cancer is not infrequent; however, there is currently no consensus as to which method of quantification should be the standard. We applied 2 distinct approaches to quantify the length of cancer foci in the Bx and compared the results to prostatectomy (RP) parameters. All patients with matched Bx and RP treated by the same medical team between 2006 and 2010 were consecutively included in the study. Tumor extent in the Bx was estimated by multiple approaches, and the length was measured in millimeters. The subset of cases with discontinuous foci of cancer in a single core was initially reported by adding each foci and ignoring the benign intervening prostatic tissue, which was designated as additive quantification (AQ). Upon slide review, these foci were reassessed as a single focus and measured by linear quantification (LQ). RPs were partially embedded according to the International Society of Urological Pathology recommendations, and the percentage of tumor was evaluated with graphic precision. Mean percentage of the tumor in RP (%RP) and in the Bx were arbitrarily classified as limited (< 6%) and nonlimited (≥ 6%). Bx parameters were then correlated with %RP and margin status. All methods of quantification of the tumor in the Bx obtained excellent correlation with %RP. LQ and AQ diverged in 14/38 patients, with a mean total length of cancer of 5.8 mm more than the length obtained by LQ in the same population, accurately upgrading 6/14 cases to nonlimited. This subset (LQ > AQ) was more often seen in Bx with significantly more positive cores ($P = 0.003$) of predominantly Gleason score 7 and associated with positive surgical margins in RP ($P = 0.034$) independent of %RP (21% vs. 19% in the margin-negative cases). However, in the subset of Bx in which the tumor infiltration was continuous (AQ = AL) positive margins were indeed associated with tumor extent (31% vs. 6% in margin-negative cases). Discontinuous foci of cancer in a single core were most often seen in Bx sampling nonlimited disease, and this event was associated with positive surgical margins. LQ of cancer improved the performance of the Bx in predicting RP tumor extent relative to the traditional millimetric sum. Our findings support the idea that discontinuous foci may represent undersampling of a larger irregular nodule; however, this study is based on routine reports and does not directly access tumor biology.

**Key Words:** prostate cancer, needle biopsy, radical prostatectomy, discontinuous, tumor extension, report

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One of the pathologists' role in the assessment of prostate needle biopsies (Bx) containing carcinoma is to quantify the extent of cancer. There is no controversy with respect to whether tumor volume in Bx specimens should be reported, but there is also no consensus regarding which method of tumor quantification should be adopted. In addition to the number of positive cores, urologists expect a more detailed estimate of cancer extent in each core such as the total length and/or the percentage of cancer.[1,2] Along with clinical and imaging findings, this information will contribute to outline the patient's treatment options.

Measuring tumor length is straightforward when 1 continuous focus is present, but significant differences exist when there are multiple foci of cancer discontinuously involving a given core: should the intervening benign prostate tissue be subtracted from the final cancer length or taken into account as 1 continuous focus? Although this situation most likely represents the same cancer nodule going in and out of the plane of the section, some argue that it could correspond to independent nodules sampled in a single core, given that prostate cancer has long been known as a multifocal

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disease.[3,4] The major concern is overestimation of tumor extent, eventually losing criteria for minimum volume disease (MVD), and excluding the option of active surveillance treatment.

Although the true biological meaning remains to be established, the situation is faced by practicing pathologists on a daily basis in any regular routine laboratory. Despite the relevance of the topic there are few studies that specifically address the issue, and most of them are conducted in academic settings.[5,6] This study was conducted in a private-practice scenario to investigate under which conditions multiple foci of cancer in a single core are most often seen and also to compare both approaches of quantification in terms of correlation with tumor extent in the prostatectomy (RP) specimens and performance in predicting limited disease and margin status in the radical RP specimens.

## MATERIALS AND METHODS

All patients with matched prostate needle sextant Bx and radical RP specimens treated by the same medical team between 2006 and 2010 were consecutively included in the study. Radiology and urology studies were conducted at Fornecedores de Cana Hospital by 2 radiologists and 3 surgeons, and pathology diagnoses were rendered initially by 2 pathologists at Instituto de Anatomia Patológica. All slides were retrospectively retrieved and reviewed by a third genitourinary pathologist (L.S.).

Clinical parameters were recorded by the urologists, such as preoperative prostate-specific antigen (PSA) value, ultrasound estimation of prostate volume, digital rectal examination, and age at RP. Two of 40 patients who had undergone preoperative hormonal treatment were excluded, rendering a final cohort of 38 patients. Bx parameters were recorded grossly as the number of cores and the total millimetric length of prostatic tissue per Bx, and microscopically as: (1) number of positive cores; (2) fraction of positive cores, defined as the number of positive cores divided by the total number of cores in the Bx; (3) total length of cancer obtained by the millimetric sum of cancer in each positive core; (4) total percentage of cancer defined by the total length of cancer divided by the total length of prostatic tissue sampled in the Bx; and (5) Gleason grade, defined as the highest Gleason sum for each Bx, according to the International Society of Urological Pathology (ISUP)/2005 modified Gleason scoring system. MVD was defined according to the Epstein criteria[7] as clinical stage T1c, PSA density (total PSA/prostate volume) $<0.15$, Bx Gleason score 6, $<3$ cores with cancer, and never exceeding 50% of a single core.

The microscopic parameter of total length of cancer in each core was graphically determined by 2 ink dots made at the beginning and end of each focus, which was then measured with a regular millimetric scale. Discontinuous foci present in the same core were initially reported by adding each cancer length independently without considering the benign intervening prostatic tissue, which was designated as additive quantification of cancer (AQ). Upon slide review, this subset of cases was then measured as 1 continuous focus independent of the benign tissue gap, which was designated as linear quantification of cancer (LQ).

RPs were grossed and reported according to ISUP recommendations.[8] After fixation and complete inking, 3- to 5-mm-thick sections were cut from the apex to the base. The cone method was applied for sampling of apical and bladder neck margins. We followed partial embedding of every posterior section of consecutive slices, as well as at least 1 mid-anterior section from both right and left lobe, rendering quarter mount sections in each slide. In comparison with total embedding, this method has been reported to accurately sample 95% to 100% of positive surgical margins and 96% of extraprostatic extension (EPE).[9,10] RP tumor extension was assessed as the total percentage of the tumor. In each slide containing cancer, the tumor area was graphically delineated with ink microscopically, then visually scored for an overall percentage of cancer in that given section. Slides that did not contain cancer were assigned as "0.0%." All slides were then taken into consideration to determine the final mean percentage of the tumor (%RP). Limited extension was arbitrarily defined as $<6\%$ of tumor either in the Bx or RP.[11] This cutoff included cases fractionated between 5% and 6% in the limited category, as routine pathologists do not report percentages as decimal numbers.

### Statistical Analysis

Mean age, PSA, prostate volume, and Bx continuous variables (millimeters and percentages) were compared using the Student $t$ test. The $\chi^2$ test was used for categorical variables (number of cores or patients, limited extension, MVD, EPE, and margin status). Backward stepwise logistic regression models based on likelihood ratios were used to evaluate the impact of the different cancer quantification methods in the Bx in predicting the percentage of tumor at RP. The ability of LQ, AQ, and MVD in predicting limited extension at RP was also measured by binary test performance parameters. A 2-tailed $P < 0.05$ was required for statistical significance. Findings were analyzed using the STATA version 9.2 (StataCorp Inc., College Station, TX) software package.

## RESULTS

### Bx Parameters and Relationship With %RP

Preoperative and postoperative parameters are summarized in Table 1. Despite similar age, PSA, prostate volume, and Bx sampling, the subset of Bx with LQ > AQ showed significantly more extensive disease compared with LQ = AQ (Fig. 1), with a mean of 5.8 mm more length than that retrieved by LQ in that population. No patient lost MVD criteria when cancer was quantified by LQ. Whereas half (12/24) of the patients with LQ = AQ qualified for MVD, only 2/14 fulfilled the criteria when LQ > AQ. The latter group also had more positive cores (mean of 5.0 vs. 3.5, $P = 0.003$) of predominantly Gleason $3+4=7$. The frequency of EPE and Gleason


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**TABLE 1.** Clinicopathologic Characteristics of the Cohort (n = 38)

| | LQ = AQ (n = 24) | LQ > AQ (n = 14) | Total (n = 38) | *P* |
|---|---|---|---|---|
| Preoperative parameters | | | | |
| Age | 59.6 (60) | 63.3 (60) | 61.9 (63) | 0.141 |
| PSA (ng/mL) | 5.6 (5.0) | 6.7 (5.5) | 6.0 (5.1) | 0.717 |
| Prostate volume* (g) | 46.7 (45.0) | 38.5 (38.5) | 43.6 (41.0) | 0.128 |
| Cores per Bx | 14.1 (13) | 13.9 (13) | 14.0 (13) | 0.565 |
| Tissue per Bx (mm) | 213 (208) | 189 (181) | 204 (204) | 0.122 |
| No. positive cores | 2.5 (2) | 5.0 (4) | 3.4 (3) | 0.003 |
| Criteria for MVD | 12/24 | 2/14 | 14/38 | 0.028 |
| Bx Gleason score | | | | |
| 6 | 14 (58) | 03 (21) | 17 (45) | 0.071 |
| 3+4 | 07 (29) | 09 (64) | 16 (42) | |
| 8 | 03 (13) | 02 (14) | 05 (13) | |
| Postoperative parameters | | | | |
| Extraprostatic extension | 3/24 | 3/14 | 6/38 | 0.467 |
| Positive margins | 3/24 | 6/14 | 9/38 | 0.034 |
| RP Gleason | | | | |
| 6 | 09 (38) | 03 (21) | 12 (32) | 0.456 |
| 7† | 13 (54) | 09 (64) | 22 (58) | |
| 8-9 | 02 (08) | 02 (14) | 04 (11) | |

Age, PSA, volume, number of cores, and mm of tissue are expressed in mean (median). Gleason score categories are displayed as n (%).
No patient lost MVD criteria when quantifying tumor by LQ.
*Estimated by ultrasound.
†Except for 1 patient, all cases scored as 3+4 = 7.

distribution was similar in both groups, although LQ > AQ showed positive margins more frequently ($P = 0.034$).

All methods for cancer quantification in the Bx showed excellent correlation with %RP, with coefficients ($R$) ranging from 0.83 to 0.90 ($P < 0.0001$) and LQ showing the best performance (Table 2). In a multivariate analysis, no single method was independently better to predict %RP. Bx Gleason score showed good correlation with RP Gleason score (R = 0.73).

## Performance of Bx Parameters in Predicting Limited Disease at RP

LQ showed better positive predictive value (PPV) and negative predictive value (NPV) when compared with AQ in predicting limited disease in the RP (Table 3). Of the 25 patients classified as having limited disease by AQ, 6 were upgraded to nonlimited by LQ, and all of them also had nonlimited disease at RP, thus LQ shows superior specificity when compared with AQ (78% vs. 48%). Of the 15 patients with limited disease at RP, 14 were accurately predicted by both AQ and LQ, both methods showing equivalent sensitivity (93%). By MVD criteria 12/15 patients with limited disease at RP were accurately predicted, rendering a lower NPV and sensitivity (80%) when compared with LQ or AQ alone. However, MVD criteria showed only 2 false-positive results, showing superior specificity (91%) and PPV.

## Bx Parameters and Relationship With Margins

Nine of 38 patients had positive margins at RP. Aside from 1 apical and 2 bladder neck margins, all other compromised margins were circumferential. Mean %RP was significantly higher ($P = 0.004$) in margin-positive (25%, range 8% to 63%) than in margin-negative specimens (10%). EPE was reported in 6 patients, of which 4 also had positive margins. All tumors with positive margins were Gleason score >6, and none of these patients had preoperative criteria for MVD.

When LQ = AQ only 3/24 patients had positive margins (Fig. 2), and these were associated with more extensive tumor at RP (mean %RP of 31% vs. 6%). Yet when LQ > AQ, positive margins were more frequent (6/14, $P = 0.034$), despite similar extension of tumor in margin-positive and margin-negative cases (mean %RP of 22% vs. 19%). Overall, of the 9 specimens with positive margins, 6 had LQ > AQ in the diagnostic Bx.

In a univariate analysis, all methods of tumor quantification in the Bx were positive predictors of margin positivity ($P < 0.008$), in addition to smaller prostate volume ($P = 0.009$) and Bx Gleason score ($P = 0.009$), whereas criteria for MVD, PSA, or PSA density were not ($P$ = NS). In a multivariate model including percentage of tumor by LQ, Bx Gleason score, PSA, and prostate volume, only percentage of tumor by LQ remained an independent predictor of margin status ($P = 0.024$).

## DISCUSSION

After surgery has been performed, prognostic value of tumor size itself is controversial in prostate cancer, mainly because of a redundancy of prognostic parameters. Tumor extent in RP correlates well with outcome but does not add to EPE, margin status, or Gleason score, which are excellent predictors of biochemical recurrence.[12,13] However, as extent of cancer in the Bx has been shown to correlate with postsurgical outcome,[5,14] its quantification may contribute to patient stratification and prognosis and ideally improve current preclinical nomograms.[15]

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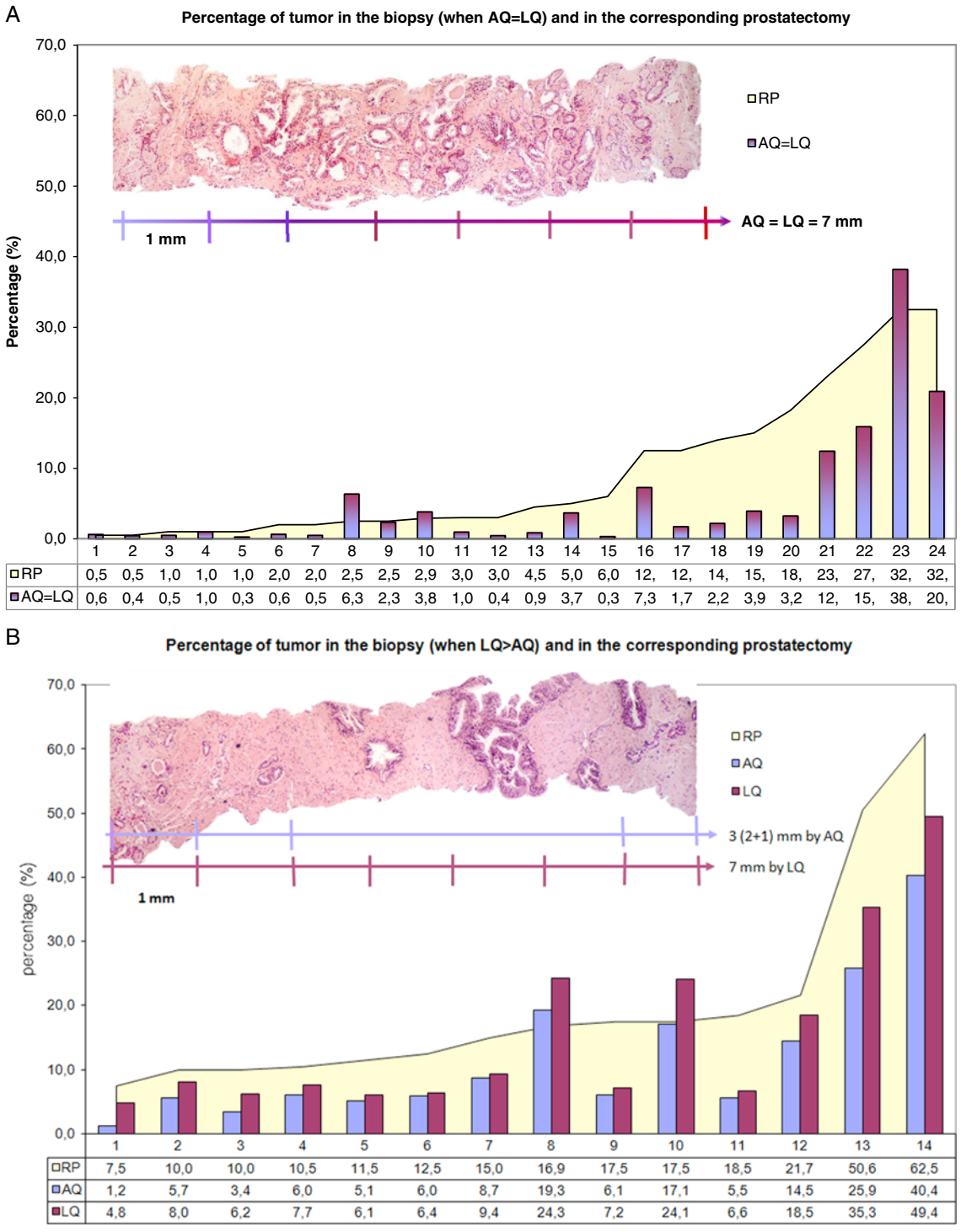


| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RP | 0,5 | 0,5 | 1,0 | 1,0 | 1,0 | 2,0 | 2,0 | 2,5 | 2,5 | 2,9 | 3,0 | 3,0 | 4,5 | 5,0 | 6,0 | 12, | 12, | 14, | 15, | 18, | 23, | 27, | 32, | 32, |
| AQ=LQ | 0,6 | 0,4 | 0,5 | 1,0 | 0,3 | 0,6 | 0,5 | 6,3 | 2,3 | 3,8 | 1,0 | 0,4 | 0,9 | 3,7 | 0,3 | 7,3 | 1,7 | 2,2 | 3,9 | 3,2 | 12, | 15, | 38, | 20, |

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RP | 7,5 | 10,0 | 10,0 | 10,5 | 11,5 | 12,5 | 15,0 | 16,9 | 17,5 | 17,5 | 18,5 | 21,7 | 50,6 | 62,5 |
| AQ | 1,2 | 5,7 | 3,4 | 6,0 | 5,1 | 6,0 | 8,7 | 19,3 | 6,1 | 17,1 | 5,5 | 14,5 | 25,9 | 40,4 |
| LQ | 4,8 | 8,0 | 6,2 | 7,7 | 6,1 | 6,4 | 9,4 | 24,3 | 7,2 | 24,1 | 6,6 | 18,5 | 35,3 | 49,4 |

**FIGURE 1.** Percentage of tumor in the Bx by LQ and AQ and correlation with the corresponding percentage of tumor in the radical RP. A, When infiltration of the core is continuous the quantification methods are equivalent and correlate well with RP tumor extension, despite usually indicating less disease than the RP final report. B, In the context of discontinuous involvement of the core by multiple foci, LQ retrieves more mm of cancer than AQ, better approaching the percentage of tumor reported in RP.

There are many methods for tumor quantification in the Bx and about as much variation in terms of performance, depending on the clinical setting and patient cohort to which they are applied.[5,6,14–17] In contemporary series, the most used methods to report tumor extent in the Bx are percentage of cancer and number of cores with


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**TABLE 2.** Tumor Extension in the Bx by Different Quantification Methods and in the RP Specimens

| | Mean (Median) | R* |
|---|---|---|
| mm by LQ | 17.23 (8.5) | 0.84 |
| mm by AQ | 14.79 (7.5) | 0.83 |
| % by LQ | 7.7% (3.8%) | 0.90 |
| % by AQ | 9.0% (5.5%) | 0.89 |
| No. positive cores | 3.45 (3) | 0.83 |
| FPC | 0.26 (0.20) | 0.85 |
| %RP | 13.6% (11.5%) | 1.00 |

*Pearson correlation coefficient with percentage of tumor in the RP.

% indicates total percentage of cancer in the entire Bx specimen; %RP, percentage of tumor in the RP; FPC, fraction of positive cores (number of positive cores/total number of cores); mm, total mm of cancer among all cores.

cancer.[18] Therefore, it has been suggested that each pathology laboratory should standardize its methods in consonance to the radiologist's practice and the urologist's expectation and understanding of the report.

This study analyzed different approaches, with special attention to quantification of discontinuous foci of cancer, in a cohort of 38 patients treated by a uniform and well-established medical care group. In concordance with the current literature, all methods for cancer quantification in the Bx showed excellent correlation with %RP and margin status in our population. Percentage of tumor by LQ showed the best performance, although in multivariate analysis no single method was independently better to predict these RP parameters. It is possible that the relative benefit of LQ in the population in this study is related to the less precise nature of the method in comparison with the millimetric sum of AQ, once the first corresponds better to the approximated visual estimate of %RP. Therefore, we believe that when standardizing the best practice each laboratory should consider equivalence of precision in the quantification methods when a better correlation between percentage of tumor in the Bx and RP is desired.

As to discontinuous foci of cancer involving a core, practicing pathologists have been even between reporting them by LQ or AQ.[19] In a study by Brimo et al,[5] this

**TABLE 3.** Performance of Tumor Extension in the Bx (Alone and in Combination With Clinical Parameters) in Predicting Limited Disease at Radical RP

| | RP | | | | |
|---|---|---|---|---|---|
| | Limited | Nonlimited | P | PPV | NPV |
| Bx | | | | | |
| Limited by LQ | 14 | 5 | > 0.001 | 0.74 | 0.95 |
| Nonlimited by LQ | 1 | 18 | | | |
| Limited by AQ | 14 | 11 | 0.004 | 0.56 | 0.92 |
| Nonlimited by AQ | 1 | 12 | | | |
| Bx + clinical | | | | | |
| Limited by MVD | 12 | 2 | > 0.001 | 0.85 | 0.87 |
| Nonlimited by MVD | 3 | 21 | | | |

MVD is defined as clinical stage T1c, PSA density < 0.15, Gleason score 6, < 3 cores with cancer, and never exceeding 50% of a single core

Limited extension is defined as ≥ 6% of tumor or fulfillment of MVD criteria.

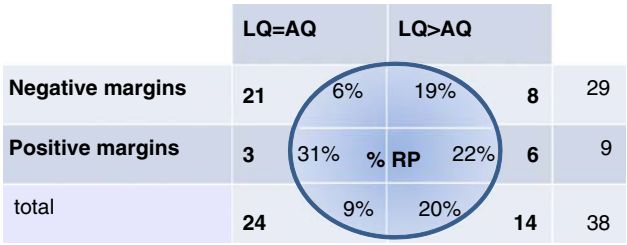


**FIGURE 2.** Prevalence of positive margins according to LQ and AQ equivalence and distribution of the mean percentage of tumor in the prostate (%RP) within each group. When LQ > AQ positive margins seem not to be related to tumor extent.

situation was identified in 54/100 Bx. By categorizing the amount of benign tissue between the foci of cancer with ocular morphometric measurement, they found that reports correlated equally with biochemical recurrence, regardless of the dimension of the gap. Most of these cases (93%) had gaps < 5 mm, similarly to the range found in the current study (1 to 6 mm), regarding the foci as "discontinuous but in close proximity." However, the precise technique utilized for the measurement does not apply to the scenario of a routine pathology laboratory, and, even if superior, differences most likely would not translate into changes in clinical management.

In this study, LQ performed better than AQ in terms of predicting limited disease at RP. Further, with the input of clinical parameters, MVD was superior to quantification of cancer by itself. Of the 16 patients with MVD by AQ, only 2 belonged to the subset in which LQ > AQ, and none of them lost criteria when applying LQ. Therefore, the parameter suffered no change according to each of the quantification methods. Although MVD was less sensitive compared with LQ and AQ, specificity and PPV were substantially higher. Considering that qualifying a patient as having limited disease in the Bx implies consideration for therapeutic options such as active surveillance or focal therapy, a high PPV is imperative to maximize the chances that an individual patient with undersampled cancer will not be undertreated. It is important to note that, although MVD was a better predictor of limited cancer, it still requires consideration of < 50% of cancer in each positive core and so does not preclude quantification of cancer extension in the Bx, in which LQ was superior.

Despite similar age, PSA, prostate volume, and Bx sampling, the subset of Bx in which LQ > AQ showed more aggressive disease when compared with LQ = AQ, with significantly more positive cores of predominantly Gleason score 7. Further, the frequency of EPE and RP Gleason score distribution were similar between these 2 group of patients, but those with LQ > AQ showed positive margins more frequently ($P = 0.034$). When LQ = AQ, only 3/24 patients had positive margins, and this event was associated with more extensive tumor at RP (31% vs. 6%). Yet when LQ > AQ, 6/14 patients had

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positive margins despite similar extension of tumor in margin-negative cases (22% vs. 19%). Overall, of the 9 specimens with positive margins, 6 had LQ > AQ in the diagnostic Bx. In a multivariate model for margin status prediction including presurgical parameters such as percentage of tumor by LQ, Bx Gleason score, PSA, and prostate volume, only percentage of tumor by LQ remained an independent predictor of margin status, indicating that accurate quantification of tumor in the Bx may bare considerable prognostic power in this context.

As RP was performed on the basis of the AQ report on tumor extension and LQ was retrospectively applied for the purpose of the study, one could presume that margins were more often positive when LQ > AQ because the surgeons were expecting less extensive disease. However, total length or percentage of tumor in the Bx is utilized by urologists mainly in conjunction with other preoperative parameters for clinical decisions. Once the surgical procedure is prompted, extension of tumor by itself should not interfere with surgical strategy.[2] In addition, we have shown that the event of discontinuous foci of cancer in a single core is more frequent in nonlimited disease, and therefore it seems unlikely that quantification by LQ would exclude a patient's option for active surveillance. In fact, although no patient was retrospectively disqualified for MVD by LQ, only 2/14 fulfilled the criteria when LQ > AQ.

Our findings support the idea that discontinuous foci of cancer may represent undersampling of more extensive tumors. Likewise, Karram et al[6] described 109 Bx with discordance of quantification methods and also found LQ as a better predictor of positive margins but only in cases with no Gleason upgrade at RP. Once the prognostic power of Gleason score was factored in, the extent of cancer in the Bx did not correlate with RP findings regardless of the quantification method, possibly reflecting that the Bx procedure in these cases not only undersampled the tumor in terms of grade but also stage.

This is the first study to describe the scenario in which discontinuous foci of cancer in a single core are mostly seen and to specifically address the differences between patient groups and performance of the different quantification methods in private-practice care. Although the true biological meaning of discontinuous foci remains to be established, it is evident that it is more frequent in nonlimited tumors and associated with margin status. Given the significant differences between LQ and AQ, we believe that pathologists should opt for one of them upon discussion with the medical team, although we support LQ as a better method for cancer quantification in the Bx. Beyond the inherent constraint of a retrospective design in a relative small cohort, the lack of outcome assessment is a significant limitation to this study. Future prospective and larger cohorts in a multidisciplinary approach would be ideal to confirm the impact of our findings.

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