# *Perineural invasion and TRUS findings are complementary in predicting prostate cancer biology*

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***Introduction:*** *Clinical variables with more accuracy to predict biologically insignificant prostate cancer are needed. We evaluated the combination of transrectal ultrasound-guided biopsy of the prostate (TRUSBx) pathologic and radiologic findings in their ability to predict the biologic potential of each prostate cancer.*

***Materials and methods:*** *A total of 1043 consecutive patients who underwent TRUSBx were reviewed. Using pathologic criteria, patients with prostate cancer (n = 529) and those treated with radical prostatectomy (RP) (n = 147) were grouped as: "insignificant" (Gleason score ≤ 6, prostate-specific antigen (PSA) density ≤ 0.15 ng/mL, tumor in ≤ 50% of any single core, and < 33% positive cores) and "significant" prostate cancer. TRUSBx imaging and pathology results were compared with the RP specimen to identify factors predictive of "insignificant" prostate cancer.*

***Results:*** *TRUSBx pathology results demonstrated perineural invasion in 36.4% of "significant" versus 5.4% of "insignificant" prostate cancers (p < 0.01) and pathologic invasion of periprostatic tissue in 7% of significant versus 0% of insignificant prostate cancers (p < 0.01). TRUS findings concerning for neoplasia were associated with significant tumors (p < 0.01). Multivariable analysis demonstrated perineural invasion in the biopsy specimen (p = 0.03), PSA density (p = 0.02) and maximum tumor volume of any core (p = 0.02) were independently predictive of a significant prostate cancer.*

***Conclusions:*** *TRUS findings concerning for measurable tumor and perineural invasion in TRUSBx specimens appear to be complementary to Epstein's pathologic criteria and should be considered to aid in the determination whether a prostate cancer is organ-confined and more likely to be biologically insignificant.*

**Key Words:** prostate cancer, insignificant, transrectal ultrasound

## Introduction

Excellent long term survival has been observed in prostate cancer patients with well differentiated tumors who were treated with a watchful waiting protocol, both in the pre prostate -specific antigen (PSA) and PSA era.[1-3] A randomized trial in patients with localized prostate cancer has shown a significant survival advantage for those treated with radical prostatectomy (RP), however, patients were mainly diagnosed after evidence of clinical symptoms and/or high levels of PSA (mean 13.5 ng/mL RP group).[4] This must be considered with contemporary prostate cancer screening that has resulted in significant lead time bias. Furthermore, large randomized, prostate cancer screening trials have demonstrated that many patients do not require radical local therapy for their prostate cancer.[5,6] Patients with tumors with "low biological potential of progression" might not be suitable for immediate radical treatment and the option of active surveillance seems to be a rational approach with the small risk of occult disease progression.[7]

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Tools to accurately predict these "biologically insignificant" tumors remain elusive. Epstein et al described how most of the patients diagnosed with clinical stage T1a prostate cancer were mainly treated with follow up without radical treatment.[8] After rigorous pathological and statistical analysis, criteria were developed that help predict when a patient had a biologically insignificant prostate cancer based upon presurgical variables.[8] Studies in other institutions, including a meta-analysis, have suggested that the term insignificant is not appropriate when utilizing Epstein's criteria, as there are a significant number of tumors that have pathologic characteristics of aggressiveness, which implies that radical local therapy is needed for potential cure.[9,10] Nevertheless, an updated report by Epstein's group showed that their criteria were able to identify organ-confined prostate cancer in 91.6% of their patients.[11]

Despite the controversy, it is clear that not all the patients are destined to experience morbidity or risk mortality from their prostate cancer and are not appropriate candidates for radical treatment. In the absence of a reliable biomarker or novel imaging modality, clinical parameters need to be further studied to determine if they may better identify patients who are suitable for conservative management. In this study we evaluated the utility of transrectal ultrasound-guided biopsy of the prostate (TRUSBx) radiologic findings and biopsy pathologic findings to predict "biologically insignificant" prostate cancer and organ-confined disease. Comparisons were made to the RP specimen, which represented the gold standard.

## Materials and methods

We retrospectively reviewed records of 1043 consecutive patients who underwent TRUSBx by one surgeon from 2007 to 2008. All the TRUSBx were performed with a technique directed to the prostatic peripheral zone to incorporate the anterior horns and the number of cores was determined at the urologist discretion with the standard template usually consisting of 10 to 12 cores. From this cohort we found 549 prostate cancer patients, of which 147 patients underwent RP.

The clinical and pathological staging was done according to the TNM (AJCC 2002). Routine pathological examination was performed on all RP specimens by sectioning and totally submitting the prostate tissue. The prostate biopsies and RP specimens were reviewed by numerous genitourinary pathologists who analyzed all specimens and synoptic reports for both the RP and TRUSBx specimens were completed according to the provincial standards.[10] Extra-prostatic extension was defined as any tumor cells identified in the extra-prostatic adipose tissue or seminal vesicles. The definition of a positive SM was any tumor cells identified at any margin on the surgical specimen.

TABLE 1. **Demographic and clinical characteristics**

| Variable | n (%) |
|---|---|
| Number of TRUSBx | 1043 |
| Patients with prostate cancer | 529 |
| Age (mean) | 66 years old (± 9.1 SD) |
| PSA (mean) | 15.0 ng/mL (± 67.3 SD) |
| Gland volume (mean) | 42.0 cc (± 19.7 SD) |
| Clinical stage | |
| T1 | 281 |
| T2 | 242 |
| T3 | 6 |

TRUS Bx = transrectal ultrasound-guided biopsy of the prostate; PSA = prostate-specific antigen

Prostate cancers were defined as: "insignificant" (Gleason score ≤ 6, PSA density ≤ 0.15 ng/mL, tumor in ≤ 50% of any single core, and < 33% positive cores) and "significant". Evaluable TRUSBx results were analyzed and compared with final RP pathology for association of "insignificant tumors" with perineural invasion, Gleason score, lymphovascular invasion, extracapsular extension and seminal vesical invasion, tumor quantitation and ultrasound findings.

Standard statistical software (SAS/STAT, Cary, NC, USA) was used to analyze and compare the pathological and clinical features in each group. Data were summarized using appropriate descriptive statistics. Between group differences were made using the Pearson chi-square test statistic for categorical endpoints,

TABLE 2. **Biopsy characteristics**

| Variable | n |
|---|---|
| # cores mean (range) | 10 (5-22) |
| Maximum volume of tumor at any core % (range) | 35% (1-100) |
| Gleason in biopsies (%) | |
| ≤ 6 | 223 (51.5) |
| > 6 | 210 (48.8) |
| PSA density (mean) | 0.39 ng/mL (± 1.5 SD) |
| Tumor involvement in a single core (mean) | 42.15% (± 32.5 SD) |

PSA = prostate-specific antigen

TABLE 3. **Correlation of Epstein's criteria of pathological analysis after RP, ultrasound findings and TRUS Bx**

| Variable | Insignificant (%) | Significant (%) | p value |
|---|---|---|---|
| Gleason | | | |
| ≤ 6 | 23 (63.9) | 24 (22.2) | p < 0.01 |
| > 6 | 13 (36.1) | 84 (77.8) | |
| Tumor volume quantitation | | | |
| < 5% | 12 (33.3) | 10 (9.1) | p < 0.01 |
| ≥ 5% | 24 (66.7) | 100 (90.9) | |
| Pathological stage | | | |
| T2 | 29 (78.4) | 47 (42.7) | p < 0.01 |
| T3 | 8 (21.6) | 54 (49.1) | |
| T4 | 0 | 9 (8.2) | |
| Extracapsular extension | | | |
| Absent | 29 (78.4) | 47 (42.7) | p < 0.01 |
| Present | 8 (21.6) | 63 (57.3) | |
| Perineural invasion | | | |
| Absent | 19 (51.4) | 12 (11.2) | p < 0.01 |
| Present | 18 (48.6) | 95 (88.8) | |
| Lymphovascular invasion | | | |
| Absent | 22 (100) | 106(89.8) | p = 0.11 |
| Present | 0 | 12 (10.2) | |
| Lymph nodes | | | |
| Absent | 38 (100) | 103 (98.1) | p = 0.39 |
| Present | 0 | 2 (1.9) | |
| Seminal vesicles | | | |
| Absent | 34 (97.1) | 95 (88) | p = 0.11 |
| Present | 1 (2.9) | 13 (12) | |
| **Correlation with Epstein's criteria for insignificant prostate cancer** | | | |
| Utrasound abnormal findings | | | |
| Absent | 87 (93.6) | 199 (62.2) | p < 0.01 |
| Present | 6 (6.4) | 121 (37.8) | |
| Perineural invasion in biopsy | | | |
| Absent | 88 (94.6) | 194 (63.6) | p = 0.012 |
| Present | 5 (5.4) | 111 (36.4) | |

ANOVA for continuous endpoints where between-group variances were similar, and the Kruskal-Wallis test for continuous endpoints where between-group variances were different. A multivariable analysis was performed. Missing data were excluded from analysis. P values less than 0.05 were considered to be statistically significant.

## Results

The demographics and clinical characteristics are shown in Table 1. Table 2 shows the biopsy characteristics of our 549 prostate cancer patients. Of the 147 patients who underwent RP, the mean gland volume was 42.0 cc (± 19.6 SD) and a total of 38 patients met all the criteria for "insignificant" prostate cancer. For our total group of prostate cancer patients and the group with "insignificant" tumors, the mean pre-biopsy PSA was 15.0 ng/mL (± 67.3 SD) and 7.8 ng/mL (± 8.2 SD), respectively.

Table 3 shows the pathological analysis after grouping in "insignificant" and "significant". Epstein's criteria were associated with Gleason ≤ 6 organ-confined tumors with ≤ 5% total volume in the final pathologic specimen, (p < 0.01) but 66.7% of this "insignificant" tumors had a volume of more than 5% and 21.6% had a pathological T3 disease. Final Gleason score (p < 0.01)

TABLE 4. **Univariate analysis to predict pT3/pT4, seminal vesicles invasion and final tumor volume > 5%**

| Variable | pT3/pT4 | Seminal vesicles | Tumor > 5% |
|---|---|---|---|
| Perineural invasion in biopsy | 0.001 | 0.5 | 0.03 |
| Ultrasound findings | 0.03 | 0.06 | 0.46 |
| PSA | 0.01 | 0.02 | 0.57 |
| PSA density | 2.22 | 0.08 | 0.41 |
| PSA density ≤ 0.15 ng/mL | 0.01 | 0.12 | 0.35 |
| DRE | 0.48 | 0.97 | 0.59 |
| Family history | 0.14 | 0.41 | 0.20 |
| Gland volume | 0.05 | 0.70 | 0.18 |
| Ratio of positive/ negative cores | 0.001 | < 0.01 | 0.01 |
| < 33% of cores positive | 0.01 | 0.04 | < 0.001 |
| Maximum volume of tumor at any core % | < 0.01 | < 0.01 | 0.02 |
| ≤ 50% of any single core | < 0.01 | < 0.01 | 0.07 |

PSA = prostate-specific antigen; DRE = digital rectal examination

and extracapsular extension were discriminated by Epstein's criteria, but not lymph node status (p = 0.39) or seminal vesicle invasion (p = 0.11).

From TRUSBx results, we found that the presence of ultrasound findings of a measurable hypoechoic lesion concerning for neoplasia were associated with significant tumors (p < 0.01). Perineural invasion was reported from TRUSBx in 36.4% of "significant" versus 5.4% of "insignificant" prostate cancer (p = 0.012) and pathologic invasion of periprostatic tissue in 7% of significant versus 0% of insignificant prostate cancer (p < 0.01).

To evaluate predictors of extraprostatic extension (pT3/pT4) and tumor quantitation > 5%, an additional univariate analysis was carried out, Table 4. For the prediction of pT3/pT4, a multivariate analysis was additionally performed including all the significant variables in the univariate analysis. The study showed that perineural invasion in the biopsy specimen, PSA density and maximum tumor volume of any core were independently predictive of a significant prostate cancer, Table 5.

TABLE 5. **Multivariate analysis to predict pT3/pT4**

| Variable | Odds ratio (95% CI) | p value |
|---|---|---|
| Perineural invasion in biopsy | 2.7 (1.07-6.9) | 0.03 |
| PSA density | 1.5 (1.08-2.1) | 0.02 |
| Maximum volume of tumor at any core % | 1.0 (1.0-1.03) | 0.02 |

PSA = prostate-specific antigen

## Discussion

In this study we demonstrated that the Epstein criteria was statistically significantly helpful to identify patients with organ-confined prostate cancer. However the term "insignificant" should be avoided considering that final pathology reports after RP revealed pathological T3 in 21.6% of these patients, and 66.7% showed tumors of more than 5% of prostatic total volume. In addition, our study demonstrated the significant predictive value of ultrasound findings concerning for neoplasia during TRUSBx and the presence of perineural invasion in the biopsy specimens suggesting that these factors should be considered as additional factors to better identify organ-confined disease.

Epstein's criteria to identify insignificant prostate cancer were initially reported in 1994[6] was supported by the definition proposed by Stamey, in which patients with low volumes of prostate cancer after cystoprostatectomy did not show any evidence of progression in the pathological analysis. These findings were consistent with Epstein's group,[13] which reported that patients with tumor volumes smaller than

0.5 mL do not have progression after RP and suggested that this group might be followed expectantly. The original study of insignificant prostate cancer criteria was updated in 2004 validating the initial findings.[11]

Other investigators have not observed the same findings. Recently it has been reported that the insignificant prostate cancer criteria sensitivity was 74% and specificity was 74% suggesting that these criteria are best used to predict organ-confined, but not insignificant prostate cancer.[9] Other studies, including a meta-analysis, have reached similar conclusions.[10,14,15] Although different studies using these criteria could not consistently and accurately predict insignificant prostate cancer, the groups discriminated by these parameters have better clinical outcomes.

In the PSA era the increased life time risk of prostate cancer detection is 16%, whereas the life time risk of dying of the disease is 3%-4%.[16] The European Randomized Study of Screening for Prostate Cancer established that 1410 patients need to be screened and 48 patients need to be treated to save one life.[5] Consequently, active surveillance is a treatment strategy for prostate cancer based on the risk of progression. Nevertheless, how to stratify the risk groups remains somewhat elusive, especially when the limitations of Epstein's criteria are considered.

This study endeavored to identify other clinical parameters routinely available to stratify patients by risk groups. Our data suggests that abnormal TRUS findings concerning for neoplasia and perineural invasion in the biopsy specimen might be complementary to Epstein's criteria to predict organ-confined disease. Perineural invasion in the biopsy has been previously reported as an adverse prognostic factor in patients treated with RP[17,18] consistent with our study. Other investigators have observed worse survival outcomes in patients following radiotherapy when they had perineural invasion on prostate biopsy.[19,20] There is also in vitro data suggesting prostate cancer with perineural invasion may be a sign of more aggressive biology.[21] However, other investigators have observed that perineural invasion on prostate biopsy did not correlate with the pathological outcomes in 139 radical prostatectomy specimens.[22]

With respect to the TRUS findings the data is more controversial. Augustin et al reported that patients with impalpable and isoechoic prostate cancer had more favorable features than prostate cancer that is radiologically visible.[23] However, other investigators have reported no differences in the prostate cancer features when the TRUS findings were evaluated and related with the RP specimen.[24] A significant limitation when the TRUS findings are evaluated in studies is the inter-operator dependency of this technology leading to difficulties in replicating results.[25] Intuitively, it seems more likely that consistent TRUS interpretation, rather than varied inter-operator radiologic interpretations may be able to generate more reliable and reproducible data. This may support the current study, as all the TRUSBx procedures were performed by a single surgeon.

Our study is limited by the retrospective collection of the data, the inherent selection bias involved and by our limited number of patients with "insignificant" prostate cancer. Further studies in other datasets are required to confirm our findings.

## Conclusion

TRUS findings concerning for measurable tumor and perineural invasion in TRUSBx specimens appear to be complementary to Epstein's pathologic criteria and should be considered to aid in the determination whether prostate cancer is organ-confined and more likely to be biologically insignificant. □

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