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# Localization of higher grade tumor foci in potential candidates for active surveillance who opt for radical prostatectomy

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**Purpose:** To investigate actual intraprostatic location of higher graded tumor foci undetected via standard transrectal ultrasound-guided prostate biopsy amongst patients who would be clinically considered appropriate candidates for active surveillance (AS) but underwent radical prostatectomy (RP).

**Methods:** We reviewed entirely-submitted and whole-mounted RP specimens from 169 men who were deemed appropriate for AS clinically, but opted for RP and were found to have higher grade tumors. For each case, tumor nodules were circled and color-coded in a grade-specific manner and digitally scanned to created tumor maps. The locations of tumor foci with Gleason grade ≥4 were stratified by specific sites: anterior, anterolateral, lateral only (not clearly anterior or posterior), posterior, and posterolateral area.

**Results:** Of 169 patients, 86% had clinical stage T1c and 14% T2a. RP Gleason score 7 in all but two men. Higher-grade tumor foci were localized to: anterior (n=66, 39%), anterolateral (n=4, 2%), lateral only (not clearly anterior or posterior) (n=5, 3%), posterior (n=52, 31%), and posterolateral (n=42, 25%) prostate, respectively.

**Conclusions:** Among patients deemed clinically appropriate for AS, higher-grade tumor foci missed by standard prostate biopsies were localized to both the anterior and posterior prostate, without predominance of a particular area. These findings lend additional support to performing repeat standard prostate biopsy in potential candidates for AS and should be considered in efforts to optimize current biopsy strategies for the selection of AS patients.

**Keywords:** Prostate, Prostatic neoplasms, Active surveillance, Prostate biopsy, Gleason score

## INTRODUCTION

Accurate identification of insignificant and/or low-risk prostate cancer (PCa) is crucial for the success of active surveillance (AS) in the current era of prostate specific antigen (PSA) screening. Various predictive nomograms have been developed to aid the selection of patients for AS [1-4]. However, inability of current staging modalities to discriminate aggressive from indolent PCa with optimal sensitivity and specificity, mostly conferred by inaccuracy of current standard transrectal ultrasound (TRUS)-guided schematic biopsy approach, remains a significant drawback. Although most smaller tumor foci missed by contemporary 12-core TRUS-guided biopsy may be clinically irrelevant, published data suggest that some of these patients may actually harbor significant tumor of higher grade [5,6]. Similarly, the therapeutic efficacy and safe-

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ty of novel focal therapies for unilateral PCa has been questioned based upon apparent inaccuracy of prostate biopsy [7].

Some reports have suggested that tumor foci in the anterior and/or apical prostate are those primarily missed by standard schematic prostate biopsy, advocating additional sampling of the corresponding areas during prostate biopsy [8,9]. However, patients included in prior studies were not limited to those who would qualify for AS. In an effort to improve accuracy in the selection of patients for AS, investigators have explored changes in prostate biopsy approaches, including implementation of saturation biopsy and/or using transperineal approach [10,11]. More definitive evidence is needed to justify such alternative approaches in prostate biopsy, at least for potential AS candidates, since they would be prone to increase biopsy-related morbidity and cost.

In order to develop a biopsy approach or protocol that would enhance accuracy in the selection of patients for AS, it is plausible to begin by examining the actual intraprostatic locations of tumor foci of higher grade missed amongst potential candidates for AS. Currently, a paucity of data exists regarding the localization and characterization of higher graded tumor foci undetected via standard TRUS–guided prostate biopsy amongst patients who would be clinically considered appropriate candidates for AS. Thus, we performed detailed histopathologic analysis of patients who were candidates for AS clinically, but opted for immediate radical prostatectomy (RP) and were found to have higher grade tumors.

## MATERIALS AND METHODS

From January 2000 to December 2010, a total of 7,016 patients underwent RP for clinically localized PCa at Memorial Sloan-Kettering Cancer Center (MSKCC). With approval from the Institutional Review Board, we reviewed our prospectively collected multidisciplinary PCa database to select patients who were deemed appropriate for AS clinically, but instead, opted for RP and were found to have higher grade tumors. Inclusion criteria included: preoperative PSA, <10 ng/mL; clinical stage, T1c–T2a; biopsy Gleason score (GS), 6; ≤3 positive cores on at least 12-core prostate biopsy; and no core with >50% cancer. For this study, only those who were not enrolled on AS prior to RP were included. Overall a total of 1,690 patients met aforementioned inclusion criteria. Among these 1,690 men, 682 had GS upgrading following RP. And of the 682, 169 men who had all the clinical variables and tumor map obtained from analyzing RP specimen available were included in our study. None of 169 patients had undergone preoperative radiation or hormonal therapy.

In all patients, RP specimens were entirely-submitted and whole-mounted for pathologic analysis. RP specimens were uniformly processed as previously reported [12,13]. After diagnosis, all cases were mapped with differential annotation of Gleason grade <3 and >4 and then digitally scanned. Review of whole-mount tumor maps to detect locations of high grade tumor foci was performed by a dedicated urologic pathologist (S.W.F) were identified. A topography–based approach was applied and the location of tumor foci with Gleason grade ≥4 were stratified by site, as follows: anterior, anterolateral, lateral only (not clearly anterior or posterior), posterior, and posterolateral area. The presence of extraprostatic extension, seminal vesicle invasion, positive surgical margin and/or lymph node involvement was also recorded.

Clinical data of patients were obtained from the review of our database and medical records. Descriptive statistics were utilized to characterize the subjects. Chi-square tests and *t*-tests were used to describe categorical and continuous variables, respectively. All analyses were conducted using STATA 12.0 (StataCorp LP., College Station, TX, USA).

## RESULTS

Table 1 summarizes the characteristics of the 169 patients. In this cohort, median age was 63.2 years (mean, 64.1 years; range, 48 to 74 years), and median PSA was 5.4 ng/mL (mean, 5.6 ng/mL; range, 0.47 to 5.51 ng/mL). Overall median prostate volume was 36.5 mL (mean, 40.5 mL; range, 5 to 120 mL). Among these 169 patients, clinical stage was T1c in 145 (86%) and T2a in 24 (14%).

Analysis of RP specimens revealed pathological GS of 7 in 99% of men. Extraprostatic extension and positive surgical margins were observed in 30 (18%) and 23 of patients (14%), respectively. Seminal vesicle invasion and lymph node involvement were not observed in any patient.

Tumor map analysis revealed that tumor foci with Gleason grade ≥4 were anterior in 66 (39%), anterolateral in 4 (2%), lateral (not clearly anterior or posterior) in 5 (3%), posterior in 52 (31%), and posterolateral in 42 (25%). There was no significant difference in the percentage of higher-graded tumor foci located in the anterior and posterior prostate ($P$=0.764).

## DISCUSSION

For more than two decades, TRUS–guided biopsy has been the standard method of detecting PCa. Although there is no consensus among experts as to which biopsy strategy is optimal, it is now widely accepted that initial prostate biopsy

**Table 1.** Patient characteristics

| Characteristic | Value |
|---|---|
| Age at RP (yr) | |
| Mean (median) | 64.1 (63.2) |
| SD | 6.6 |
| RP type | |
| Open | 84 (49.7) |
| Robotic | 16 (9.5) |
| Pure laparoscopic | 69 (40.8) |
| PSA (ng/mL) | |
| Mean (median) | 5.6 (5.4) |
| SD | 2.0 |
| TRUS volume | |
| Mean (median) | 40.5 (36.5) |
| SD | 15.9 |
| Clinical stage | |
| T1c | 145 (85.8) |
| T2a | 24 (14.2) |
| Biopsy Gleason score | |
| <6 | 0 (0) |
| 6 | 169 (100) |
| No. positive cores | |
| 1 | 83 (49.1) |
| 2 | 61 (36.1) |
| 3 | 25 (14.8) |
| No. total biopsy cores | |
| 12 | 133 (78.7) |
| ≥13 | 36 (21.3) |
| Maximum % core involvement with cancer | |
| Mean (median) | 14.1 (10.0) |
| SD | 11.7 |
| Pathologic Gleason score | |
| 7 | 167 (98.8) |
| ≥8 | 2 (1.2) |
| Extracapsular extension | 30 (17.8) |
| Seminal vesicle invasion | 0 (0) |
| Positive surgical margin | 23 (13.6) |

Values are presented as number (%) unless otherwise indicated.
RP, radical prostatectomy; SD, standard deviation; PSA, prostate specific antigen; TRUS, transrectal ultrasound.

should include at least 10 to 12 cores [14]. Even with that standard, a false-negative biopsy rate up to 30% for initial TRUS–guided biopsies and up to 50% for repeat biopsies has been reported. Sampling error is an inherent feature of any biopsy approach and is compounded by the difficulty in accessing certain regions of the prostate using the transrectal approach. As treatment approaches such as AS and focal therapy gain more attention, the diagnostic accuracy of prostate biopsy has been further challenged.

Several groups have compared the pathologic findings from prostate needle biopsy and RP in potential candidates for AS. In a retrospective analysis of 366 European men who received RP for clinically insignificant PCa, Jeldres et al. [6] reported that 8.3% had non–organ-confined disease on RP and 24% actually had cancer of higher (≥7) GS. A retrospective study reviewing outcomes after RP in 398 potential AS candidates from the SEARCH database revealed GS upgrading in 36%, extraprostatic extension in 16% and seminal vesicle invasion in 2% [15]. Similarly, a recent European multicenter study on 919 patients, who fulfilled relatively more stringent selection criteria for AS (PSA, ≤10 ng/mL; clinical stage, T1c; GS, <7; and a single positive core with tumor length, <3 mm), found GS upgrading in 34% and only 26% of patients with pathologically insignificant cancer [16]. Finally, among 626 patients enrolled in Prostate Cancer Research International: Active Surveillance (PRIAS) study who underwent immediate RP, GS upgrading was present in 44.9% [17]. Although the selection criteria for AS differ by institutions, this collective data clearly demonstrates that a single session of TRUS–guided biopsy offers limited accuracy in revealing tumor aggressiveness in potential candidates for AS.

A number of investigators have examined the ability of contemporary extended prostate biopsy to predict the exact location of tumor in RP specimens. From observing low negative predictive values for right (24.7%) and left (31.3%) biopsy in predicting tumor laterality, Schulte et al. [18] concluded that standard 12-core biopsies failed to provide reliable localization of tumors to specific areas of the prostate. They found no useful preoperative predictors for predicting pathologic agreement between biopsy and RP specimens for patients with low-risk PCa. Furthermore, Iremashvili et al. [19] analyzed the diagnostic performance of individual biopsy localization and found that lateral cores from the mid and base prostate along with apical cores showed lower diagnostic accuracies for detecting tumor foci than other cores in patients who all had systematic 12-core TRUS–guided prostate biopsy. Focusing on patients with unilaterally negative preoperative biopsy, Bolenz et al. [20] observed that dorsolateral regions, followed by anterior apical area were the most frequent locations of tumor foci undetected by biopsy in RP specimens.

Meanwhile, a paucity of data exists on the actual locations of tumor foci with higher Gleason grade undetected by contemporary prostate biopsy schemes amongst the potential candidates for AS. From analyzing RP specimens of 66 patients who met selection criteria (PSA<10 ng/mL and only one positive core showing either GS 3+3 of <3.0 mm or 3+4 of <2.0 mm) for AS, Davis et al. [21] found that tumor foci of transition zone origin contributed to a significant number of cases of an underestimated tumor volume. In a study of 51 patients with early stage PCa who were on AS and later un-


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derwent RP, Washington et al. [22] reported that biopsy correctly identified the sextant with the highest grade in only 37% of RP specimens and that identification of dominant grade did not differ significantly by location in the prostate (<50% accuracy for apex, mid, and base, respectively). Neither study offers additional analysis on the actual locations of higher-graded tumor foci undetected by initial biopsy in patients with upgrading. Importantly, pathologic examination in these two studies was not performed using whole-mounted specimens. In the current study of patients who were candidates for AS clinically, but opted for immediate RP and were found to have higher grade tumors, we observed that tumor foci with Gleason grade ≥4 were localized to both the anterior and posterior prostate, without predominance of a particular area.

In an attempt to increase the accuracy of prostate biopsy in predicting GS preoperatively some have opted for a transperineal saturation biopsy approach. Hossack et al. [23] compared RP histopathologic findings of patients who received both transperineal and transrectal biopsy as the modality used to identify the initial cancer and found that transperineal biopsy detected proportionally more anterior tumors (16.2% vs. 12%) and identified them at smaller size (1.4 $cm^3$ vs. 2.1 $cm^3$) and stage (extraprostatic extension 13% vs. 28%) than transrectal biopsy. A computer simulation study evaluating different prostate biopsy strategies found that standard 12-core TRUS biopsy performs poorly for detecting clinically significant PCa compared to template mapping biopsies (TMB) in which median of 48 cores were obtained via transperineal approach [10]. They suggested that only marginal improvement can be achieved by adding anterior cores to TRUS biopsy and that the performance attained by TMB would be optimal. However, others have reported on the increased prevalence of tumors in the apex, suggesting the need for additional sampling of apical area during the prostate biopsy [24,25]. In a prospective trial in which all patients underwent a standard 12-core biopsy plus 2 additional cores taken from anterior apex, Moussa et al. [26] observed that additional apical cores achieved the highest rate of unique cancer detection and increased overall cancer detection because of the preponderance of PCa at this site.

Overall, our findings do not advocate additional sampling of a particular area only. Results of the current study can be interpreted as providing support to performing repeat standard extended TRUS biopsy in potential candidates for AS. Berglund et al. [27] found that immediate repeat biopsy in cases of AS with selective delayed intervention resulted in 27% being upgraded or up staged and those were more likely to show higher grade and stage disease at RP. From their findings, they recommended performing repeat biopsy in potential candidates for AS. Barzell et al. [28] recently compared repeat TRUS biopsy with transperineal TMB in ruling out clinically significant cancer in men with presumed favorable risk PCa being considered for AS. They found that repeat TRUS biopsy failed to detect up to 80% of clinically significant cancers detected by TMB and identified the anterior apex as the area most commonly missed by repeat TRUS biopsy. From such findings, they suggested that TMB would outperform TRUS biopsy regardless of number of TRUS biopsy cores obtained since TRUS biopsy would miss many anterior tumors. However, the actual locations of tumors were verified by pathologic evaluation of RP specimens in less than 15% of subjects in their study. Moreover, others have disputed the advantage of TMB over standard TRUS biopsy regimens citing cost-related and procedural issues [29].

Although a nonnegligible proportion of clinically insignificant PCa continues to be reclassified as significant disease after RP as aforementioned, a question remains as to whether such upgrading is clinically important. To date, prospective AS series have provided satisfactory clinical outcomes despite the clear risks of upgrading and/or upstaging [30]. Additional long-term follow-up is clearly needed to determine whether there is a difference between pathologic and disease outcome in such group of patients.

The current may be limited by the following factors: 1) only patients who opted for curative surgery were included, possibly eliciting selection bias; 2) the exact reason for proceeding to surgery could not be specified in all cases; 3) biopsies in many of our subjects were performed outside the institution (although all were reviewed at our institution). We did not analyze the locations of missed lesion with largest tumor volume, as the GS is a more dominant prognostic factor than tumor volume regarding PCa. Additionally, the threshold tumor volume used to define clinically significant cancer remains open to debate.

In conclusion, among PCa patients deemed clinically appropriate for AS, higher grade tumor foci missed by standard prostate biopsies were localized to both the anterior and posterior prostate, without predominance of a particular area. These findings lend support to performing repeat standard prostate biopsy in potential candidates for AS and should be considered in efforts to optimize current biopsy strategies for the selection of AS patients.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was re-

ported.

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