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Optimizing Spatial Biopsy Sampling for the Detection of Prostate Cancer

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Abstract

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Purpose: The appropriate number of systematic biopsy cores to retrieve during magnetic resonance imaging (MRI)-targeted prostate biopsy is not well defined. We aimed to demonstrate a biopsy sampling approach that reduces required core count while maintaining diagnostic performance.

Materials and Methods: We collected data from a cohort of 971 men who underwent MRI-ultrasound fusion targeted biopsy for suspected prostate cancer. A regional targeted biopsy (RTB) was evaluated retrospectively; only cores within 2 cm of the margin of a radiologist-defined region of interest were considered part of the RTB. We compared detection rates for clinically significant prostate cancer (csPCa) and cancer upgrading rate on final whole mount pathology after prostatectomy between RTB, combined, MRI-targeted, and systematic biopsy.

Results: A total of 16,459 total cores from 971 men were included in the study data sets, of which 1,535 (9%) contained csPCa. The csPCa detection rates for systematic, MRI-targeted, combined, and RTB were 27.0% (262/971), 38.3% (372/971), 44.8% (435/971), and 44.0% (427/971), respectively. Combined biopsy detected significantly more csPCa than systematic and MRI-targeted biopsy ($p < 0.001$ and $p=0.004$, respectively) but was similar to RTB ($p=0.71$), which used on average 3.8 (22%) fewer cores per patient. In 102 patients who underwent prostatectomy, there was no significant difference in upgrading rates between RTB and combined biopsy ($p=0.84$).

Conclusions: A RTB approach can maintain state-of-the-art detection rates while requiring fewer retrieved cores. This result informs decision making about biopsy site selection and total retrieved core count.

Keywords

prostatic neoplasms; image-guided biopsy; biopsy; adverse effects; ultrasonography; interventional; magnetic resonance imaging

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The current gold standard for prostate cancer diagnosis involves a targeted biopsy of suspicious magnetic resonance imaging (MRI) regions of interest (ROIs) combined with a systematic template biopsy; together, they form a combined biopsy procedure consisting of, at our institution, an average of 17 retrieved biopsy cores. When compared to MRI-targeted biopsy, systematic biopsy has been shown to detect higher rates of clinically insignificant cancer, defined using the International Society of Urological Pathology prostate cancer grading system as grade group (GG) 1, and lower rates of clinically significant prostate cancer (csPCa), defined as GG ≥2 (these same GG designations are used in this study).[1,2] Nevertheless, combined biopsy is widely recommended since studies have shown that in 14%–16% of patients who underwent both procedures and received a csPCa diagnosis, the csPCa was detected by systematic biopsy alone.[3,4]

The combined biopsy approach requires obtaining significantly more biopsy cores than either systematic biopsy or MRI-targeted biopsy alone, increasing the cost, length, and discomfort of the procedure as well as the risk for sepsis, hematospermia, and pelvic and perineal pain.[5–7] In order to reduce these risks, it is prudent to retrieve the minimal number of biopsy cores required to adequately assess the patient's current cancer status.

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Although a precedent has been set establishing combined biopsy as the most robust prostate biopsy protocol,[8] no study to date has rigorously investigated the spatial relationship between systematic biopsy cores and MRI targets using the measured locations of obtained cores. As a result, little evidence is available to guide the determination of the optimal total number and location of biopsy cores that should be obtained from a patient; instead, most attention has been focused on determining the appropriate number of cores sampled from each ROI in the targeted biopsy component.[9–12]

Tschirdewahn et al used a retrospective analysis to examine the use of a targeted saturation biopsy strategy in which biopsies were taken only from the MRI target and adjacent areas,[13] an approach suggested in some scenarios by the Prostate Imaging Reporting and Data System® (PI-RADS®) committee.[14] This analysis found that restricting sampling to targeted locations within ROIs and systematic biopsy locations within adjacent Ginsburg sectors was superior to targeted or systematic biopsy alone. However, the true biopsy retrieval coordinates were not available to enable a complete analysis of the relationship between distance and yield. In addition, without prostatectomy data, upgrading and downgrading rates could not be assessed, making a full sensitivity assessment impossible.

In this study, we propose a biopsy site selection strategy, which we refer to as “regional targeted biopsy” (RTB). This strategy optimizes the selection of additional biopsy sites by focusing on regions of the prostate located within the 2 cm penumbra of a radiologist-designated ROI with a high suspicion index (ie PI-RADS score). Prior work that places MRI underestimation of prostate cancer tumors when compared to whole mount at a median of 13.5 mm per tumor, along with clinical intuition from the urologists and radiologists involved in this study, helped inform the decision to use a 2 cm margin as the basis for constructing a RTB.[15] A sensitivity analysis of this threshold choice is provided. We hypothesized that this strategy would achieve equivalent detection rates for clinically significant prostate cancer while requiring the retrieval of fewer biopsy cores.

In order to evaluate the potential impact of this strategy, we retrospectively calculated the results of a RTB, in which we discarded cores obtained from combined biopsy that are located outside of the 2 cm ROI penumbra. This location assessment was enabled using a retrospective sensor fusion approach that provides the 3-dimensional localization of each retrieved biopsy core within the prostate. We compared both csPCa detection rates across our entire cohort and GG upgrading and downgrading rates of a subcohort that underwent radical prostatectomy across 4 different protocols: systematic biopsy, MRI-targeted biopsy, combined biopsy, and RTB.

MATERIALS AND METHODS

Study Inclusion and Exclusion Criteria

We retrospectively collected data from a cohort of patients at our institution who underwent standardized 3 Tesla multiparametric MRI followed by standardized MRI-ultrasound fusion combined (both systematic and targeted) biopsy using spatially localized targets on a single system with specialized fusion software between 2011 and 2018. Patients were included regardless of how many biopsies they may have had previous to the study period or

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their prostate specific antigen value. However, for patients with repeat biopsies during the study period, only the first biopsy session was included for analysis. To ensure a fair comparison of cancer detection rates, we chose to include only the subset of patients who received at least 10 systematic biopsy cores. This minimum threshold of 10 systematic cores was consistent with recommendations from the European Association of Urology and others.[16–18] All MRI lesions were graded by one of 3 experienced genitourinary radiologists (SR, DL, and EF with 22, 29, and 5 years of domain-specific experience, respectively) using a published institutional score for lesions graded between 2011 and 2014 and the PI-RADS version 2 score for lesions graded between 2015 and 2018.[19] The institutional score is a 1 to 5 Likert score based on quantitative metrics that has been shown to have a similar csPCa detection rate to PI-RADS version 2.[20] Patients were excluded from analysis if their biopsy procedure was performed under a clinical trial protocol to avoid confounding from protocol differences, and were also excluded from analysis if real-time positional data were corrupt or unavailable for 1 or more of their biopsy cores. The study was approved by the UCLA Institutional Review Board (IRB Nos. 11–001580 and 16–001087).

MRI and Biopsy Protocols

As a part of routine clinical interpretation, MRI target ROI contours were drawn on axial T2-weighted scans by one of 3 experienced genitourinary radiologists using commercially available annotation software. To maximize specificity, the clinical annotation protocol required ROI margins to be drawn tightly around suspicious targets. These MRI annotations were then transferred to the MRI-ultrasound fusion device to enable the biopsy procedure. During the procedure, real-time sensor fusion was used to determine the 3-dimensional spatial coordinates of the tip and base of each individual biopsy core retrieved, including both targeted and template cores. Patients were anesthetized using a periprostatic nerve block of 20 cc 1% lidocaine, and all cores were retrieved by a single urologist (LSM) with 10 years of fusion biopsy experience. Computerized targeting guidance was provided for both systematic and targeted cores. For systematic cores, a target marker was designated on the procedural console and the operator retrieved a core from the designated location. For targeted cores, a radiologist-delineated ROI was displayed on the procedural console, and the operator retrieved cores from the ROI. Our combined biopsy protocol uses the “target+standard” approach for all biopsies, wherein targeted cores were taken before systematic cores. All cores that were intended to be targeted at an ROI were designated as targeted cores, and all cores that were intended to be systematic were designated as such, regardless of their position relative to the ROI. Cores were taken every 5 mm along the longest axis for irregularly shaped ROIs, and in a cross-hair pattern for regularly shaped ROIs. The standard minimum number of cores per ROI was 2, although a single patient in our data set received 1 core for their ROI.

All retrieved biopsy cores were interpreted by a sub-specialized group of genitourinary pathologists with 5–15 years of experience in prostate cancer interpretation and assigned Gleason scores and GGs.[21] For the purposes of this study, clinically significant prostate cancer included any biopsy core assigned an International Society of Urological Pathology GG of 2 or higher.

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Biopsy Distance Calculations

For each patient, the 3-dimensional spatial coordinates corresponding to each biopsy core were retrieved. The distance between a targeted or systematic biopsy core and an ROI was determined by both a distance from the edge of the ROI and the distance from the centroid of the ROI. If multiple ROIs were present, the smallest distance of the core to any ROI was used.

To determine an individual biopsy core's distance from the edge of an ROI, we first used the ray-casting algorithm to determine if the core intersected the ROI.[22] A distance of 0 was assigned to biopsy cores intersecting the ROI, while the shortest 3-dimensional distance between the set of points representing the biopsy core and ROI margin was assigned to biopsy cores not intersecting the ROI. In addition to the distance from the edge, we computed the shortest 3-dimensional distance between each core and the ROI centroid as an alternative distance metric.

Statistical Methods

To compare the cancer detection rates of systematic biopsy, MRI-targeted biopsy, combined biopsy, and RTB, as well as subsequent whole mount GG upgrading and downgrading of each of these methods, the 2-tailed, 2-proportion z-test was used. All tests were evaluated at a significance level of $p < 0.05$.

RESULTS

Patient Cohort

The initial study cohort included 1,705 patients. We excluded 239 patients with fewer than 10 systematic biopsy cores, 233 patients who participated in the Prospective Assessment of Image Registration for the Diagnosis of Prostate Cancer (PAIREDCAP) clinical trial,[2] and 262 patients who had missing biopsy core positional data. The final study cohort included 971 patients who underwent 3 Tesla multiparametric MRI and MRI-ultrasound fusion biopsy between April 2011 and December 2018 (fig. 1) with a mean±SD age of 64.5±7.4 years, prostate specific antigen level of 8.4±7.9 ng/ml, and prostate volume of 49.9±24.2 cm^3 (table 1). The average ROI volume was 0.9±2.2 cm^3, and when the ROI volume was expanded by 2 cm, the average expanded ROI volume was 26.4±9.0 cm^3.

Of these 971 patients, 117 underwent prostatectomy after biopsy, and 855 were placed on active surveillance or received other medical treatment. For our prostatectomy subset analysis, we excluded 15 patients whose biopsies occurred more than a year before prostatectomy, yielding a final prostatectomy subcohort of 102 patients. This 1-year cutoff was chosen to align with our active surveillance protocol, in which repeat biopsy is not generally performed less than 12 months after the previous biopsy.

Biopsy Core Distance Analysis

In the primary analysis cohort of 971 patients, 16,459 cores were obtained, including 13,515 no cancer cores, 1,409 GG 1 cores, 941 GG 2 cores, 243 GG 3 cores, 168 GG 4 cores, and

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183 GG 5 cores. The cumulative proportion of cores with csPCa as a function of distance from the ROI is shown in figure 2.

Biopsy Prostate Cancer Detection Rates

The cancer detection rates of different regional target penumbra sizes as well as the number of cores saved for each size are shown in table 2. Systematic, MRI-targeted, combined, and RTB (defined with a chosen 2 cm margin around the ROI) detected csPCa in 27.0% (262/971), 38.3% (372/971), 44.8% (435/971), and 44.0% of patients (427/971), respectively. Although combined biopsy detected significantly more patients with csPCa compared to systematic and MRI-targeted biopsy ($p < 0.001$ and $p = 0.004$, respectively), it detected a similar number of patients with csPCa to RTB ($p = 0.71$). The RTB approach resulted in a 22.1% decrease (3,644/16,459) in the overall number of biopsy cores (an average of 3.8 cores per patient) when compared to combined biopsy (fig. 3 and table 1). MRI-targeted biopsy utilized an average of 3.97 cores per ROI, while RTB, which expanded the ROI size, utilized an average of 10.58 cores per ROI.

The cancer detection rates of RTB, MRI-targeted, and systematic biopsy were additionally stratified by PI-RADS score and compared to combined biopsy (table 3). RTB maintained a cancer detection rate above 95% (with the number of csPCa cases found by combined biopsy used as ground truth) for PI-RADS 3, 4, and 5 cases, while MRI-targeted biopsy improved steadily from 74.5% to 85.7% to 93.3% for PI-RADS 3, 4, and 5, respectively.

Systematic biopsy, MRI-targeted biopsy, combined biopsy, and RTB detected only cancer-negative cores in 434/971 (44.7%), 446/971 (45.9%), 323/971 (33.3%), and 353/971 patients (36.4%), respectively, and detected at most GG 1 cancer in 275/971 (28.3%), 153/971 (15.8%), 213/971 (21.9%), and 191/971 patients (19.7%), respectively. Combined and RTB detected only cancer-negative cores in a similar number of patients ($p = 0.15$) but significantly fewer than MRI-targeted and systematic biopsy ($p < 0.001$). Systematic biopsy detected significantly more GG 1 prostate cancer compared to combined, MRI-targeted, and RTB ($p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively).

Locations of Positive Biopsies outside MRI Targets

In 63 of 971 patients (6.5%), csPCa was detected only on systematic biopsy. In 8 of these 63 cases (12.7%), a systematic core that detected csPCa was greater than 2 cm from an MRI target (ie outside the regional penumbra). Every csPCa systematic core found for these 8 patients was of GG 2. Of the 63 patients for whom systematic biopsy alone found csPCa, 18 had bilateral or midline targets and 45 had unilateral targets. Within the set of 45 patients with unilateral targets, csPCa was detected only ipsilateral to the target in 25 patients (55.6%), only contralateral to the target in 16 patients (35.6%), and both ipsilateral and contralateral to the target in 4 patients (8.9%). Entirely omitting contralateral biopsy would have thus missed csPCa in 16/971 patients (1.6%). The locations and GG of the positive cores found outside of unilateral MRI targets are shown in table 4.

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Whole Mount Histopathology Analysis

For the subcohort of 102 patients who underwent robotic prostatectomy and MRI-sectioned axial whole mount histopathology within a year of combined biopsy, 20.6% (21/102) and 12.7% (13/102) were upgraded to GGs ≥2 and ≥3, respectively, when compared to the maximum GG assigned to any retrieved biopsy core (ie any combined biopsy core; fig. 4). When only RTB cores within 2 cm of a target were included in the comparison, 25 (24.5%) and 14 patients (13.7%) were upgraded to GG ≥2 and GG ≥3, respectively. These upgrading rates were not significantly different when compared to combined biopsy (p=0.50 and p=0.84, respectively). When the upgrading results of MRI-targeted biopsy alone or systematic biopsy alone were compared to combined biopsy, all upgrading rates were significantly higher, except for the GG 3 upgrading of MRI-targeted biopsy (19 vs. 13 cases, p=0.25). Downgrading on whole mount pathology occurred in relatively few cases without significant differences between biopsy protocols (p >0.05 for all comparisons).

DISCUSSION

An ideal prostate biopsy protocol would maximize the detection of csPCa using the fewest biopsy samples to optimize clinical utility while minimizing morbidity and cost. In this study, we used a retrospective analysis to evaluate a regional targeted biopsy strategy, in which biopsy cores are only sampled from MRI targets (and their 2 cm margins) with a PI-RADS related score of 3 or higher. We found that this optimized strategy performed similarly to combined biopsy in the detection of csPCa, while requiring significantly fewer biopsy cores (on average 3.8) per patient and 22% fewer cores overall.

In the entire study cohort, we found that 94.2% and 97.0% of GG 2 or higher prostate cancers were detected even if cores retrieved more than 1.5 cm and 2 cm, respectively, from the edge of the MRI target were discarded. The high csPCa detection rate of cores in the penumbral region of MRI targets confirms the importance of the MRI-derived ROI as a hub of csPCa, and supports the role of an institutional Likert and PI-RADS based ROI scoring system as a predictor of underlying csPCa.[23–25] This study also confirms that MRI targets that are drawn for specificity can underestimate the true size and extent of tumor volumes.[15,26] Our analysis of the relationship between RTB distance thresholds and the resulting cancer detection rates may also have implications for optimal margin size determination for focal therapy (table 2).

A major advantage of this study is the use of whole mount histopathology data to indicate the ground truth presence of csPCa. We found that the prostate cancer upgrade rates after prostatectomy for combined biopsy and for RTB did not exhibit a statistically significant difference, despite the fewer biopsy cores used for the regional strategy. In contrast, systematic biopsy and MRI-targeted biopsy alone had significantly higher upgrade rates than combined biopsy. This aligns with other studies that show that combined biopsy demonstrates the fewest upgrades on prostatectomy compared to systematic and MRI-targeted, and that MRI-targeted biopsy tends to have fewer upgrades than systematic biopsy.[8,27] Ultimately, the results of our whole mount analysis suggest that a regional targeted biopsy can be an effective method for maximizing csPCa yield by achieving the sensitivity benefit of combined biopsy with fewer sampled cores.

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One limitation of our work is the retrospective analytic approach we used to evaluate regional targeted biopsy. In this approach, we censored certain systematic cores based on a defined distance from the ROI as a stand-in for a true regional targeted biopsy. Thus, this study cannot establish the prospective efficacy of a true regional targeted biopsy when compared to combined biopsy. Since systematic biopsy cores were obtained after targeted biopsy cores, it is also possible that the operator's knowledge of the target location influenced the placement of systematic cores. In addition, results are from a single tertiary institution with genitourinary MRI and pathology expertise, and all biopsy procedures were performed by a single urologist (LSM) with significant MRI-ultrasound fusion biopsy experience; as such, our findings may not be representative of those obtained in other care settings. The real-time sensor fusion approach we used to determine biopsy core locations has a 2–3 mm registration uncertainty, which may have led to inaccuracies in the calculation of biopsy distances.[28] Additionally, the designation of ROIs was done by a single radiologist for any given patient, and may be subject to inter-reader differences in boundary delineation.

CONCLUSIONS

We found that a regional targeted biopsy strategy had statistically similar sensitivity for clinically significant prostate cancer as a combined biopsy approach while requiring fewer cores, outperforming the MRI-targeted and systematic biopsy approaches alone. The success of the strategy was driven by the propensity of the most significant biopsy cores retrieved to be in the penumbral region of MRI targets with a PI-RADS related score of 3 or higher. These findings can be useful to clinicians when determining the optimal set of biopsy locations for an individual patient, and suggest that the regional targeted biopsy approach should be further evaluated as an alternative to combined MRI-targeted and systematic biopsy.

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Abbreviations and Acronyms

csPCa	clinically significant prostate cancer
GG	grade group
MRI	magnetic resonance imaging
PI-RADS®	Prostate Imaging Reporting and Data System®
ROI	region of interest
RTB	regional targeted biopsy

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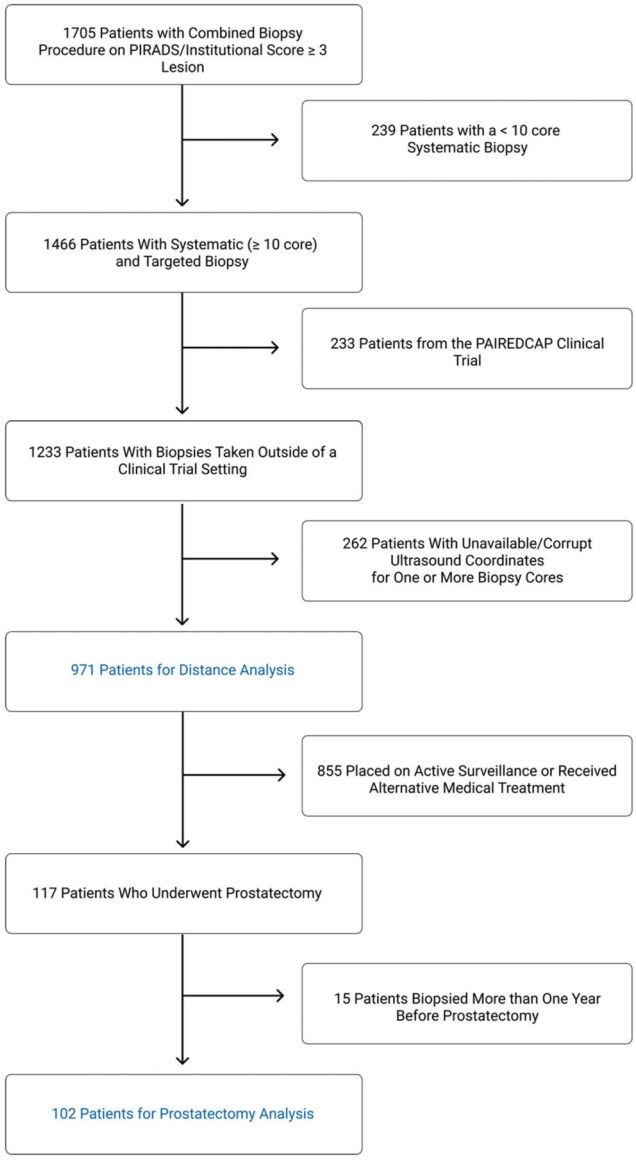

Figure 1.

Patient exclusion criteria. Initial study cohort of 1,705 patients underwent combined biopsy at our institution. Patients were excluded if they received systematic biopsy with fewer than 10 cores, if they were subjects in PAIREDCAP trial, or if they were missing coordinates for 1 or more biopsy cores. Primary distance analysis set therefore includes 971 patients. Among these 971 patients, 102 underwent prostatectomy less than 1 year after biopsy and were included in prostatectomy subset.

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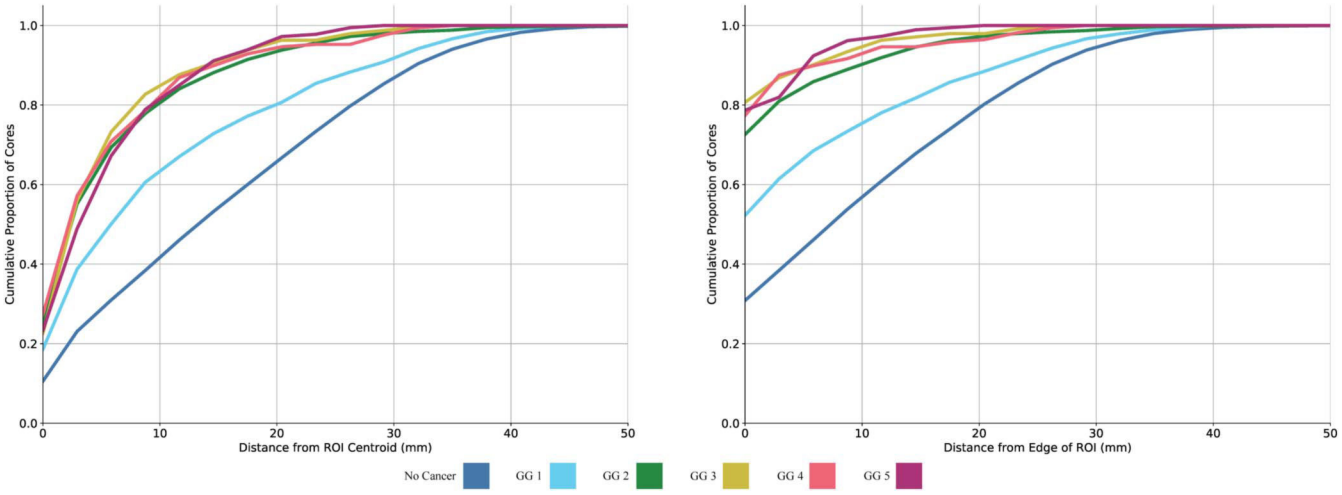

Figure 2.

Cancer capture with distance from ROI. Proportion of cores found within varying distances of edge of closest ROI and centroid of closest ROI is shown, stratified by GG. Of GG 2 or higher cores 94.2% and 97.0%, respectively, are found within 1.5 cm and 2 cm of edge of ROI, and 86.8% and 92.7%, respectively, are found within 1.5 cm and 2 cm of ROI centroid.

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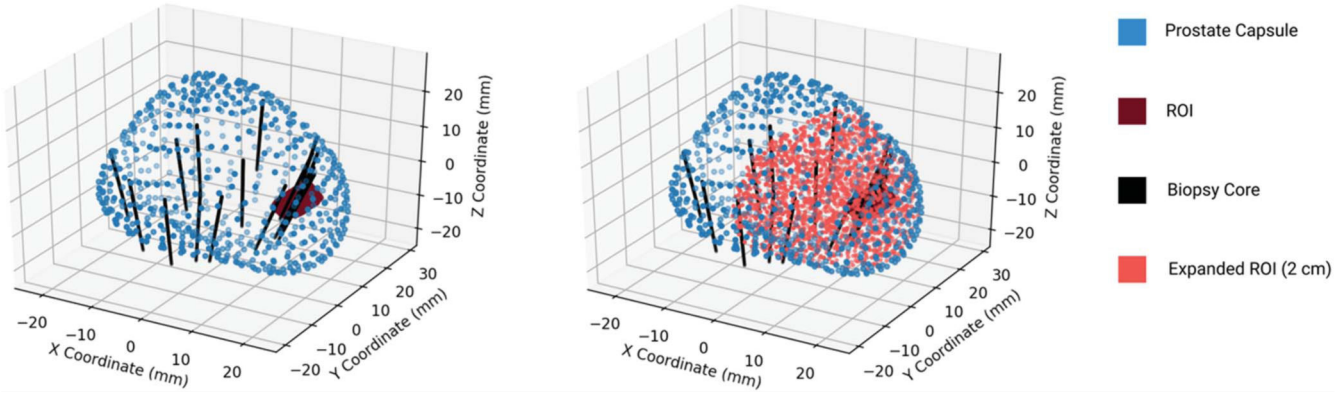

Figure 3.

Expanded 3-dimensional representation of ROI for regional targeted biopsy shows patient's prostate with original (left) radiologist-derived ROI (maroon) and regional target (right) covering 20 mm in all directions from edges of ROI.

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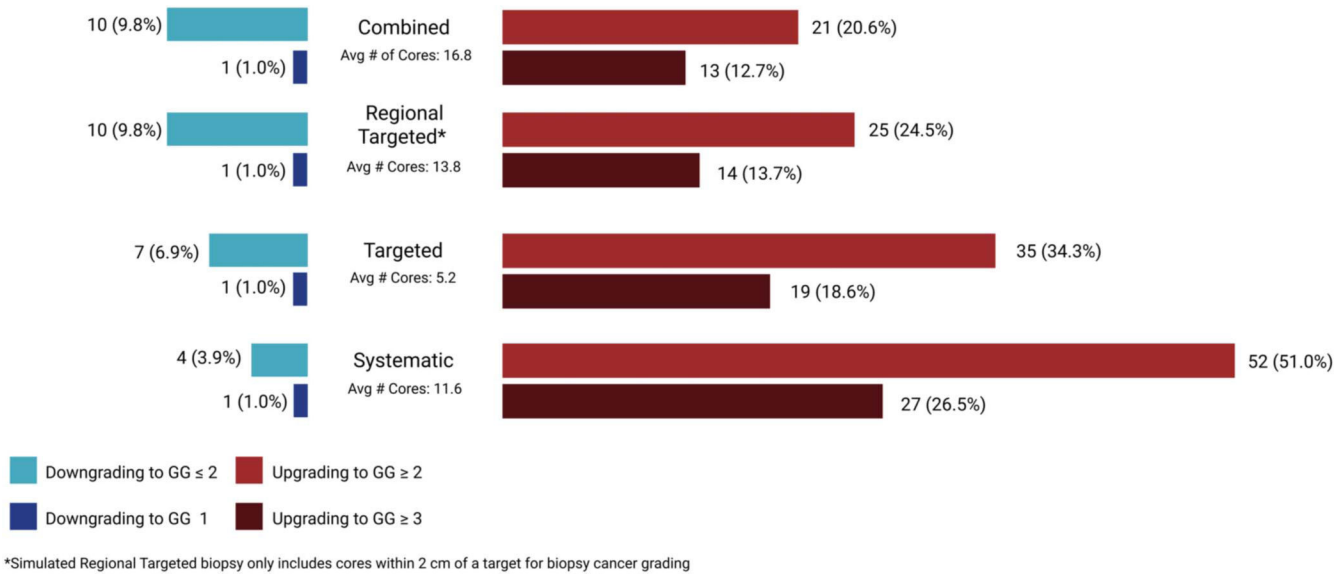

Figure 4.

Upgrading and downgrading of csPCa diagnosis after robotic prostatectomy. Highest GG from biopsy and subsequent prostatectomy GG were compared. Upgrading and downgrading of these GGs for each of 4 biopsy methods is shown, using whole mount prostatectomy as ground truth.

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Table 1.

Clinical and demographic information for both patient cohorts

	All Pts	Prostatectomy
No. pts	971	102
Mean±SD age (yrs)	64.5±7.4	62.2±6.1
No. race (%):		
Caucasian	616 (63.4)	72 (70.6)
Asian	54 (5.6)	6 (5.9)
African American	37 (3.8)	4 (3.9)
Hispanic	22 (2.3)	3 (2.9)
American Indian	1 (0.1)	0
Mixed	1 (0.1)	0
Other	19 (2.0)	2 (2.0)
Unknown	221 (22.8)	15 (14.7)
Mean±SD prostate specific antigen (ng/ml; normal <4)	8.4±7.9	8.2±6.8
Mean±SD prostate vol (cm^3)	60.8±29.1	46.5±18.1
Mean±SD ROI vol (cm^3)	0.9±2.2	0.7±0.9
Mean±SD regional targeted ROI vol (cm^3)	26.4±9.0	23.4±7.3
No. max ROI score (%):		
3	415 (42.7)	34 (33.0)
4	380 (39.1)	37 (36.2)
5	176 (18.1)	31 (30.4)
No. previous biopsy (%):		
0	309 (31.8)	39 (38.2)
1	413 (42.5)	41 (40.2)
>1	246 (25.3)	22 (21.6)
Unknown	3 (0.3)	0
Mean±SD No. targets	1.3±0.6	1.4±0.6
Mean±SD No. targeted cores	5.0±1.9	5.2±1.9
Mean±SD No. systematic cores	11.9±1.1	11.6±0.9
Mean±SD No. combined biopsy cores	17.0±2.0	16.8±1.9
Mean±SD No. simulated regional targeted cores	13.2±1.5	13.8±3.5
Mean±SD No. csPCa targeted cores	1.0±1.7	2.0±1.7
Mean±SD No. csPCa systematic cores	0.5±1.2	1.2±1.4
Mean±SD No. csPCa combined biopsy cores	1.6±2.5	3.2±2.6
MeaniSD No. csPCa simulated regional targeted cores	1.5±2.5	3.1 ±2.6

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Table 2.

Cancer detection rates of RTB with varying penumbra size

RTB Penumbra Distance (mm)	No. Pts with csPCa Found	Proportion of Total csPCa Pts Detected	Av No. Fewer Cores Relative to Combined Biopsy	p Value for RTB vs. Combined
5	396	0.91	9.658	0.074
10	413	0.949	7.45	0.314
15	421	0.968	5.501	0.522
20	427	0.982	3.753	0.715
25	432	0.993	2.211	0.891
30	434	0.998	1.064	0.964

Cancer detection rates of regional targeted biopsy with increasing ROI margin are shown, along with average number of cores saved relative to combined biopsy. P value represents results of 2-proportion z-test comparing cancer detection rate of each regional targeted biopsy method with combined biopsy.

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Table 3.

Cancer detection rates of RTB, MRI-targeted, systematic, and combined biopsy by PI-RADS score

PI-RADS Score	No. RTB (2 cm) csPCa Detection (%)	No. MRI-Targeted csPCa Detection (%)	No. Systematic csPCa Detection (%)	No. Combined Biopsy csPCa Detection
3	105 (95.5)	82 (74.5)	69 (62.7)	110
4	173 (98.9)	150 (85.7)	111 (63.4)	175
5	149 (99.3)	140 (93.3)	82 (54.7)	150

Number of csPCa cases found by each of 4 biopsy methods discussed is stratified by PI-RADS scores. Number in parentheses shows each biopsy method's number of csPCa cases detected as percentage of total number of csPCa cases detected by combined biopsy for that PI-RADS score.

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Table 4.

GGs of positive cores found outside unilateral MRI targets

	Ipsilat Lesions	Contralat Lesions
No. lesions	37	25
No. Gleason GG:		
2	28	23
3	4	2
4	4	0
5	1	0

Positive core counts in each group are presented; all cores originate from 45 patients who had only ipsilateral MRI targets and positive cores outside those targets. Four of these patients had both ipsilateral and contralateral positive cores, which have been allocated to appropriate columns.