

Location and Grade of Prostate Cancer Diagnosed by Transperineal Template-guided Mapping Biopsy After Negative Transrectal Ultrasound-guided Biopsy

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Objectives: To determine the location and grade of prostate cancer diagnosed by transperineal template-guided mapping (TTMB) after negative transrectal ultrasound-guided (TRUS) biopsy.

Materials and Methods: This analysis consisted of 1118 consecutive patients who underwent TTMB from January 2005 to August 2015. Eight hundred thirty-five underwent TTMB after at least 1 negative TRUS biopsy and 283 underwent TTMB as the first biopsy procedure. The study population was divided into cohorts based on the number of prior TRUS biopsy sessions (0, 1, 2, and ≥ 3). No patient underwent multiparametric magnetic resonance imaging. Differences in location and cancer grade detected on TTMB were evaluated as a function of the number of prior TRUS biopsies.

Results: Of the 1118 patients, 679 were diagnosed with prostate cancer. This included 208, 325, 104, and 42 patients who underwent 0, 1, 2, and ≥ 3 prior TRUS biopsies. The incidence of cancer detection on TTMB decreased as the number of prior TRUS biopsies increased (73.5% vs. 62.4% vs. 51.7% vs. 37.2%, $P < 0.001$); however, it became increasingly likely that TTMB would detect anterior prostate only as the number of prior TRUS biopsies increased ($P = 0.007$). Moreover, the incidence of high grade cancer (Gleason score ≥ 7) in the anterior gland increased with the number of previous TRUS biopsies.

Conclusions: TTMB detected prostate cancer in over half of the patients with one or more negative TRUS biopsies. The majority of TTMB detected cancers were Gleason score ≥ 7 . As the number of prior TRUS biopsies increased, there was a commensurate increase in the proportion of high-grade, anterior only disease.

Key Words: prostate cancer, diagnostic techniques, mapping biopsy, transperineal biopsy

(*Am J Clin Oncol* 2016;00:000–000)

The American Urologic Association recommends a 12-core prostate biopsy, with sampling methodology that incorporates the apical and far-lateral regions of the gland, as the standard diagnostic procedure for detection of prostate

cancer.¹ <https://www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Biopsy-WhitePaper.pdf> Tissue specimens are most commonly obtained under ultrasound guidance using a transrectal approach. Biopsy schemes with a higher number of cores, such as extended or saturation biopsy, have generally been shown to increase prostate cancer detection rates compared with a 12-core biopsy; however, there is concern that these methods may result in over-detection of cancers with an indolent biology.^{1,2}

Although the optimal core number for initial prostate biopsy continues to be a subject of vigorous debate, the role for extended/saturation biopsy in the setting of repeat biopsy is better established. Contemporary clinical data estimates a false negative rate of $\sim 30\%$ with the standard 12-core biopsy procedure.³ Higher biopsy core number may help to improve diagnostic yield in the subset of patients where there is persistent clinical suspicion of cancer despite a negative 12-core biopsy.⁴

Extended/saturation biopsy can be accomplished using either a transrectal or transperineal approach. It has been suggested that the standard method of obtaining a tissue diagnosis using transrectal ultrasound-guided (TRUS) biopsy is susceptible to a high degree of sampling error due to its inability to adequately access the anterior regions of the prostate. Multiple studies have shown that a transperineal approach improves surgical access to the anterior prostate and increases the likelihood of detecting occult cancer in the anterior zones of the gland.^{5–7} It is for this reason that some investigators have proposed that a transperineal mapping biopsy is the preferred procedure for those patients where there is clinical suspicion of a false negative on TRUS biopsy.

Herein, we report our institutional experience with 1118 consecutive men who underwent transperineal template-guided mapping biopsy (TTMB) of the prostate either as an initial diagnostic procedure or after negative TRUS biopsy. The following analysis focuses primarily on the location and grade of the cancers detected when TTMB was used as a repeat biopsy procedure.

MATERIALS AND METHODS

This analysis includes a total of 1118 patients who underwent TTMB between January 2005 and August 2015. Among these 1118 patients, there were 835 who underwent TTMB after at least 1 negative 12 core TRUS biopsy and 283 who underwent TTMB as their first biopsy procedure. The majority of patients who underwent TTMB as an initial biopsy

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ISSN: 0277-3732/16/000-000

DOI: 10.1097/COC.0000000000000352

TABLE 1. TTMB Parameters of the Study Population

Continuous Variables	No. Prior Biopsies										
	0 (n=283)		1 (n=521)		2 (n=201)		≥ 3 (n=113)		P	Total (n=1118)	
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median		Mean ± SD	Median
No. TTMB cores	54.7 ± 9.2	55.0	58.0 ± 9.1	59.0	58.4 ± 9.5	59.0	59.8 ± 11.4	62.0	<0.001	57.4 ± 9.6	59.0
Prostate volume											
Volumetric	51.9 ± 24.2	45.6	59.7 ± 30.5	52.1	67.4 ± 39.9	58.1	87.2 ± 52.0	76.4	<0.001	61.9 ± 35.1	53.4
Ellipsoid	46.0 ± 22.9	39.6	53.1 ± 28.4	46.2	60.6 ± 37.1	52.9	77.8 ± 46.0	70.1	<0.001	55.1 ± 32.4	47.5
Transition zone volume											
Ellipsoid	20.5 ± 16.4	15.3	25.7 ± 21.4	18.7	31.4 ± 27.1	25.2	44.1 ± 33.6	35.7	<0.001	27.3 ± 23.9	19.5
Prebiopsy prostate specific antigen (ng/mL)	6.4 ± 4.0	5.2	6.5 ± 5.2	5.6	8.5 ± 4.6	7.7	13.2 ± 14.8	9.7	<0.001	7.5 ± 6.8	6.1
Prostate specific antigen density*	0.17 ± 0.16	0.13	0.15 ± 0.19	0.12	0.17 ± 0.11	0.14	0.21 ± 0.25	0.15	0.010	0.16 ± 0.18	0.13
Transition zone prostate specific antigen density†	0.53 ± 0.75	0.32	0.44 ± 0.73	0.28	0.47 ± 0.47	0.30	0.49 ± 0.72	0.30	0.361	0.47 ± 0.70	0.30
Transition zone index‡	0.41 ± 0.23	0.38	0.43 ± 0.14	0.41	0.46 ± 0.14	0.46	0.52 ± 0.13	0.53	<0.001	0.44 ± 0.17	0.42

*Total serum prostate specific antigen divided by ellipsoid prostate volume.

†Total serum prostate specific antigen divided by ellipsoid transition zone volume.

‡Ellipsoid transition zone volume divided by ellipsoid prostate volume.

TTMB indicates transperineal template-guided mapping biopsy.

procedure were self-referred. In the setting of repeat biopsy, TTMB was most commonly performed for a persistently rising prostate specific antigen despite negative TRUS biopsy. TTMB was generally done within 3 to 6 months of the most recent TRUS biopsy. None of the patients in this analysis underwent multiparametric magnetic resonance imaging (mp-MRI) as image-guidance for the biopsy procedure.

The technique used for TTMB has previously been described in detail.⁸ The procedure was performed in the operating room with the patient under general anesthesia in the dorsal lithotomy position. Transrectal ultrasound was used to visualize the prostate in axial and sagittal dimensions. Images were collected from the level of the proximal seminal vesicles/prostate base to apex using a 5.0/7.5 MHz Sonoline transducer

(Siemens Inc., Issaquah, WA). Prostate volume was determined by a planimetric approach. Prostate and transition zone volumes were estimated as an ellipsoid using the formula, length × width × height × 0.5236.

Transperineal biopsies were obtained through template apertures corresponding to 24 regional biopsy locations. The specific biopsy locations have been described in detail in a prior publication.⁸ For each of the 24 regions, 1 to 3 biopsy cores were obtained using an 18 gauge 25 cm Max-Core biopsy needle (Bard Peripheral Vascular Inc., Tempe, AZ). The cumulative number of biopsy cores in any given patient was determined by prostate volume, with more cores obtained from each of the 24 regions in patients with a larger prostate. The template coordinate and offset from the base were recorded for

TABLE 2. Characteristics of Cancers Detected on Transperineal Template-guided Mapping Biopsy

Continuous Variables	No. Prior Biopsies										
	0 (n = 208)		1 (n = 325)		2 (n = 104)		≥ 3 (n = 42)		P	Total (n = 679)	
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median		Mean ± SD	Median
No. mapping cores	53.3 ± 9.7	54	56.7 ± 8.6	58	55.2 ± 9.8	58	54.9 ± 10.9	57	0.001	55.3 ± 9.3	56
Mean % positive biopsies	21.6 ± 19.9	15.7	14.9 ± 13.5	10.3	14.8 ± 12.2	12.1	17.4 ± 18.2	8.8	<0.001	17.1 ± 16.1	12.3
Categorical variables	Count	(%)	Count	(%)	Count	(%)	Count	(%)	P	Total Count	Total %
Gleason Score											
6	77	37.0	148	45.5	41	39.4	15	35.7	0.053	281	41.4
7 (3 + 4)	53	25.5	95	29.2	31	29.8	9	21.4		188	27.7
7 (4 + 3)	30	14.4	44	13.5	12	11.5	8	19.1		94	13.8
8-10	48	23.1	38	11.7	20	19.2	10	23.8		116	17.1
No. positive cores											
1-3	62	29.8	108	33.2	37	35.6	19	45.2	0.001	226	33.3
4-12	72	34.6	146	44.9	45	43.3	11	26.2		274	40.4
13-20	38	18.3	50	15.4	16	15.4	5	11.9		109	16.1
>20	36	17.3	21	6.5	6	5.8	7	16.7		70	10.3

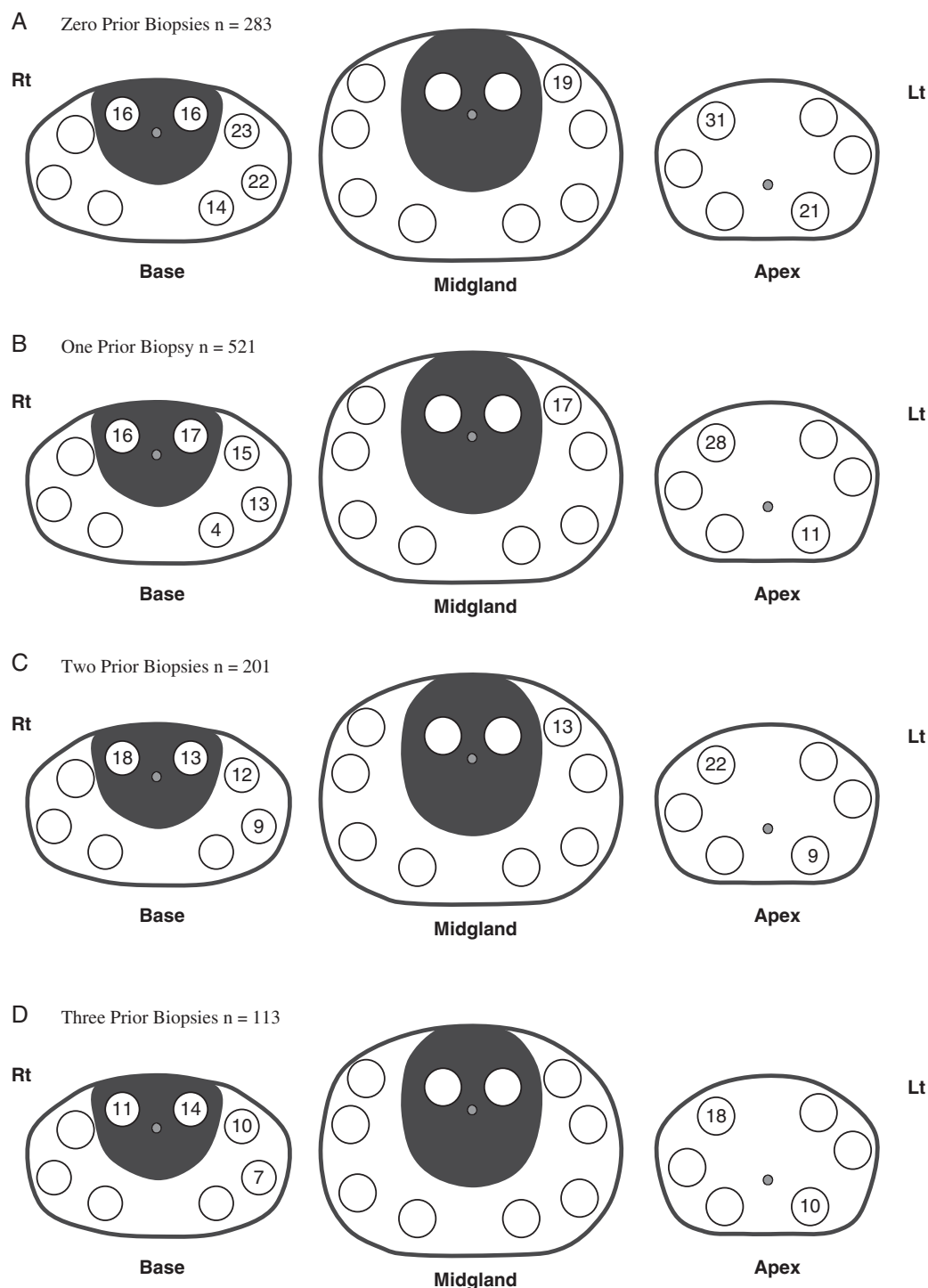


FIGURE 1. Cancer location (percentage of positive cores) following transperineal template-guided mapping biopsy.

each submitted biopsy core. The location, number, and percent of positive biopsy cores were recorded for each patient. All biopsy specimens were reviewed by a single pathologist with expertise in urologic pathology (E.A.). For the purposes of this analysis, the anterior prostate encompassed regions 1, 6, 9, 10, 15, 16, 19, and 24. The posterior prostate encompassed regions 2, 3, 4, 5, 11 to 14, and 20 to 23.

The procedure was performed on an outpatient basis and the average operative time was <1 hour. Tamsulosin (0.8 mg daily) was initiated 2 days preoperatively and continued an additional 2 weeks postoperatively. All patients received preoperative antibiotic therapy which consisted of 400 mg of IV ciprofloxacin with 80 mg of gentamicin added in patients with joint replacements and/or recent valve replacements.

TABLE 3. Association Between Number of Biopsies and Cancer

Cancer Sites	No. Prior Biopsies (Count [%])			Total
	0	1	≥ 2	
(A) Association between number of prior biopsies and location of cancer sites (Pearson χ^2 : $P=0.007$)				
Anterior only	43 (20.7)	97 (29.9)	52 (35.6)	192 (28.3)
Posterior only	21 (10.1)	42 (12.9)	20 (13.7)	83 (12.2)
Anterior and posterior	144 (69.2)	186 (57.2)	74 (50.7)	404 (59.5)
Total	208 (100)	325 (100)	146 (100)	679 (100)
(B) Association between number of prior biopsies and location of Gleason score ≥ 7 cancer (Pearson χ^2 : $P=0.009$)				
Anterior only	10 (7.6)	36 (20.3)	22 (24.4)	68 (17.0)
Posterior only	9 (6.9)	13 (7.3)	7 (7.8)	29 (7.3)
Anterior and posterior	112 (85.5)	128 (72.3)	61 (67.8)	301 (75.6)
Total	131 (100)	177 (100)	90 (100)	398 (100)

The Pearson χ^2 test was used to identify differences in cancer grade and/or location between the different biopsy cohorts. All data were analyzed with SPSS, version 17.0 with statistical significance considered at $P \leq 0.05$.

RESULTS

Clinical and Pathologic Characteristics of the Study Population

The study population consisted of 1118 men who underwent TTMB of the prostate between January 2005 and August 2015. For the purposes of this analysis, the study population was divided into different cohorts based on the number of prior TRUS biopsies that had been performed (0, 1, 2, and ≥ 3). The number of patients who underwent 0, 1, 2, and ≥ 3 prior TRUS biopsies were 283, 521, 201, and 113, respectively. The median number of prior TRUS biopsy cores for the different cohorts were 0, 12, 20, and 31, respectively. Clinical characteristics were well-matched between these cohorts, but there was a higher average age (64.5 vs. 64.9 vs. 65.3 vs. 67.4 y, $P=0.10$) and a higher pre-TTMB prostate specific antigen (6.5 vs. 6.5 vs. 8.5 vs. 13.0 ng/mL, $P<0.001$) in patients who had undergone a greater number of TRUS biopsies.

The different variables that characterize prostate volume are examined as a function of biopsy cohort in Table 1. A higher average prostate volume and a correspondingly higher average TTMB core number were observed as the number of prior TRUS biopsies increased. The incidence of cancer detection on TTMB decreased as the number of prior TRUS biopsies increased (73.5% vs. 62.4% vs. 51.7% vs. 37.2%, $P<0.001$). The pathologic features of the cancer detected in the different TTMB cohorts are summarized in Table 2.

Cancer Location as a Function of Biopsy Cohort

Of the 1,118 patients in this study, there were 679 who were diagnosed with prostate cancer on TTMB. This included 208, 325, 104, and 42 patients who underwent 0, 1, 2, and ≥ 3 prior TRUS biopsies, respectively. In the 679 patients with cancer detected on TTMB, the cancer was located in the anterior gland only, posterior gland only, or in both the anterior and posterior gland in 28.3%, 12.2%, and 59.5% of cases, respectively. The location of all detected cancer as a function of biopsy cohort is summarized in Figure 1. As the number of prior TRUS biopsies increased, it became increasingly likely that TTMB would detect cancer in the anterior prostate only ($P=0.007$, Table 3).

Cancer Grade as a Function of Biopsy Cohort

Among the patients with TTMB-detected cancer, there were 281 who were diagnosed with Gleason score 6 cancer and 398 diagnosed with Gleason score ≥ 7 cancer. The incidence and location of Gleason score 6 cancer as a function of biopsy cohort is summarized in Figure 1. The incidence and location of Gleason score ≥ 7 cancer as a function of biopsy cohort is summarized in Figure 2. The location of Gleason score 6 cancer did not change significantly as function of biopsy cohort; however, the incidence of higher grade cancer (Gleason score ≥ 7) in the anterior gland increased with the number of previous TRUS biopsies ($P=0.009$) (Fig. 3).

DISCUSSION

The standard 12-core TRUS biopsy is susceptible to a certain degree of sampling error. This has the potential to result in false-negative biopsy and/or incorrect risk stratification of disease.^{3,9,10} TTMB has been shown in multiple studies to improve diagnostic accuracy with lower incidence of Gleason score upgrading and higher cancer detection rate compared with TRUS biopsy.^{11,12} For this reason, TTMB may be the preferred diagnostic procedure for those patients where there is a high clinical suspicion of malignancy despite negative TRUS biopsy.

In this study, we report our experience with 1118 patients who underwent TTMB, without mp-MRI. Prostate cancer was detected by TTMB in over 56% of patients with at least 1 negative TRUS biopsy. Cancer detection became progressively less likely as the number of prior TRUS biopsies increased; however, it is noteworthy that cancer was still detected in over one-third of the patients who had undergone 3 or more negative TRUS biopsies. Of particular interest, the TTMB-detected cancers were more likely to reside in the anterior regions of the prostate as the number of prior biopsies increased. Moreover, the incidence of high grade cancer (Gleason score ≥ 7) in the anterior gland increased with the number of previous TRUS biopsies.

Our study contributes to a growing body of literature showing that TRUS biopsy frequently misses clinically significant prostate cancer. It has been estimated that under-sampling with TRUS biopsy occurs in roughly 30% to 80% of patients with prostate cancer.¹³ In our series of patients, TRUS biopsy failed to detect cancer in the range of 37% to 73% of cases, depending on the number of prior biopsy attempts.

One explanation for this observation is that the trans-rectal biopsy approach offers limited access to certain regions of the prostate gland. Our analysis showed that TRUS biopsy

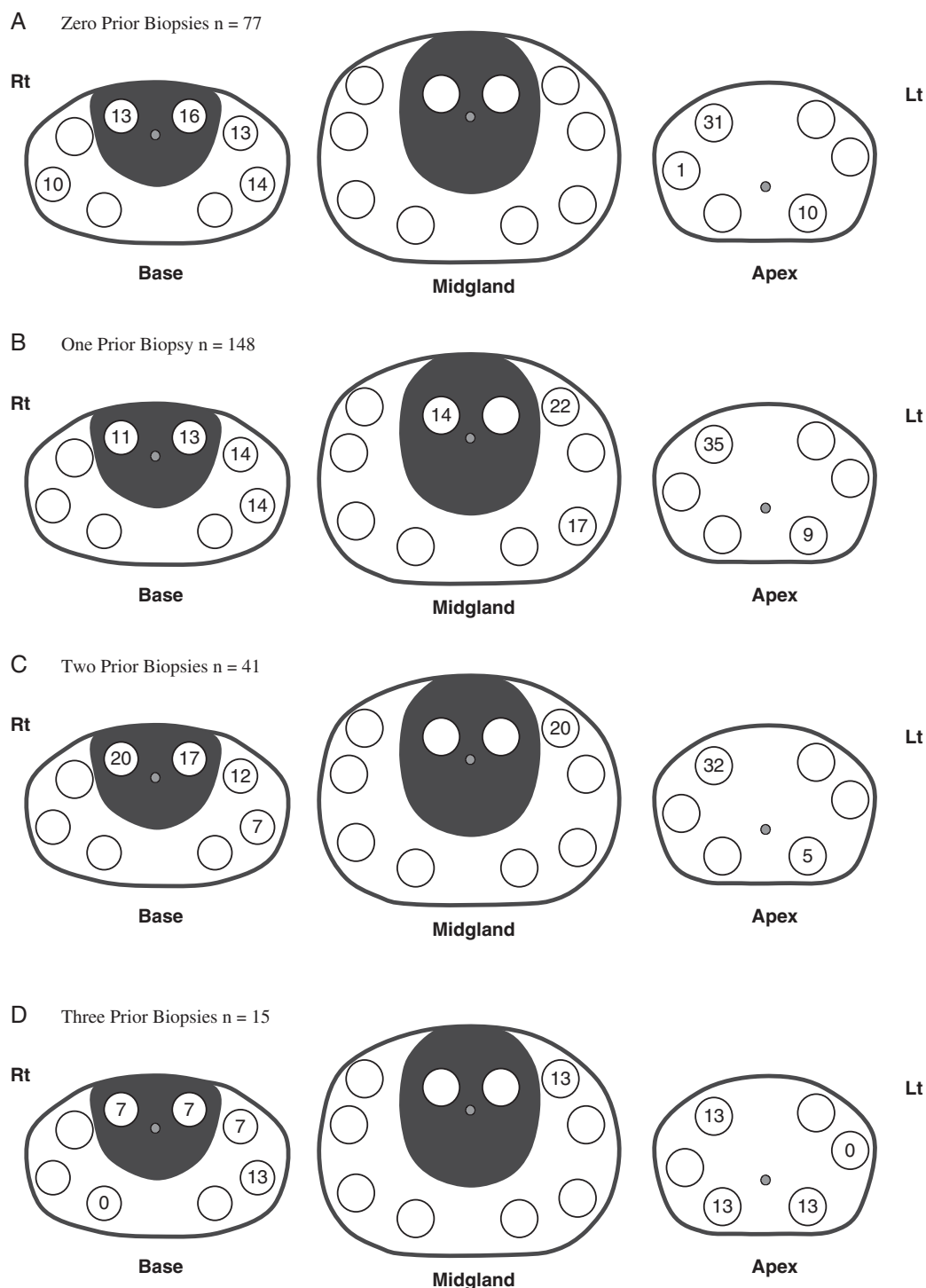


FIGURE 2. Gleason score 6 cancer distribution (percentage of positive cores) following transperineal template-guided mapping biopsy.

will often fail to identify anterior cancer and that the likelihood of undetected anterior cancer increases proportionally with the number of prior TRUS biopsies. Previous investigators have also observed this trend with transperineal biopsy (TPB). Ong et al⁵ recently published their experience of 160 patients who underwent transperineal prostate biopsy.

In their study, 25% of the TPB-detected cancers were confined exclusively within the anterior region of the prostate compared with only 5% with TRUS biopsy. Huang et al⁶ published their series of 110 patients who underwent TPB at a single institution. They reported that 21% of TPB-detected cancers involved the anterior zone only after a previously

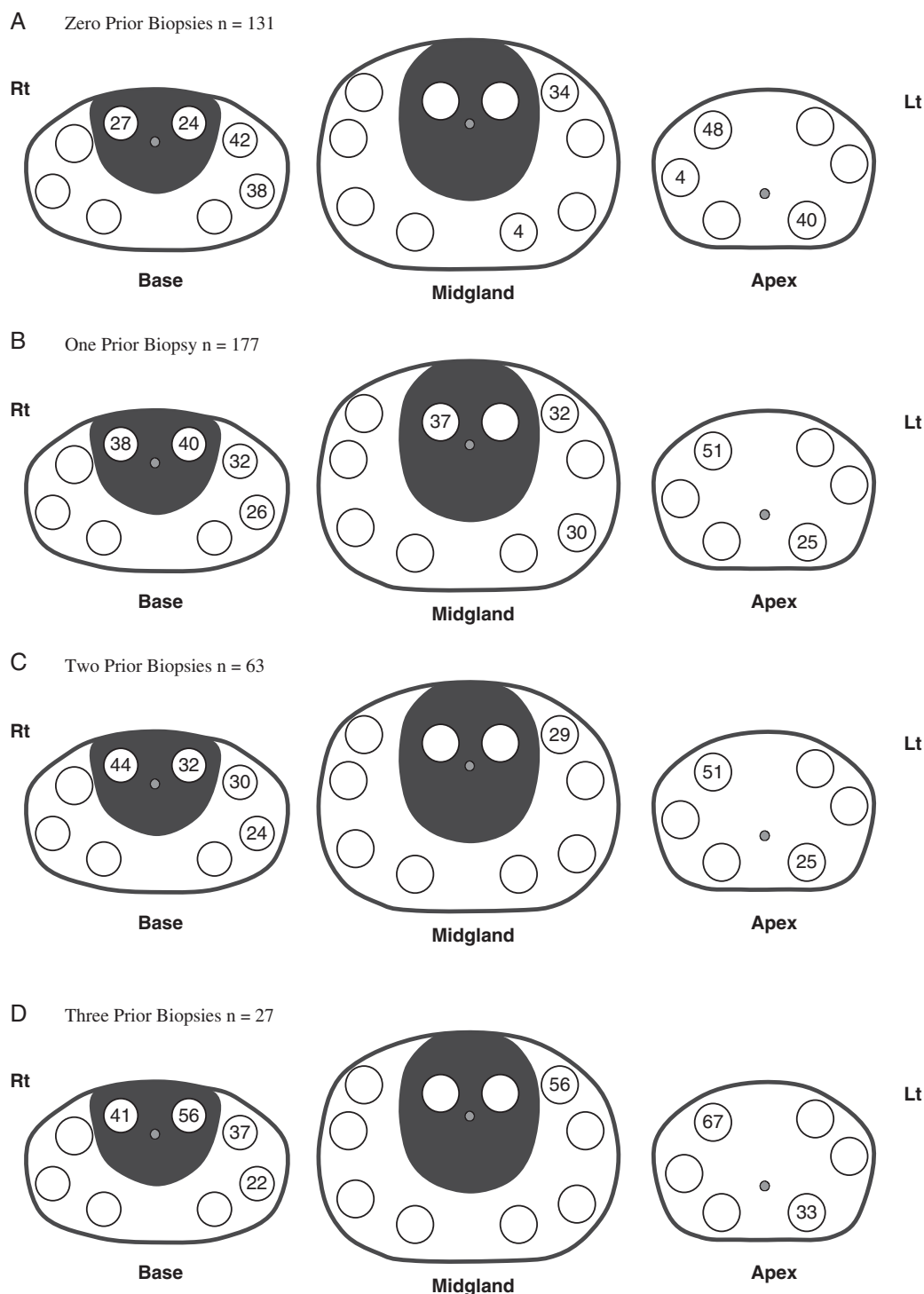


FIGURE 3. Gleason score ≥ 7 cancer distribution (percentage of positive cores) following transperineal template-guided mapping biopsy.

negative TRUS biopsy. In our series of patients, roughly 28% of patients had only anterior disease on TTMB. In the subset of patients with two or more TRUS biopsies, that proportion increased to nearly 36%.

The diagnostic tools at the disposal of the urologic oncologist are evolving rapidly. Imaging modalities, including

mp-MRI, are increasingly being utilized to improve the diagnostic yield of prostate biopsy and to provide better targeting of cancerous lesions. Although these new imaging technologies have generated enthusiasm and may ultimately result in a paradigm shift for prostate cancer diagnosis, there are better data to suggest that image-guided targeted biopsy and

transperineal mapping biopsy will continue to act as a complement to one another. Early data are beginning to show that MRI-guided prostate biopsy has a false-negative rate in the range of 20% to 30% and interestingly, the majority of these false negatives are located in the anterior sectors of the prostate.^{14,15} For example, Serrao et al¹⁴ examined the false negative rate of mp-MRI in 148 consecutive patients. The greatest proportion of missed cancers (21/46) were anterior based.¹⁴ On the basis of this data, one can certainly conceive of a future scenario where MRI-guided biopsy is used in conjunction with a sector-based TPB to optimize the accuracy of prostate biopsy. Alternatively, prebiopsy MRI may prove to be useful in selecting the most appropriate surgical approach for biopsy, with a transperineal approach utilized for MRI-detected abnormalities that reside within the anterior and/or apical regions of the prostate. At the present time however, a 12-core TRUS biopsy remains the standard of care for initial prostate biopsy. Our data suggest that TTMB should be strongly considered in the setting of repeat biopsy with particular attention given to the anterior regions of the prostate.

CONCLUSIONS

TTMB detected prostate cancer in over half of the patients with one or more negative TRUS biopsies. The majority of TTMB detected cancers were Gleason score ≥ 7 . As the number of prior TRUS biopsies increased, there was a commensurate increase in the proportion of high-grade, anterior only disease.

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