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Original Citation: Availability: This version is available at: 11577/3332126 since: 2020-03-21T15:19:41Z *Publisher:* Elsevier Inc.

Published version: DOI: 10.1016/j.urpr.2016.11.010

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Author's Accepted Manuscript

Effect of Level of Urology Training on Gleason Score and Prostate Volume Estimation Agreement Between Transrectal Ultrasound-Guided Biopsy and Radical Prostatectomy Specimen

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 PII:
 S2352-0779(16)30277-1

 DOI:
 10.1016/j.urpr.2016.11.010

 Reference:
 URPR 258

To appear in: Urology Practice Accepted Date: 29 November 2016

Please cite this article as: Morlacco A, Murphy CR, Rangel LJ, Mynderse LA, Thompson RH, Karnes RJ, Effect of Level of Urology Training on Gleason Score and Prostate Volume Estimation Agreement Between Transrectal Ultrasound-Guided Biopsy and Radical Prostatectomy Specimen, *Urology Practice* (2017), doi: 10.1016/j.urpr.2016.11.010.

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1	Effect of Level of Urology Training on Gleason Score and Prostate Volume Estimation
2	Agreement Between Transrectal Ultrasound-Guided Biopsy and Radical Prostatectomy
3	Specimen
4	
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11	Running title – Effect of level of training on TRUS biopsy accuracy
12	
13	Keywords: prostate biopsy, residency, training, TRUS, Gleason grading, prostatic cancer,
14	ultrasonography
15	
16	Abstract word count: 240
17	Total word count (excluding abstract): 2485
18	Tables: 5
19	Supplementary tables: 4
20	Figures: 0
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28	Conflict of interest: none
29	
30	Financial support: none relevant
31	

32 Abstract

33

Introduction: TRUS-guided prostatic biopsy may be performed by operators with different level 34 35 of training. Little is known about the impact of training level on biopsy results. This study aims 36 to evaluate the effect of level of training on the accuracy of TRUS-guided prostate biopsy 37 findings. 38 Methods: We retrospectively reviewed 500 consecutive patients who underwent TRUS-guided 39 prostate biopsy and subsequent radical prostatectomy (RP). TRUS operators were stratified based on level of training: junior, senior, chief, fellow, or staff. 40 Linear regression was performed to analyze the effect of training level on volume estimates. A 41 42 weighted Kappa statistic evaluated agreement between biopsy and pathologic Gleason scores, 43 while an adjusted cumulative logistic regression model analyzed effects of training level. 44 Results: 482 patients were included in the final analysis. TRUS biopsy was performed by staff in 78 (16%) patients, by fellows in 18 (4%), chief residents in 48 (10%), senior residents in 126 45 46 (26%), and by junior residents in 212 (44%). There was no significant difference between TRUS 47 and RP specimen volume estimates between the training levels. Level of training was not significantly associated with pathologic features including Gleason score, primary Gleason 48 49 grade, highest single Gleason grade, and estimated tumor volume. Limitations include the 50 retrospective design, and the variability between members of the same group. **Conclusions**: Agreement between biopsy and pathologic Gleason scores is high for all levels of 51 52 training. Level of training has no impact on prostate volume estimations or prediction of 53 pathologic features.

55 Introduction:

57	Transrectal ultrasound (TRUS) was first introduced in the field of urology approximately 40
58	years ago, and became one of the most important diagnostic tools available to the urologist ¹ .
59	Today, its most common use remains imaging of the prostate especially in the setting of prostate
60	core needle biopsies: despite being increasingly challenged by MRI-guided techniques, TRUS-
61	guided biopsy still remains the gold standard for prostate cancer diagnosis. A wide range of
62	cancer detection rates have been reported for TRUS biopsy, ranging from 25-49%, the variation
63	depending on the indications used for biopsy as well number of cores taken and various
64	templates used over the years ²⁻⁸ .
65	
66	Numerous studies evaluated templates for both the optimum number and location of cores to be
67	sampled. Overall detection rates were shown to increase with the number of cores taken ⁹ . Use
68	of extended 10-12 core systematic biopsy templates, which include samples of the lateral
69	peripheral zone, in addition to sampling suspicious lesions was shown to improve cancer
70	detection rates ⁹⁻¹³ . In addition, an extended template biopsy has been shown to decrease the
71	probability of a positive repeat biopsy following an initial negative extended biopsy ¹⁴ .
72	Furthermore, the extended 12 core biopsy template has been shown to have no significant
73	difference in quality of life and return to daily activity, work, or exercise compared to a sextant
74	biopsy ¹⁵ . The constellation of these findings, along with other similar studies, led to the adoption
75	of a 12 core template including sextant and lateral peripheral zone sampling at base, mid-gland
76	and apex bilaterally for TRUS-guided prostate biopsy in addition to biopsy of any palpable

abnormalities on DRE or suspicious lesion on TRUS as the standard of care according to NCCN
and EAU guidelines^{16, 17}.

79

In addition to guiding prostate biopsy, prostate volume estimation is another tool that TRUS
offers to the urologist; this is commonly calculated using an ellipsoid formula. Volume
measurements may be helpful in surgical planning and are necessary in calculating PSA density
which may be used adjunctively in determining whether to recommend a biopsy or in prognostic
models to predict surgical outcomes¹⁸⁻²⁰.

85

TRUS-guided prostate biopsy is one of the first urologic procedures taught to urology residents. 86 87 Whether experienced urologists better sample the prostate during biopsy compared to urology residents has not been extensively studied: guality standards for prostate biopsy have been 88 established and include length of the core and percentage of cores with no prostatic tissues. 89 Accuracy of prostate cancer detection has been shown to be influenced by the length of biopsy 90 cores²¹. Benchikh et al studied average length of biopsy cores taken by residents and reported 91 92 significant improvement in average core length from the first to twelfth biopsies performed, after which point average core length plateaued²². A few studies have examined the performance of 93 94 urology residents in TRUS prostate biopsies with regards to cancer detection, and have shown residents at all levels of training perform equally well^{22, 23}. In our program, prior to autonomy, 95 96 residents have formal didactics and supervised training during their internship (PGY-1) year.

98 The objective of this study is to evaluate the performance of residents at various levels of

training to accurately biopsy the prostate and estimate volume, using the RP specimen as a goldstandard.

101

102 Materials and Methods:

We retrospectively reviewed 500 consecutive patients who underwent TRUS-guided transrectal
prostate biopsy and subsequent RP for definitive treatment of prostate cancer at our institution
from 2005-2007. The minimum standard was a 12-core biopsy template. TRUS operators were
stratified based on level of training : junior resident (PGY2), senior resident (PGY3-4), chief
resident (PGY5-6), fellow, or staff.

108

109 Prostate volume:

110 Prostate dimensions in terms of length (craniocaudal), width, and height (anteroposterior) were

111 measured using TRUS. Prostate volume was estimated by applying an ellipsoid equation

112 $(\pi/6 * l * w * h)$.

113 Volume of the RP specimen was calculated from the true dimensions of the fresh specimen

applying the same ellipsoid equation. Differences between TRUS-estimated and RP specimen-

estimated volumes were compared within each level of training as were differences between the

116 various levels of training. Logarithmic transformation of both volume estimates was performed

to facilitate linear regression analysis to assess the value of TRUS volume and level of training

as predictors of RP specimen-estimated volume.

119

120 Gleason Score: For practical purposes, Gleason scores were categorized into three different 121 groups – low (Gleason 6), intermediate (Gleason 7), and high (Gleason 8-10) – in accordance with prostate cancer risk stratification. Both biopsy and RP specimen examinations were 122 123 performed by experienced uropathologists at our institution. Analysis of agreement between 124 biopsy and pathologic Gleason scores for each level of training was done using a weighted 125 Kappa statistic. Kappa values <0.2 indicate poor to slight agreement while values of 0.2-0.4, 126 0.4-0.6, 0.6-0.8 and >0.8 indicate fair, moderate, substantial, and near perfect agreement, 127 respectively. An adjusted cumulative logistic regression model was used to evaluate how 128 prediction of pathologic Gleason score from the biopsy Gleason score was affected by level of 129 training. Sub-analyses evaluating the highest single (3, 4, or 5) clinical and pathologic Gleason 130 grades as well as the primary clinical and pathologic Gleason grades (3, 4, or 5) were done using 131 the same methods.

132

The percentage of positive core from each individual biopsy core was summed and divided by the sum of each individual biopsy core length to calculate percentage of positive cores for the entire biopsy. Tumor volume was estimated using the ellipsoid formula and the pathologic specimen. Logarithmic transformation of estimated tumor volume was performed to facilitate linear regression analysis to evaluate percentage of positive cores in the biopsy and level of training as predictors of estimated tumor volume.

139

140 **Results**:

142	This IRB approved study included 482 patients who provided their consent for research
143	purposes. TRUS biopsy was performed exclusively by staff in 16.2% (78/482), fellows in 3.7%
144	(18/482), chief residents in 10% (48/482), senior residents in 26.1% (126/482), and junior
145	residents in 44% (212/482).
146	
147	Mean and median TRUS-estimated and RP specimen-estimated volumes stratified by level of
148	training are displayed in Table 2. Overall, there was no significant difference between TRUS-
149	estimated volume and RP specimen-estimated volume (p=0.33) nor were there any significant
150	differences between volume estimations within each experience level (Table 1). The differences
151	between the various experience levels were not significant (p=0.24).
152	
153	Overall, level of training did not significantly affect prediction of the RP specimen-estimated
154	volume (p=0.26) nor did the TRUS volume slope vary by level of training (p=0.58). There was a
155	significant difference in the prediction of RP specimen-estimated volume by junior residents
156	compared to staff (p=0.045). Preoperative PSA and TRUS volume were found to be
157	significantly associated with RP specimen-estimated volume (Table 2).
158	
159	Using the three different classifications of Gleason score, agreement between clinical and
160	pathologic Gleason scores for junior residents, senior residents, chief residents, fellows and staff
161	was 76.7%, 72.2%, 72.3%, 83.3%, and 87.0%, respectively. Using the weighted Kappa statistic,
162	the highest concordance indices were observed for staff and fellows (both $\kappa = 0.72$) and the
163	lowest for senior residents ($\kappa = 0.46$); however, this method does not allow adjustment for

164 covariates. When clinical and pathologic Gleason scores differed, biopsy Gleason score was

more frequently lower than pathologic Gleason score, a trend consistent across all levels of

166	training (Table 3).
167	
168	On logistic regression, level of training had no significant effect on prediction of pathologic
169	Gleason score by clinical Gleason score using staff as a reference ($p = 0.30$). Clinical/biopsy
170	Gleason score and estimated tumor volume were found to be significant predictors of pathologic
171	Gleason score (Table 4). Additionally, there was no evidence that the effect of training varied by
172	clinical Gleason score ($p = 0.13$).
173	
174	Similar sub-analyses evaluating agreement between single highest clinical and pathologic
175	Gleason grades (Supplementary Tables 1-2), and primary clinical and pathologic Gleason grades
176	(Supplementary Tables 3-4) were performed. Results from both these focused analyses mirrored
177	those of the total clinical and pathologic Gleason scores in that level of training did not
178	significantly impact prediction of these pathologic features.
179	
180	Finally, the prediction of estimated tumor volume by the percentage of positive cores in the
181	biopsy was not affected by level of training overall (p=0.08) nor did its effect vary significantly
182	by maximum clinical Gleason grade (p=0.50). The percentage of positive cores in the biopsies
183	and preoperative PSA were significant predictors of estimated tumor volume (Table 5).
184	
185	Discussion:

186

187 To our knowledge, the findings of resident-performed TRUS-guided prostate biopsies –

specifically Gleason score and volume estimation have not been compared to radical

189 prostatectomy (RP) specimens to determine the potential effect the level of training may have on

190 their accuracy.

191

Experience has previously been studied for potential effect on cancer detection for TRUS-guided prostate biopsy. Lawrentschuk et al evaluated the difference in prostate cancer detection in over 4500 TRUS biopsies performed by four different uro-radiologists³. The authors reported cancer detection ranged from 43.8-52.4% among the four operators and noted the operator to be a significant predictor of cancer detection; however, no learning curve was detected. Rather, differences in cancer detection rates between operators were concluded to be the result of difference in expertise and/or technique.

199

Previous studies have examined how level of training impacts the rate of cancer detection when performing TRUS-guided prostate biopsy and found no significant differences between resident training levels in overall cancer detection²²⁻²⁴. Benchikh et al described a learning curve for residents on the basis of improvement of the average biopsy core length, which plateaued after 12 procedures²². However, this learning curve did not seem to affect cancer detection rates, which were stable throughout the study period²².

206

Our study evaluates the impact level of training may have on the accuracy of prostate biopsy by
comparing the Gleason score from the RP specimen to that from the TRUS-biopsy. Obviously,
even in the most experienced hands there is not 100% concordance between clinical/biopsy and

pathologic/RP-specimen Gleason scores. At all levels, clinical variables appropriately predicted
the corresponding pathological variables. Using staff performance as a reference, we found level
of training to have no significant effect on predicting the pathologic Gleason score.

214 In sub-analyses of the both the highest single Gleason grade and the primary Gleason grade, both 215 biopsy Gleason grades remained predictive of their pathologic counterpart and no significant 216 differences were observed between levels of training. It should be noted that when biopsy 217 Gleason score was not in agreement with pathologic Gleason score, biopsy Gleason score was 218 more frequently lower than pathologic Gleason score. This was true for overall, maximum, and 219 primary Gleason scores, with no relationship to the level of training. When examining individual 220 contrasts with staff, it was noted that senior residents differ from staff in prediction of primary 221 Gleason grade (OR 5.530; p=0.015).

222

We also evaluated the effect of level of training on the accuracy of TRUS prostate volume
estimations. TRUS, in the hands of experienced operators, yields precise volume estimations
such that there is good agreement when TRUS is either repeated by the same operator or
performed by different, experienced operators²⁵. Sech et al evaluated the effect level of training
had on TRUS-estimated prostate volumes having a junior resident, senior resident, and attending
physician perform TRUS on the same 121 patients²⁶. The study authors reported an
intraexaminer correlation of 0.96 (0.95-0.97) for total volume²⁶.

230

However, while TRUS has been shown to be precise in its volume estimations, its accuracy hasbeen questioned as studies have shown TRUS generally underestimates prostate volume by as

233	much as 20% when compared to prostate specimen weight following RP ²⁷⁻²⁹ . More recently,
234	Rodriguez et al suggested the ellipsoid formula is the primary source for inconsistency in TRUS
235	prostate volume estimations as they showed volume estimations using an ellipsoid formula and
236	measurements from RP specimens also underestimated actual gland weight ²⁹ .
237	
238	We compared TRUS-generated volume estimates to volume estimates from RP specimens
239	calculated using the same ellipsoid formula and dimensions of the RP specimen, similar to
240	Rodriguez et al. Since both estimations use the same ellipsoid formula, the formula is not a
241	confounder in our evaluation of level of training's potential effect on accuracy of the TRUS-
242	volume estimation.
243	
244	Within each level of training, there was no significant difference between TRUS-estimated
245	volume and RP specimen-estimated volume. Furthermore, the differences between TRUS-
246	estimations and RP specimen estimations were not significantly different for the various levels of
247	training. Trends were noted for both junior residents and chief residents to overestimate prostate
248	volume with TRUS by a median of 0.9 cc and 3.0 cc (p=0.06 and p=0.09), respectively.
249	
250	Linear regression analysis confirmed that prediction of RP specimen-estimated volume, as
251	expected, is affected by changes in TRUS volume and preoperative PSA (Table 2). However,
252	level of training overall did not significantly affect the prediction of RP specimen-estimated
253	volume. When examining individual contrasts with staff, junior residents differed from staff in
254	their prediction of RP specimen-estimated volume (p=0.045). However, given the modest p-

value and the number of comparisons, the actual relevance of this finding is uncertain.

Additionally, the smaller magnitude of the regression coefficient (0.09) for this difference fromstaff may carry little clinical significance.

258

259 While this study is novel in assessing accuracy of TRUS biopsy findings among different levels 260 of training, it is not devoid of limitations beginning with its retrospective nature. We also did not 261 utilize a strictly prospective and standardized biopsy protocol. However, all residents are 262 required to complete the same ultrasonography training course in which they are taught 263 appropriate technique for prostate biopsy prior to performing biopsies in clinic, thus there is 264 minimal variation in their education regarding how to perform this procedure. Of interest, no 265 staff members were regularly present in the room when residents/fellows performed the biopsy, 266 thus minimizing the possible exteral influence on the operator. However, use of a standardized 267 biopsy protocol is likely to increase both inter-group and interobserver agreement, further 268 reducing the differences among different training level groups. Additionally, there was no 269 distinction made between office-based biopsies and those conducted in an outpatient surgical 270 center setting; in spite of that, in our clinical practice we do not observe any difference in core 271 number among different training grups.

Finally, there are some aspects that could limit the applicability of our findings. First of all, the present study was carried out at an acedemic institution with a structured training program, therefore it might only partially apply to institutions without a well-organized training program. Moreover, while the use of RP pathology as a reliable gold standard is an advantage of the present work, on the other hand, this choice could theoretically limit the generalization of our findings to other groups of patients such as those managed with active surveillance of radiation therapy.

279

280	Nonetheless, this novel study provides evidence to support the idea that prostate cancer
281	management is not compromised when residents perform TRUS-guided prostate biopsy.
282	However, confirmation of these training level and achievement of appropriate skills will need to

283 be re-assessed as more advanced biopsy techniques are introduced into our biopsy schemes.

284

- 285 In conclusion, our findings show that the level of training does not significantly impact the
- accuracy of TRUS-guided prostate biopsy findings and the procedure can be safely performed by
- relatively inexperienced urology residents without compromising patient care.

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	Junior mean (SD) median	Senior mean (SD) median	Chief mean (SD) median	Fellow mean (SD) median	Staff mean (SD) median	Total mean (SD) median	
TRUS	41.5 (20.2)	41.9 (22.1)	42.2 (21.6)	36.4 (15.7)	34.9 (16.2)	40.4 (20.2)	7
volume	36.8	37.3	36.9	33.4	30.8	35.9	
RP	39.6 (20.4)	41.2 (23.9)	38.8 (18.4)	38.2 (13.0)	37.0 (16.2)	39.5 (20.3)	
volume	34.0	34.0	33.5	39.6	33.0	33.9	
Difference	(n=185)	(n=114)	(n=42)	(n=18)	(n=67)	(n=426)	p value
mean (SD)	-1.9 (13.3)	+0.1 (19.3)	-3.4 (12.6)	+1.8 (15.8)	+2.1 (12.5)	-0.7 (15.1)	0.2428
p value	0.0606	0.9686	0.0907	0.6307	0.1740	0.3335	

Table 1: Differences between TRUS-estimated and RP specimen-estimated volumes for level of training and comparison between these differences by level of training

Table 2: : Linear regression of logarithm of RP specimen-estimated volume by logarithm of TRUS volume controlling by level of training, its interaction with logarithm of TRUS volume and preoperative PSA

Variable	Coefficient (SE)	p value
Log(TRUS volume)	0.73 (0.03)	< 0.001
Junior (reference is staff, junior = 1, staff = 0)	-0.09 (0.04)	0.0450
Senior (reference is staff, senior = 1, staff = 0)	-0.05 (0.05)	0.3280
Chief (reference is staff, chief = 1, staff = 0)	-0.11 (0.06)	0.0663
Fellow (reference is staff, fellow = 1, staff = 0)	-0.00 (0.08)	0.9981
Preoperative PSA	0.06 (0.01)	< 0.0001

Level of training	Ν	к (SE)	% agreement	% Bx < RP	% Bx > RP
Junior	210	0.58 (0.05)	76.7 %	18.6 %	4.7 %
Senior	126	0.46 (0.07)	72.2 %	22.2 %	5.6 %
Chief	47	0.50 (0.12)	72.3 %	14.9 %	12.8 %
Fellow	18	0.72 (0.14)	83.3 %	16.7 %	0.0 %
Staff	77	0.72 (0.09)	87.0 %	13.0 %	0.0 %
Total	478		~	2	

Table 3 : Kappa statistic and percent agreement between clinical and pathologic Gleason scores (grouped as 2-6, 7, and 8-10) for each level of training

	OR	95% CI	p-value
Clinical Gleason score (unit increase in group)	16.360	9.480 - 28.232	<0.0001
Junior (reference is Staff)	1.096	0.552 - 2.177	0.7924
Senior (reference is Staff)	1.541	0.739 - 3.215	0.2488
Chief (reference is Staff)	0.716	0.272 - 1.887	0.4999
Fellow (reference is Staff)	0.982	0.272 - 3.547	0.9777
Clinical stage (reference is T1ab, T1c)	1.246	0.749 - 2.071	0.3975
Log (RP specimen-estimated volume)	0.774	0.435 - 1.377	0.3836
Log (estimated tumor volume)	1.523	1.308 - 1.773	< 0.0001
Preoperative PSA	1.028	0.990 - 1.067	0.1506

Table 4: Cumulative logistic regression odds ratios of pathologic Gleason score (2-6, 7, 8-10) by clinical Gleason score, controlling by level of training, clinical stage, logarithm of RP specimenestimated volume, logarithm of estimated tumor volume, and preoperative PSA

Table 5: Linear regression of logarithm of estimated tumor volume by percentage of positive cores controlling by level of training, interaction with percentage of positive cores, clinical stage, logarithm of RP specimen-estimated volume and preoperative PSA

	Coefficient (SH	E) p value
% positive cores	3.94 (0.46)	< 0.0001
Junior (reference is staff, junior = 1, staff = 0)	0.24 (0.26)	0.3468
Senior (reference is staff, senior = 1, staff = 0)	0.06 (0.29)	0.8276
Chief (reference is staff, chief = 1, staff = 0)	0.71 (0.37)	0.0564
Fellow (reference is staff, fellow = 1, staff = 0)	0.81 (0.54)	0.1321
Clinical stage (reference is T1ab, T1c)	0.31 (0.20)	0.1179
Log (RP specimen-estimated volume)	-0.42 (0.22)	0.0560
Preoperative PSA	0.03 (0.01)	0.0044

Abbreviations:

- DRE digital rectal examination
- PGY post-graduate year
- PSA Prostate-specific antigen
- PSAD prostate-specific antigen density
- RP radical prostatectomy
- TRUS transrectal ultrasound

Level of training	Ν	κ (SE)	% agreement	% Bx < RP	% Bx > RP
Junior	210	0.59 (0.05)	79.0 %	18.1 %	2.9 %
Senior	126	0.47 (0.07)	73.0 %	22.2 %	4.8 %
Chief	47	0.51 (0.13)	76.6 %	17.0 %	6.4 %
Fellow	18	0.61 (0.07)	77.8 %	2.2 %	0.0 %
Staff	77	0.70 (0.09)	87.0 %	13.0 %	0.0 %

Supplementary Table 1: Kappa statistic and percent agreement between clinical and pathologic highest Gleason grade for each level of training

Supplementary Table 2: Cumulative logistic regression odds ratios of maximum pathologic Gleason grade by maximum clinical Gleason grade, controlling by level of training, clinical stage, logarithm of RP specimen-estimated volume, logarithm of estimated tumor volume and preoperative PSA

	OR	95% CI	p-value
Maximum clinical Gleason grade (unit increase)	23.718	12.510 - 44.971	<0.0001
Junior (reference is Staff)	1.106	0.543 - 2.251	0.7818
Senior (reference is Staff)	1.633	0.765 - 3.487	0.2052
Chief (reference is Staff)	1.003	0.375 - 2.682	0.9957
Fellow (reference is Staff)	1.200	0.331 - 4.353	0.7821
Clinical stage (reference is T1ab, T1c)	1.208	0.718 - 2.032	0.4767
Log (RP specimen-estimated volume)	0.861	0.479 - 1.549	0.6180
Log (estimated tumor volume)	1.553	1.330 - 1.814	< 0.0001
Preoperative PSA	1.031	1.000 - 1.063	0.0504

Level of training	Ν	κ (SE)	% agreement	% Bx < RP	% Bx > RP
Junior	210	0.78 (0.07)	95.2 %	2.4 %	2.4 %
Senior	126	0.47 (0.11)	87.3%	10.3 %	2.4 %
Chief	47	0.38 (0.19)	85.1 %	6.4 %	8.5 %
Fellow	18	0.63 (0.17)	88.9 %	11.1%	0.0 %
Staff	77	0.64 (0.19)	96.1 %	1.3 %	2.6 %

Supplementary Table 3: Kappa statistic and percent agreement between clinical and pathologic primary Gleason grade for each level of training

Supplementary Table 4: Cumulative logistic regression odds ratios of primary pathologic Gleason grade by primary clinical Gleason grade, controlling by level of training, clinical stage, logarithm of RP-specimen-estimated volume, logarithm of estimated tumor volume and preoperative PSA

	OR	95% CI	p-value
Primary Gleason grade (unit increase)	40.930	16.585 - 101.012	<.0001
Junior (reference is Staff)	1.753	0.452 - 6.800	0.4173
Senior (reference is Staff)	5.530	1.396 - 21.903	0.0149
Chief (reference is Staff)	1.414	0.254 - 7.865	0.6921
Fellow (reference is Staff)	5.038	0.739 - 34.361	0.0988
Clinical stage (reference is T1ab, T1c)	0.936	0.421 - 2.079	0.8711
Log (RP specimen-estimated volume)	0.736	0.299 - 1.809	0.5042
Log (estimated tumor volume)	1.356	1.070 - 1.717	0.0117
Preoperative PSA	1.006	0.973 - 1.040	0.7256

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