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VALUE OF INCREMENTAL BIOPSY CORES FOR MICRO-ULTRASOUND TARGETED PROSTATE BIOPSIES

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VALUE OF INCREMENTAL BIOPSY CORES FOR MICRO-ULTRASOUND TARGETED PROSTATE BIOPSIES

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Abstract:

Objectives:

To determine the optimal number of cores needed during Micro-ultrasound informed prostate biopsy for the detection of clinically significant prostate cancer (csPCa, defined as Gleason Grade Group ≥2).

Methods:

A retrospective review of 1011 consecutive patients between Sep 2021 and July 2023 at our institution were identified; 536 underwent Micro-ultrasound biopsy and 475 underwent MRI/US targeted biopsy. Lesions were given a Prostate Risk Identification using Micro-ultrasound (PRI-MUS) score, with lesions PRI-MUS ≥3 targeted. MRI lesions were scored with Prostate Imaging-Reporting and Data System (PI-RADS) and lesions PI-RADS ≥3 were targeted. The primary outcome is the detection of csPCa stratified by number of cores.

Results:

138 patients underwent targeted biopsies for Micro-ultrasound only lesions, 182 for Micro-ultrasound and MRI lesions and 426 underwent MRI/US for MRI lesions. The first targeted core detected 78.0% (46/59), 77.8% (63/81) and 78.8% (216/274) of csPCa for Micro-ultrasound, Micro-ultrasound+MRI and MRI/US respectively. Comparing first to third core, there was not a significant difference in overall detection of csPCa by Micro-ultrasound, though MRI/US was significantly different (28.4% vs 36.4% p=0.12, 32.5% vs 41.8% p=0.06, 42.5% vs 53.9% p<0.001 for Micro-ultrasound, Micro-ultrasound+MRI and MRI/US respectively). PI-RADS 3 and PRI-MUS 3 lesions had lower first core detection rates compared to PI-RADS 5 and PRI-MUS 5 lesions (44.4% vs 85.4% p=0.01, 65.2% vs 81.4% p=0.14, 60% vs 83.1% p=0.07 for Micro-ultrasound, Micro-ultrasound+MRI and MRI/US respectively).

Conclusions:

A three-core targeted biopsy per Micro-ultrasound lesion improves detection rate of clinically significant prostate cancer and should be considered to improve diagnostic accuracy.

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Introduction

Prostate cancer remains a significant global health concern, affecting millions of men each year. [1] Early and accurate diagnosis is pivotal for timely intervention and

improved patient outcomes. Conventional diagnostic methods, such as transrectal ultrasound (TRUS) and multiparametric magnetic resonance imaging (MRI), have provided valuable insights, but limitations persist in terms of resolution, sensitivity, and specificity. [2,3] The introduction of Micro-ultrasound (microUS), a high-resolution imaging modality, holds promise in improving the accuracy of prostate cancer detection compared to conventional diagnostic methods[4–6].

MicroUS represents a technological advancement with superior spatial resolution compared to traditional ultrasound methods. By utilizing higher-frequency sound waves, microUS offers the ability to visualize prostate tissue at a finer scale. This enhanced resolution contributes to improved identification and localization of suspicious lesions[5–8]. MicroUS utilizes the prostate risk identification using micro-ultrasound (PRI-MUS) scoring system, which similarly to the PI-RADS scoring system, utilizes a likert score from 1 to 5, with lesions ≥3 being at higher risk for prostate cancer[9].

Accurate biopsy core sampling is essential for characterizing the nature of suspected lesions. Historically, systematic biopsies have been the norm, but recent studies have demonstrated the benefit of targeted biopsies, guided by imaging findings, due to their ability to increase diagnostic accuracy and reduce unnecessary procedures[3,10,11]. However, the optimal number of cores to obtain per target remains a matter of discussion for MRI and has not been assessed for microUS to date [12–16].

Optimizing the number of cores is a delicate balance between maximizing diagnostic yield and minimizing patient discomfort, costs, and procedural time. While the potential benefits of microUS are evident, there is a need to determine the optimal number of biopsy cores needed to effectively sample a target lesion. The primary objective of this

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study is to determine the incremental benefit of additional microUS targeted cores for the detection of clinically significant prostate cancer (csPCa), defined as Gleason Grade Group ≥2.

Materials and Methods

Patients

This retrospective review was performed for patients biopsied between September 2021 and July 2023 at a single center in Alberta, Canada. In total there were 1011 consecutive patients who underwent transrectal prostate biopsy (Supplemental Figure 1). 536 of these patients underwent microUS biopsy and 475 patients underwent MRI/US targeted biopsy. Only patients who were documented as receiving targeted cores beyond the standard systematic cores were included for the analysis. These patients were then further subdivided into those with only microUS targets (n=138), overlapping microUS/MRI targets (n=182) and only MRI targets (n=426).

Imaging

Patients undergoing microUS guided transrectal prostate biopsy utilizing the ExactVu MRI/microUS fusion device (Exact Imaging, Toronto, Canada) were scored using the prostate risk identification using micro-ultrasound (PRI-MUS) protocol. The surgeon performing the microUS prostate biopsy had undergone the mastery course designed by Exact Imaging. The UroNav system (Philips Healthcare, USA) was utilized for patients who underwent MRI/US fusion biopsy. Patients who underwent a 3T MRI prior to their biopsy were given a Prostate Imaging Reporting & Data System version 2.1 (PI-

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RADS) score. These MRI were read by experienced radiologists and lesions were marked for the UroNav or ExactVu systems.

Biopsy

All patients underwent a systematic 12 core standard biopsy. The surgeon was not blinded to the results of the MRI (if performed). MicroUS targeted sampling of lesions PRI-MUS ≥3 was performed. For patients who received an MRI prior to the biopsy, lesions PI-RADS ≥3 would undergo targeted sampling. All targeted cores were required to be numbered incrementally for inclusion and sent for pathological assessment. Lesions that were targeted had the first core taken from approximately the center of the lesion, with the second and third biopsy approximately 5-10mm away in opposite directions from the center along the longest axis of the target. All pathology samples were analyzed by experienced uropathologists.

Ethical Approval

This study protocol was approved by the Health Research Ethics Board of Alberta (HREBA.CC-21-0388).

Outcomes

The primary outcome was the incremental detection of clinically significant prostate cancer stratified by number of cores taken. Secondary outcomes included overall detection of cancer and detection when stratified by biopsy naïve patients as well as by lesion PI-RADS and PRI-MUS scores.

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Statistical Analysis

Mean values and standard deviations are reported for continuous variables and categorical variables are reported as frequencies (%). ANOVA and T tests were used to compare continuous variables where appropriate, and chi square test was used to compare the categorical variables. Multivariate analysis was performed with multiple linear regression analysis. A two-sided p-value of <0.05 was considered to be significant.

Results

Patient demographics are shown in Table 1. A total of 746 patients were included in the analysis, with 138 in the microUS only group, 182 in the microUS+MRI group, and 426 in the MRI/US group. There was no significant difference between the three groups for age, ethnicity, family history of prostate cancer, abnormal DRE, median PSA, prostate volume or PSA density. There was a significant difference in the biopsy indication with a higher percentage in the microUS groups undergoing an active surveillance biopsy (38% and 43% vs 28% for the MRI/US group), with associated higher biopsy naïve patients in MRI/US (p=0.01).

There was a significant difference between the groups for the number of targeted lesions. In the microUS only, microUS+MRI, and MRI/US groups, 71%, 93%, and 81% of patients had one targeted lesion, while 29%, 7%, and 19% had two targeted lesions, respectively (p=0.002). PRI-MUS scores were available for the microUS only and the microUS+MRI groups and there was no significant difference between the groups

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(p=0.13). PI-RADS scores were available for microUS+MRI and the MRI/US groups, and there was no significant difference between the two groups (p=0.11).

In each group the proportion of csPCa detected increased as the number of biopsy cores increased. For lesions in the microUS only group, csPCa was detected in 28.4% (46 of 162), 33.3% (54 of 162) and 36.4% (59 of 162) by one, two and three cores respectively (Table 2, Supplemental Figures 2 and 3). For this group, there was no significant difference for the detection of csPCa by incremental cores (Table 3).

For lesions in the microUS+MRI group, csPCa was detected in 32.5% (63 of 194), 38.7% (75 of 194) and 41.8% (81 of 194) by one, two and three cores respectively (Table 2, Supplemental Figures 2 and 3). For this group, there was no significant difference for the detection of csPCa by incremental cores (Table 3).

For lesions in the MRI/US group, csPCa was detected in 42.5% (216 of 510), 50.0% (254 of 510) and 53.9% (254 of 510) by one, two and three cores respectively (Table 2, Supplemental Figures 2 and 3). For this group, there was a significant difference in the detection of csPCa from core 1 to core 2 and from core 1 to core 3. (Table 3).

A subgroup analysis was performed on all three groups looking at the detection rates stratified by PRI-MUS score for microUS patients and PI-RADS for the MRI/US patients (Figure 1). When stratifying by PRI-MUS score, the microUS only group detected 44.4% of csPCa by first core for PRI-MUS 3 lesions and 85.4% for PRI-MUS 5 lesions (p=0.01). The microUS+MRI group detected 65.2% of csPCa by first core for PRI-MUS 3 lesions and 81.4% for PRI-MUS 5 lesions (p=0.14). For MRI/US patients

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when stratifying by PI-RADS score, 60.0% of csPCa was detected by first core for PI-RADS 3 lesions, and 83.1% of csPCa for PI-RADS 5 lesions (p=0.07).

A multivariable logistic regression was performed using target lesions and biopsy indication. There was a significant difference in csPCa detection for biopsy naïve patients as reference compared to the other biopsy indications for all three groups. Therefore, a subgroup analysis was performed using data from biopsy naïve patients only. This subgroup analysis (Supplemental Table 1, Supplemental Figures 4 and 5) showed higher overall csPCa detection rates for all groups. The initial detection of csPCa by core 1 was 81.8%, 81.4% and 83.1% for the microUS only, microUS+MRI groups and MRI/US groups respectively. This was similar to the detection rate by first core for the entire cohort. Similarly, there was no significant difference between the detection of csPCa when comparing a 1 core biopsy method to the 3-core method for microUS patients, though, there was a significant difference in the MRI patients (50.2% vs 60.4%, p=0.01).

The overall csPCa detection rate for the microUS alone group was 59% (82/138), with 66% (54/82) detected by both targeted and systematic biopsy, 6% (5/82) by targeted biopsy alone and 28% (23/82) by systematic biopsy alone. For the microUS+MRI group, overall csPCa detection rate was 54% (98/182), with 67% (66/98) detected by both targeted and systematic biopsy, 15% (15/98) by targeted biopsy alone and the remaining 17% (17/98) by systematic biopsy alone. For the MRI/US group, the overall csPCa detection rate was 67% (287/426), with 70% (202/287) found by both targeted and systematic biopsy, 13% (38/287) by targeted biopsy alone, and 16%

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(47/287) by systematic biopsy alone. In the MRI/US group, there were 22 anterior lesions, with 41% (9/22) containing csPCa.

The detection rate of csPCa detection by cores over time was further assessed by quartiles (Supplemental Figure 6). The fourth quartile had lower rates of csPCa by first core, at 64%, when compared to 78%, 73% and 95% for the first, second and third quartiles respectively (p=0.009).

Discussion

This study demonstrates increased detection rates of csPCa with increasing number of cores. For microUS only patients, incremental cores detected 78.0%, 91.5% and 100% of csPCa, microUS+MRI detected 77.8%, 92.6% and 100% and the MRI/US group had a detection rate of 78.8%, 92.7% and 100%. When looking at biopsy naive patients, a similar pattern was observed for the detection of csPCa with 81.8%, 81.4% and 83.1% of csPCa cancers detected by core 1 for the microUS, microUS+MRI and MRI/US groups respectively. This study further demonstrated that for patients with intermediate lesions (PRI-MUS 3 or PI-RADS 3), there is a lower detection rate of csPCa by a single core when compared to higher risk lesions (PRI-MUS 5 or PI-RADS 5). The false negative rate of targeted biopsy was 28% (23/82), 17% (17/98) and 16% (47/287) in the microUS, microUS+MRI and MRI/US groups respectively.

This is to our knowledge the first study looking at the value of incremental cores for the detection of csPCa for microUS lesions. Several reports have used microUS technology, and documented improvements in csPCa detection rate with its implementation [5–8,17]. However, there has not been a standard number of cores taken

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per microUS lesion. There is also not a standard number of targeted biopsy cores for MRI targets, though the current AUA guideline recommends at least 2 cores and the EAU recommends a minimum of 3-5 cores per lesion [18,19].

We demonstrated that for microUS targets, 1 core detected 78% of csPCa detected by targets and for MUS+MRI, 77.8%. For both groups, this was not statistically significantly different from the detection rates seen by three cores, however this discrepancy would likely be clinically significant given that over 20% of csPCa would have been missed without a three core strategy. This was similar to the detection by MRI/US which also found 78.8% of csPCa by the first core. Unlike microUS however, there was a significant difference in the difference between detection rate by the first and third cores. Despite the similarities in percentage of cancers detected by core number, the MRI/US group did have a higher overall detection rate by lesion, and this was also observed in the biopsy naive group. While there are no microUS groups to compare our results, the detection rate by initial core in our group by microUS is similar to detection rates by MRI first core in the literature which can range from 65-92% [12,14,15,20,21].

Stratifying patients by PI-RADS and PRI-MUS score showed higher detection rate of csPCa by first core for more suspicious lesions (PI-RADS and PRI-MUS 5), when compared to the indeterminate lesions (PI-RADS and PRI-MUS 3). While there are no other microUS groups to compare to, the lower detection rate by 1 core for PRI-MUS 3 lesions compared to PRI-MUS 5 lesions was hypothesized to be related to the nature of these lesions. A higher PRI-MUS score indicates more irregularities when compared to standard prostatic tissue, and as such may require fewer cores to detect

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the csPCa when compared to less irregular lesions [9]. The increased detection by 1 core for PI-RADS 5 lesions compared to PI-RADS 3 lesions was felt to be similar as these lesions would indicate higher likelihood of containing csPCa and could be in a larger area than a PI-RADS 3 lesion.

There was an expectation that microUS could potentially require a lower number of targeted cores per lesion when compared to MRI imaging. This was hypothesized due to live visualization, scoring, and sampling of prostate lesions by microUS whereas MRI fusion biopsies rely on imperfect cognitive or image fusion which could result in misregistration of the region of interest. However, this was not shown in this study, and could be related to an imperfect PRI-MUS scoring system that is currently in its first version. Another limitation of the first version of the PRI-MUS scoring system is that there is no score for anterior lesions. In the MRI/US group, there were 22 anterior lesions, with 41% found to contain csPCa. These lesions could have been missed in the microUS groups.

When stratifying patients by time, there was no significant difference between the quartiles for the detection of csPCa in biopsy naïve patients (86% vs 79% vs 96% vs 65%, p=0.07). The fourth quartile did appear to trend to lower csPCa detection by first core, however these patients were not randomized which could have affected results. Previous literature on learning curves in microUS showed improvements in csPCa detection up to the first 100 cases, and further work on microUS learning curves is required[22].

Another emerging technology is PSMA PET which utilizes a radioligand that binds to prostate specific membrane antigen that is overexpressed in prostate cancer

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tissue[23]. It has already been shown to be superior for the detection of lymph node and metastatic disease compared to conventional imaging[23]. It has also been found to have similar csPCa detection rate at prostate biopsy when compared to MRI in early studies[24,25]. The forthcoming DEPROMP trial should provide further evidence for the use of PSMA-PET scans for primary diagnosis of prostate cancer[26].

The detection rate of csPCa by lesion was comparatively higher in the MRI/US group when compared to the microUS lesions, with 36.4%, 41.8% and 53.9% of lesions with csPCa in the microUS, microUS+MRI and MRI/US groups respectively. There was a significant difference in the biopsy indication, with a higher percentage of active surveillance undergoing microUS biopsy. When accounting for only biopsy naïve patients, there was still a comparatively higher detection rate by lesion for the MRI/US group, with 60.4% of lesions detecting csPCa when compared to 48.9% and 45.3% of microUS and microUS+MRI lesions. Further studies would be necessary to compare the detection rate per lesion, which is currently under investigation with the Optimization of Prostate Biopsy – Micro-Ultrasound versus MRI (OPTIMUM) trial [27].

There are several limitations of this study. This study is a retrospective, single site design which excluded a number of patients due to lack of standardization of the biopsy technique. Further, these results were performed by one operator, though the addition of the MRI/US targets was to show internal validity of targeted biopsies. The operator was not blinded the MRI results, and the operator was also unable to be blinded to the microUS results given live scoring at the time of biopsy. Furthermore, the value of adding incremental cores above 3 remains unknown. However, as previously

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published increasing number of cores had diminishing returns and detected an additional 1-2% of csPCa in MRI/US[12,14,20,21].

Conclusion

Increasing the number of biopsy cores per targeted micro ultrasound lesion improved the detection rate of clinically significant prostate cancer at a similar rate to MRI targeted lesions and a three-core per lesion strategy is recommended to improve diagnostic accuracy.

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Figure Legends

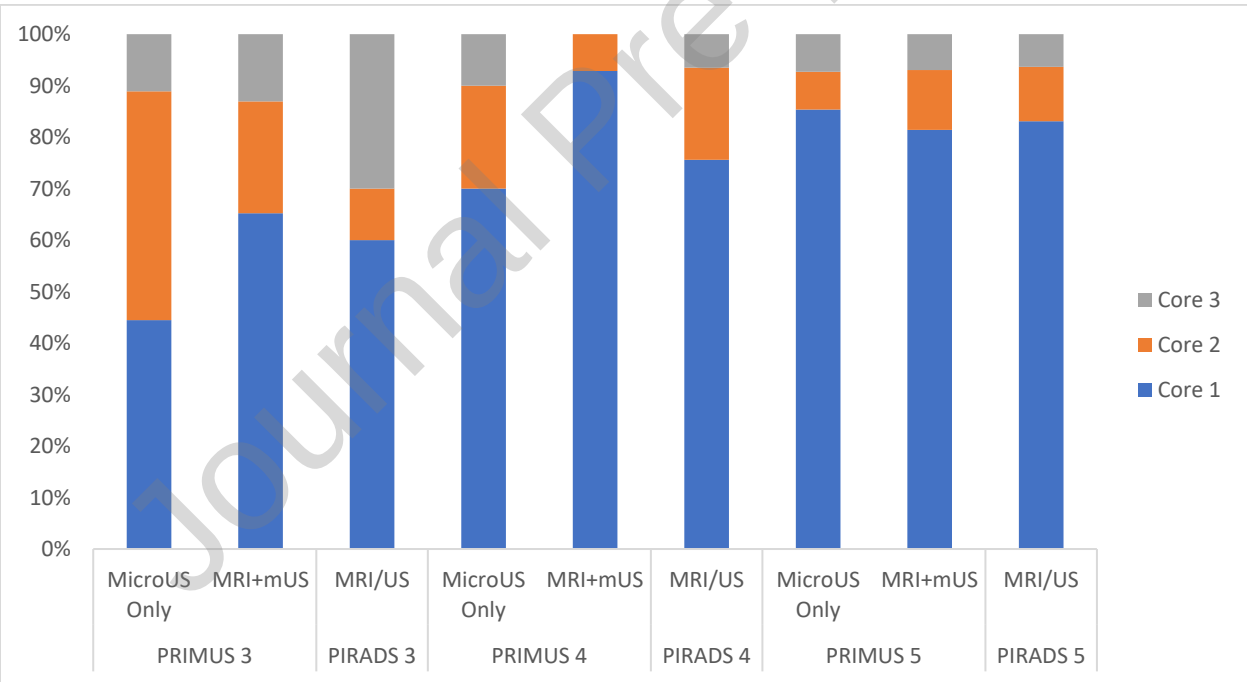

Figure 1 – Detection rates of clinically significant prostate cancer by number of cores for MicroUS only, MRI+microUS and MRI/US Targets stratified by PRI-MUS and PI-RADS score

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Table 1. Baseline patient characteristics – microUS vs microUS+MRI vs MRI/US

	mUS only (n=138)	mUS+MRI (n=182)	MRI/US (n=426)	**P value**
Age, mean (SD)	65.2 (6.2)	65.8 (6.5)	66.4 (8.0)	0.27
Ethnicity, (%)				0.29
Asian	7 (5)	18 (10)	38 (9)	
Black	4 (3)	6 (3)	11 (3)	
Caucasian	118 (86)	153 (84)	360 (85)	
Hispanic	0 (0)	1 (1)	4 (1)	
Indigenous	8 (6)	4 (2)	11 (3)	
Unknown	1 (1)	0 (0)	2 (0)	
Family History of Prostate Cancer, (%)	45 (33)	61 (34)	126 (30)	0.41
Abnormal DRE, (%)	14 (10)	32 (18)	83 (19)	0.06
PSA (ng/mL), median (IQR)	8.6 (6-12)	7.8 (5.4-10.8)	8.4 (6.2-12.1)	0.18
Prostate volume (cc), median (IQR)	44 (33-63)	47 (34-61)	49 (36-70)	0.09
PSA Density (ng/mL/cc), (%)				0.58
<0.15	53 (38)	79 (43)	184 (43)	
≥0.15	85 (62)	103 (57)	242 (57)	
Biopsy Indication, (%)				**0.01**
Active Surveillance	53 (38)	78 (43)	121 (28)	

Biopsy Naïve Prior Negative Biopsy 1 year after focal therapy	77 (56) 8 (6) 0 (0)	87 (48) 16 (9) 1 (1)	261 (61) 40 (9) 4 (1)	
Number of Targeted Lesions, (%) 1 2 3	 114 (71) 24 (29) 0 (0)	 170 (93) 12 (7) 0 (0)	 344 (81) 80 (19) 2 (0)	**0.002**
Lesion PRI-MUS score, (%) 3 4 5	 43 (27) 41 (25) 78 (48)	 65 (34) 57 (29) 72 (37)	 N/A	0.13
Lesion PI-RADS score, (%) 3 4 5	 N/A	 16 (8) 119 (61) 59 (30)	 42 (8) 272 (53) 196 (38)	0.11

(Abbreviations- SD: standard deviation, mUS: Microultrasound, MRI: Magnetic resonance imaging, US: Ultrasound)

Table 2. Number of cores and detection of clinically significant prostate cancer for microUS only, MRI+microUS and MRI/US Targets

No. of Cores	**MicroUS Only (n=162)**			**MRI + MicroUS (n=194)**			**MRI/US (n=510)**		
	No. of ≥GG2 cancers detected	% of ≥GG2 cancers detected	% Detection Rate	No. of ≥GG2 cancers detected	% of ≥GG2 cancers detected	% Detection Rate	No. of ≥GG2 cancers detected	% of ≥GG2 cancers detected	% Detection Rate
1	46	78.0	28.4	63	77.8	32.5	216	78.8	42.5
2	54	91.5	33.3	75	92.6	38.7	254	92.7	50.0
3	59	100	36.4	81	100	41.8	274	100	53.9

Table 3. Comparison of detection rate of clinically significant prostate cancer by number of cores for MicroUS only, MRI+microUS and MRI/US Targets

	MicroUS Only (n=162)	**MRI + MicroUS (n=194)**	**MRI/US (n=510)**
Core 1 vs Core 2	28.4 vs 33.3 (p=0.34)	32.5 vs 38.7 (p=0.20)	42.5 vs 50.0 **(p=0.02)**
Core 2 vs Core 3	33.3 vs 36.4 (p=0.56)	38.7 vs 41.8 (p=0.39)	42.5 vs 53.9 (p=0.21)
Core 1 vs Core 3	28.4 vs 36.4 (p=0.12)	32.5 vs 41.8 (p=0.06)	42.5 vs 53.9 **(p<0.001)**

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CONFLICT OF INTEREST

1) Patrick Albers no conflict
2) Jacob Bennett, no conflict
3) Moira Evans, no conflict
4) Ella St Martin, no conflict
5) Betty Wang, no conflict
6) Stacey Broomfield, no conflict
7) Anaïs Medina Martín, no conflict
8) Wendy Tu, no conflict
9) Christopher Fung, no conflict
10) Adam Kinnaird, Funding received by Exact Imaging for unrelated studies

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