ORIGINAL RESEARCH

Accuracy of the Standard Systematic 12-Core Transrectal Ultrasound-Guided Biopsy on a Prostate Phantom Model

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Objective: The detection rate of the current standard systematic 12 core transrectal ultrasound (TRUS) guided prostate biopsy remains low despite numerous modifications of the technique. This non-randomized experimental study evaluated the accuracy of standard TRUS-guided systematic prostate biopsy as performed by selected urologists in obtaining samples representative of the peripheral zone of the prostate, by analyzing virtual biopsies performed on a prostate phantom model.
Materials and Methods: Thirty (30) urologists (26 consultants and 4 senior residents) were invited to perform two consecutive simulation TRUS guided 12-core biopsies on a phantom prostate model. The task was to hit twelve equal sized spherical targets which would correspond to the lateral and extreme lateral areas of the base, mid gland and apex of the peripheral zone of the phantom prostate, which would represent the usual biopsy technique. Degree of agreement (kappa) was computed. Eight (8) operators had below satisfactory kappa values and were excluded from the succeeding analysis. Accuracy was calculated by dividing the number of accurately hit targets by the number of virtual cores (12). Data were encoded in MS Excel and Stata MP v.14 was used for data analysis.
Results: Overall, the mean accuracy was 63.17% and median accuracy was 60% (95% CI: 49.2-65.15) for the 22 operators included in the study. The lateral regions, particularly the midgland (95.8%-100% accuracy) were the most frequently biopsied areas and were often resampled. The targets at the prostatic base were missed by most operators (36.05% accuracy).
Conclusion: Systematic TRUS guided prostate biopsy, in the manner that it is performed, has its inherent flaws, compounded by limitations in imaging capability and intra-operator variability resulting in low accuracy rates. A shift to newer prostate biopsy technique and methodologies with significantly higher accuracy rates is recommended.

Key words: 12-core transrectal ultrasound-guided biopsy, prostate phantom model

Introduction

Transrectal ultrasound (TRUS) guided systematic biopsy of the prostate is still the gold standard for prostate cancer detection in patients suspected of harboring prostate cancer. Despite modifications in number of cores and having laterally-directed cores, this strategy would only yield a 30-50% cancer detection rate at best.[1,2,3] In the repeat biopsy setting, prostate cancer detection utilizing the same technique would have a detection rate of 11%-47%.[2,3,4] Inter-operator and intra-operator variability as well as prostate gland characteristics (mostly non-modifiable factors) may contribute to the low cancer detection rate of the systematic prostate biopsy. Determining the accuracy of this technique in the hands of different operators with different levels of

expertise could reveal an inherent, operator-independent shortcoming of the said procedure. The current standard TRUS-guided biopsy utilized a two dimensional (2D) ultrasound machine that precludes a more thorough visualization of the prostate and may prove to be the underlying reason for its low prostate cancer detection rate.

An organ phantom is a synthetic physical construct manufactured and used for simulation of actual organs, for purposes of machine calibration, quantitative dositometry, quality control and research.[5] Each phantom is designed based on its contemplated application, with the dimensions of the organ or tissue being simulated as its most basic property. Its use obviates the utilization of live subjects for research involving invasive procedures which is impractical and grossly unethical. The prostate phantom as an ex vivo surrogate to an actual prostate has been used and validated for the purposes previously mentioned.[6,7,8]

This study aims to evaluate the accuracy of standard transrectal ultrasound-guided systematic biopsy in obtaining tissue samples representative of the entire peripheral zone of the prostate, using the virtual transrectal biopsy function of the Koelis Trinity ultrasound unit, on a phantom prostate model. In addition, the authors also want to identify the areas of the peripheral zone commonly missed and resampled during TRUS-guided systematic prostate biopsy. To their knowledge, no study has been published with a similar study design. There have been published papers showing the inferiority of the present prostate biopsy standard compared to newer modalities, but the present study design and objectives remain unique.

Materials and Methods

This is a non-randomized, prospective experimental study that would evaluate the accuracy of the conventional systematic 2D TRUS guided prostate biopsy in sampling the desired regions of the peripheral zone of the prostate as represented by a phantom model.

A total of 30 urologists (26 consultants and 4 residents) performed two consecutive 12-core virtual 2D TRUS-guided systematic biopsy on a CIRS-053 tissue equivalent prostate phantom (Computerized Imaging Reference Systems, Norfolk, Virginia) using a Koelis Trinity ultrasound unit (Koelis, La Tranche, France) (Figures 1a & 1b).

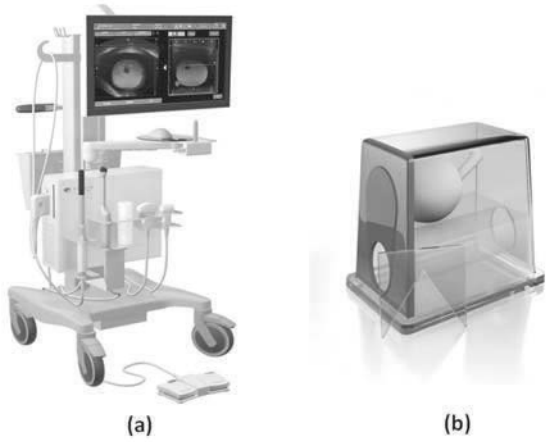

Figure 1. The (a) Koelis Trinity 3D Ultrasound Unit (Koelis, La Tranche, France)[9] and the (b) CIRS-053 tissue equivalent prostate phantom were used in the study.[10]

Prior to performing the biopsies, a 3D reconstruction (reference volume) of the phantom prostate was done using 2D axial and sagittal sweeps from the apex to the base of the phantom prostate, with a transrectal ultrasound probe. Final contouring of the reconstructed image was done to closely simulate the actual dimensions and outline of the prostate phantom, using an elastic registration algorithm[11,12] (Figure 2a). Twelve equal-sized spherical target lesions were then plotted onto the reconstructed phantom prostate to cover the entire peripheral zone (Figure 2b). These target lesions correspond to lateral and medial regions of the left and right peripheral zones of the phantom prostate's apex, mid gland and base. These reconstructed volumes and targets were not visible to the operator during the actual performance of the biopsies.

The operators carried out the virtual biopsies in the usual manner that they would perform a standard systematic 12 core TRUS-guided prostate biopsy in the actual clinical setting. The objective of each operator was to correctly hit the unseen plotted spherical targets by performing simulated

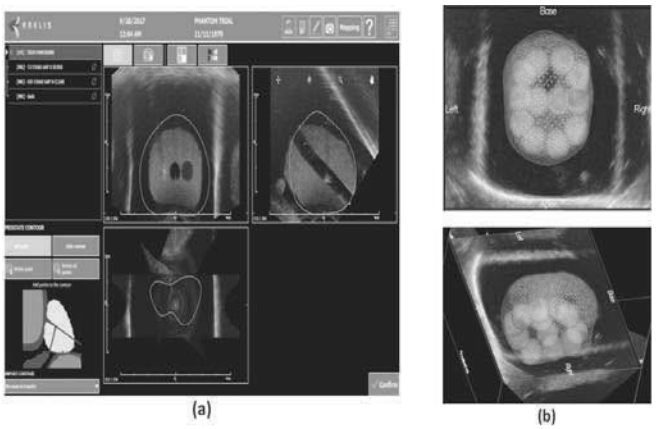

Figure 2. (a) Reconstruction and contouring of phantom prostate with elastic registration. (b) Twelve (12) equal sized spherical targets were plotted at the peripheral zone of the reconstructed phantom prostate.

12-core random systematic biopsies, using the 2D ultrasound mode of the Koelis Trinity. This was equivalent to sampling the corresponding areas of the peripheral zone during actual standard prostate biopsies. For the exercise, the ultrasound probe was trained onto the desired biopsy location and the virtual biopsy needle was fired by stepping on a footswitch. After each virtual biopsy, the ultrasound probe position was maintained for 3 seconds to allow for acquisition of the phantom's 3D volume.[11,12] Each virtual biopsy fired was mapped and registered onto the reconstructed 3D interface, and the image was analyzed (Figure 3). Results were only revealed to the operator once the biopsy session was done. A successful biopsy was recorded when the virtual biopsy marker was able to reach and penetrate the target spherical lesion. Multiple hits on a single target only counted as one hit and represent re-sampling of the same area during actual biopsy. Since the number of virtual biopsies fired and the number of target lesions corresponding to the peripheral zone of the prostate was the same (12 biopsies, 12 targets), the ratio of correctly biopsied targets gave us the accuracy of the biopsy procedure.

Intra-rater and inter-rater reliabilities were assessed using the overall percentage of agreement and the kappa statistic. Kappa statistic was interpreted using the benchmark of agreement set by Landis and Koch.[13] <0.00 Poor; 0.00-0.20 Slight; 0.21-0.40 Fair; 0.41-0.60 Moderate; 0.61-0.80 Substantial; and 0.81-1.00 Almost Perfect.

$$\text{Biopsy Accuracy} = \frac{\text{Total Number of Correctly Hit Targets}}{\text{Total Number of Cores Fired(12)}}$$

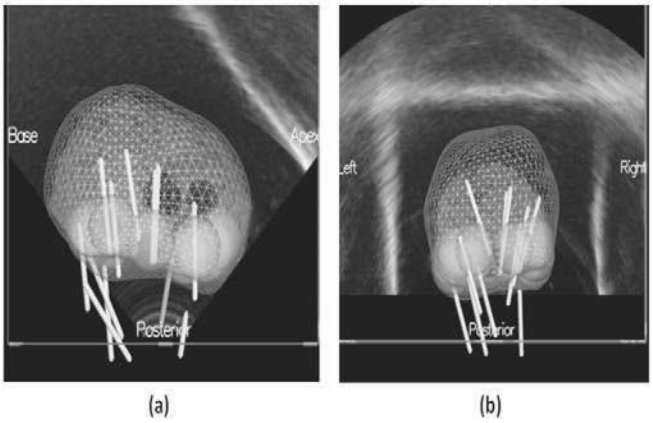

Figure 3. The virtual biopsies fired by the operator were revealed at the end of the procedure for evaluation. Sagittal (a) and coronal (b) views of the phantom prostate under 2D ultrasound and the corresponding virtual biopsies done by the operator are shown in this figure. Note the non-uniform sampling of the peripheral zone and note the presence of missed and resampled targets.

Kappa of 0.2 and above was deemed acceptable. Comparison of the degrees of agreement between two attempts for each individual operator was done. Eight of the 30 operators who initially participated, were excluded in the succeeding analyses due to poor agreement of their biopsy trials (Table 1). Data analysis and accuracy studies were based on the biopsy trial with higher accuracy rate done by each of the 22 operators who had at least a 0.2 kappa coefficient.

Data were encoded in MS Excel and Stata MP version 14 was used for data analysis. Accuracy was computed by dividing the number of correct hits by the number of biopsy cores fired (12 cores). Accuracy and resampling were presented as frequency/percentage and analyzed using Chi square test of the Fisher exact test.

Results

Degree of agreement between the two attempts for each individual operator was obtained to determine the precision or reliability of the data generated. Twenty-two (22) out of the 30

operators had kappa values >0.2, which show that the biopsy attempts of these operators were consistent, reliable, and not merely due to chance. Biopsy attempts from these operators were compared, and data from the more accurate trial were included in the final analysis. Poor agreement coefficients were noted for 8 operators and data from their biopsy trials were excluded from the study. This was done to maintain reliability of the study by correcting the intraoperator variablity. Nonetheless, these findings show that even when both systematic biopsy attempts were consecutively done by the same person, with the same image guidance, with the same targets, on the same prostate phantom, variability of intra-operator factors may still significantly affect the biopsy outcomes.

Table 1. Operator-specific intra-rater reliability analysis. Degrees of agreement of 2 biopsy trials based on the kappa values are as follows: <0.00 Poor; 0.00-0.20 Slight; 0.21-0.40 Fair; 0.41-0.60 Moderate; 0.61-0.80 Substantial; and 0.81-1.00 Almost Perfect. Values with* are those with non-acceptable kappa coefficients and data from these operator were excluded from the study.

Operator	Percent agreement (%)	Cohen's Kappa K	SE
1	43.75	0.2421	0.10
2	50	0.2928	0.12
3	37.50*	0.1960*	0.11*
4	50	0.2849	0.11
5	37.50*	0.1960*	0.11*
6	31.25*	0.0638*	0.12*
7	12.50*	-0.0566*	0.09*
8	37.50	0.2344	0.10
9	56.25	0.4343	0.12
10	50	0.3600	0.12
11	50	0.3695	0.11
12	43.75	0.2727	0.12
13	31.25*	0.1287*	0.11*
14	68.75	0.5210	0.15
15	37.50	0.2079	0.11
16	31.25*	0.0928*	0.12*
17	50	0.3632	0.12
18	37.50*	0.1960*	0.11*
19	62.50	0.5248	0.12
20	56.25	0.3913	0.11
21	81.25	0.7433	0.12
22	31.25*	0.1156*	0.10*
23	50	0.3600	0.12
24	43.75	0.2906	0.12
25	56.25	0.4372	0.12
26	43.75	0.2906	0.12
27	50	0.2928	0.12
28	50	0.3663	0.11
29	62.50	0.5200	0.12
30	50	0.3469	0.11

The simulated 12-core systematic biopsies of the 22 different operators using 2D TRUS guidance on the phantom prostate yielded a mean accuracy rate of 63.17% and median accuracy of 60% (95% CI: 59.2-65.15; range: 33.33-75) (Table 2). Accuracy of the biopsy per operator was obtained as previously described.

Table 2. Mean and median accuracy of 2D TRUS guided systematic biopsy for the population of operators included in the study (n=30).

	Mean ± SD	95% CI	Median (IQR)	Range	Coefficient Of Variation
Accuracy rate	63.17% ± 10.24	59.20 -65.15	60 (53.66-70.33)	33.33 - 75	0.20

The proportion of operators who were able to successfully hit the specified targets was obtained and is presented in Figure 4. Among the different areas of the peripheral zone, the mid-gland targets (especially the targets at the R1 and L1) were successfully biopsied by the most number of operators (21 and 22 operators, respectively). The left lateral mid-gland was hit by all of the operators and had the highest accuracy among all areas of the peripheral zone (100%) ($p<0.001$). Targets located in the base of the prostate phantom were hit by the least number of operators (36.05% cumulative accuracy for all the areas of the base), compared to mid gland and apex. Also for the base, a significantly lower proportion of operators hit the targets at the right medial (4 operators) compared to left medial, left lateral and right lateral areas (10, 11 and 8 operators, respectively) ($p=0.009$). Total accuracy rate for the targets at the apex was 67.7% (Figure 4).

Figure 5 shows the frequency of resampling of the phantom prostate's base, midgland and apex. Data showed that the re-sampled targets were biopsied a minimum of two times to a maximum of 3 times. The highest number of operators resampled the midgland, especially R1 (n=20) and L1 (n=21). For the apex, all regions were resampled by at least one of the operators. The target at the left lateral apex had the highest resampling rate for this area of the prostate phantom (54.5%). The area least resampled was

the prostate base and there was no resampling noted for targets at the Lm and Rm sites (Figure 5).

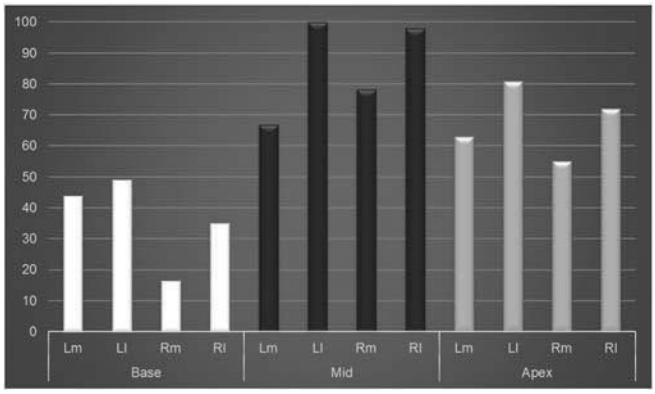

Figure 4. Proportion of operators who successfully hit targets at the base, mid gland and apex at least once. (Ll) Left Lateral, (Lm) Left Medial, (Rl) Right Lateral, (Rm) Right Medial.

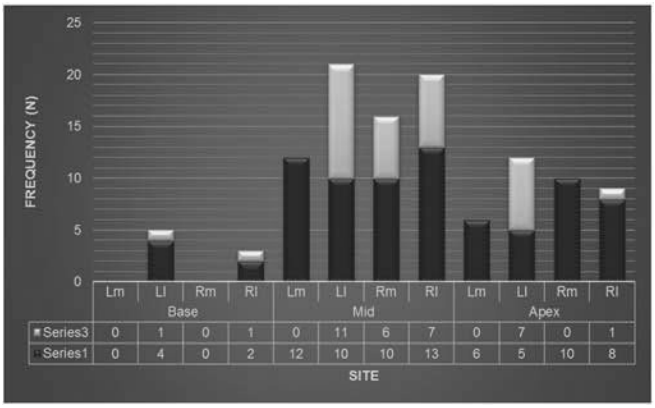

Figure 5. Frequency of operators who biopsied each site at least twice (resampling). Series 2: sampled 3 times; Series 1: sampled 2 times.

Discussion

Planning errors in prostate biopsy is a function of image resolution, target distance estimation and needle track projection capabilities of the imaging device used, but it may also be affected by operator-dependent variables.[4] The lack of real-time representation for depth coupled with poor image contrast in current 2D systems, leave the accuracy of the biopsy at the mercy of the operator's subjective spatial estimation of the target areas on the prostate, based on 2D ultrasound echoes. The degree of agreement (kappa) analysis showed that, all other factors being equal, significant variability can still be observed in the outcomes of two consecutive 2D TRUS-guided systematic biopsies, even when performed by the same operator.

The goal of the systematic 12-core prostate biopsy is to cover all of the areas of the peripheral zone of the prostate. Ideally, all of the 12 targets covering the entire peripheral zone should have been hit by all the operators. Present results however, showed that the operators were only able to hit the left and right lateral regions of the mid gland with high accuracy (Figure 4). Incidentally, the regions of the prostate which were consistently resampled by the highest number of operators, were also the left and right lateral regions of the mid gland (Figure 5). The base of the phantom prostate was notably undersampled by the operators in the study for an accuracy rate of only 36.05%. A study showed similarly high accuracy rates in the mid gland (100%) with relatively lower accuracy (53%) for the base.[12] This may be a reflection of the operators' inclination to biopsy the lateral regions of the prostate during actual prostate biopsies, as espoused by guidelines, to improve yield.[1,2]

In actual live biopsies, the unique physical properties of each individual prostate may contribute to the overall sampling error. Its effect on needle deflection, the presence of artifacts picked up on ultrasound, real-time deformation with every movement from the transrectal probe and subtle to significant volume changes with each core driven into it, also influence the outcome of the procedure.[4,11] In the same manner, operator-dependent factors may also decrease accuracy of the procedure. Present results showed that even in experienced hands, with inter-operator and intra-operator variability kept at a minimum, the limited image guidance that 2D TRUS affords the operator, or the manner by which systematic prostate biopsies are conducted, appears to be inadequate in facilitating the accurate sampling of all the target regions of the peripheral zone.

The biopsy trials were not done on live patients and actual prostate glands for obvious reasons, however, ex vivo phantom studies have been shown to reflect actual outcomes.[3,4,6] Present study

showed that 2D TRUS guided systematic prostate biopsy has a low accuracy rate on a phantom model. The authors maintain that the low accuracy rate observed in the gold standard for prostate biopsy- largely due to inherent flaws in the procedure- significantly contributes to its low cancer detection rates. Furthermore, a number of studies showed a poor concordance of biopsy specimen Gleason score to that of the resected prostate in the final histopathologic analysis (63% in one report), as well as a false negative rate of 30% reported in literature.[14,16] Obviously, there should be ways to improve the technique or a motivation to adopt more efficient prostate biopsy strategies.

The key to improving the accuracy of prostate biopsies would depend on the improvement of the operator, or the improvement of the technique and equipment.[15] Fitt's law model of human performance stipulates that an experienced user will have a higher index of performance compared to a novice user.[16] In the present study, despite different levels of expertise in the operator population, the mean accuracy of 2D TRUS guided systematic biopsy was uniformly low (63.17%) with minimal inter-operator variability, as evidenced by a narrow confidence interval, low standard deviation value and even lower coefficient of variation (Table 1). The burden of re-training seasoned and novice urologists alike to do biopsy, and overcoming an undefined learning curve, in order to improve the accuracy of prostate biopsy, without improving the image guidance system is however, inefficient, impractical and ultimately futile.

As an alternative, improving the localization of the target lesions has been shown improve biopsy accuracy by reducing sampling errors.[17,18] More sophisticated image guidance such as the 3D TRUS/MRI Fusion biopsy systems that can direct the operator to pre-localized suspicious lesions in real-time, are already available and validated for prostate biopsy. These systems allow for elastic registration and virtual reconstruction of the prostate and decreasing the effect of prostate deformation during the procedure. Biopsy trajectory feedback is possible with these machines, resulting in improved operator targeting by allowing for real time readjustments before firing the actual biopsy, thus increasing accuracy rates (97% in one study).[13,14,16] They have the potential to decrease the morbidity of multiple biopsy cores and detection of clinically insignificant cancers, while increasing detection of high grade cancers.[15] Although these procedures and technology come at a higher price, the significantly high rate of successful targeted biopsies make them highly suitable alternatives to the present system.

Conclusion

The actual task of performing biopsy on the prostate gland demands a high degree of accuracy, which is dependent on a variety of factors. Present study shows that random systematic prostate biopsies done with current 2D transrectal ultrasound guidance, have inherent problems on several levels (operator, imaging, conduct of the procedure) resulting in sampling errors- demonstrated by inefficient sampling of the peripheral zone, and ultimately, low accuracy (63.17%). These findings demonstrate the need for a change in the present diagnostic standard. Acceptance and utilization of more efficient and highly accurate technologies for prostate cancer detection is necessary and inevitable.

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