ORIGINAL RESEARCH

Accuracy of the Multiparametric Magnetic Resonance Imaging (MRI) and Multiparametric MRI Ultrasound Cognitive Fusion Biopsy in the Detection of Prostate Cancer Among Patients at a Tertiary Hospital

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Objective: Image-guided targeted biopsy techniques have been proposed to address problems of systematic transrectal ultrasound guided prostate biopsies that lead to the suboptimal cancer detection rate as well as inaccurate grading of the disease. This study aims to provide local data on the diagnostic accuracy of multiparametric MRI (MP-MRI) and MP-MRI ultrasound cognitive fusion biopsy in identifying areas of clinically significant malignancy of the prostate.

Materials and Methods: This is a validity study involving patients who underwent MP-MRI and MP-MRI ultrasound cognitive fusion biopsy, who eventually underwent robot-assisted laparoscopic radical prostatectomy (RALRP). Outcome measures included sensitivity, specificity, positive and negative predictive values of MP-MRI and MP-MRI ultrasound cognitive fusion biopsy. Reference standard used was the final histopathologic report obtained after RALRP.

Results: MP-MRI has a sensitivity of 35.5%, specificity of 95.2%, positive predictive value of 97.1%, and negative predictive value of 25%. MP-MRI ultrasound fusion biopsy had similar results, with sensitivity of 34.4%, specificity of 81.0%, positive predictive value of 88.9%, and negative predictive value of 21.8%.

Conclusion. The high specificity and positive predictive value of MP-MRI (95.2% and 97.1% respectively) indicates the necessity for a prostate biopsy and supports the utility of a targeted MP-MRI guided ultrasound cognitive fusion biopsy. However, the low sensitivity and negative predictive value (25% and 35% respectively) of 35.5% indicates that MP-MRI guidance does not limit the number of biopsy samples only to visible MP-MRI lesions, since negative areas on MP-MRI still contains tumors in 75% of cases.

Key words: Multiparametric MRI, multiparametric MRI ultrasound cognitive fusion biopsy

Introduction

Current contemporary diagnostic pathway for prostate cancer entails a random 12-core systematic biopsy strategy to confirm the diagnosis when abnormal PSA levels and/or digital rectal examination findings raise clinical suspicion. With this strategy, multifocal, small, prostate cancers intermingled with benign stroma are frequently missed.[6] Such sampling errors often lead to incorrect risk stratification of clinically significant tumors as low volume or low grade. Attempts to overcome sampling error through repeat biopsy or through increasing the number

of cores obtained have been proven unsuccessful and placed the patient in undue stress or discomfort and additional cost.[6]

Image-guided targeted biopsy techniques have been proposed to address problems of systematic "blind" prostate biopsies.[7] The challenge is to avoid detection of insignificant cancers by decreasing the number of systematic biopsy cores and to detect and locate significant cancers using imaging and targeted biopsies.[5]

High-resolution MRI appears to offer the most readily available and useful imaging for the diagnosis, staging and prognosis of prostate cancer.[8] Multiparametric MRI (MP-MRI) uses a combination of diffusion-weighted, dynamic contrast-enhanced sequences and conventional T2-weighted sequences. The technique produces optimized results and improves specificity.[9] The images of each parameter in turn can be interpreted utilizing the PIRADS system to report on the probability of harboring malignancy. A PIRADS score of 3 or greater denotes a possibility of clinically significant prostate cancer. (Appendix I). The PIRADS scoring version 2, as discussed by the American College of Radiology, was designed to improve detection, localization, characterization, and risk stratification in patients with suspected prostate cancer and with an overall objective to improve outcomes for patients.[18]

MP-MRI may allow better detection of clinically significant disease with fewer biopsy cores, more accurate risk stratification, avoidance of the detection of indolent disease and may allow for better risk stratification among patients considering active surveillance.[6] This led to the development of the several biopsy techniques with MP-MRI guided fusion biopsies. Several studies have shown the superior accuracy of the MP-MRI guided biopsy in detecting clinically significant prostate cancer foci over the standard 12-core systematic biopsy.[10] Moreover, further studies found that the MP-MRI guided biopsy is equivalent to the standard-of-care 12-core biopsy in terms of cancer detection, but superior in detecting higher grade disease.[15]

In a review of comparative studies by Toner et al., data suggest that the sensitivity and specificity for prostate cancer detection is 80% to 90%, and 50% to 90%, respectively.[12] In a diagnostic meta-analysis by Rooij, et al. pooled sensitivity and specificity of the MP-MRI were 74% and 88% respectively, with a negative predictive value of 65% to 94%.[13]

MP-MRI guided fusion biopsy may be accomplished by "in gantry" technique done in the MRI suite[19], MP-MRI guided fusion ultrasound biopsy merging MRI images with high resolution ultrasound in real time and the ultrasound cognitive fusion, wherein lesions in the MRI are located based on estimated positions in the prostate done with a prostate brachytherapy template as a guide.[6]

This study aims to measure the diagnostic accuracy of the MP-MRI and MP-MRI cognitive ultrasound fusion biopsy in the detection of prostate cancer compared to final histopathology of corresponding whole mount specimen gathered after RALRP. To the authors' knowledge, this is the first local study on these diagnostic modalities since the technology is new in the country. Unlike the previous studies on the sensitivity and specificity of either MP-MRI cognitive fusion biopsy, the current study compares both modalities against the reference standard.

Materials and Methods

Study Design

The study is a sensitivity and specificity study involving patients who underwent MP-MRI and MP-MRI ultrasound cognitive fusion biopsy, who eventually underwent RALRP. Data were gathered retrospectively by reviewing patient records.

Time Frame and Target Population

Patients who underwent RALRP from March 2015 to February 2017 were included in the study.

Inclusion and Exclusion Criteria

Patients who had serum PSA levels between 2.5ng/dl to 20ng/dl with normal DRE and at least

a PIRADS 3 lesion in the prostate demonstrated on MP-MRI were included. All of these patients have a proven prostate cancer as documented by biopsy results post MP-MRI cognitive fusion biopsy and who later underwent RALRP were included in the study. All the MP-MRI interpretation, the MP-MRI cognitive fusion biopsy, the RALRP and pathology interpretations were done by a single MRI radiologist, a single urologic oncologist and uropathologist, respectively.

Patients unfit for general or spinal anesthesia, or had any contraindication to MRI were excluded. Patients with metastases on bone scan, lymph node involvement on MRI, and extraprostatic extension on MRI were also excluded. No criterion on whether a repeat or first time biopsy was delineated.

Operational Definitions

Positive for prostate cancer is defined as clinically significant prostate cancer with a Gleason score of 7 (3 + 4 or above) with a maximum cancer core length of 6mm or longer upon biopsy.

Multiparametric MRI acquisition was performed with 3 sequences - triplanar T2-weighted, dynamic contrast-enhanced and diffusion-weighted imaging. Images were evaluated by a specialized MRI radiologist trained specifically on the PIRADS version 2 five-point category scale.

Multiparametric MRI cognitive fusion biopsy was performed via transperineal cognitive fusion using BK flex 800 ultrasound scanner with endocavity biplane 8848 transrectal probe attached to a civco brachytherapy stepper and stabilizer unit.

Data Collection and Analysis

Data gathered included preoperative data (age, PSA, DRE findings, prostate size on imaging, areas of suspected prostate cancer on MP-MRI), post fusion biopsy data (area of malignancy, and Gleason score), and postoperative outcomes (areas of malignancy and Gleason score). The MRI results were analyzed by a single radiologist specialized in MP-MRI and the PIRADS classification; Both MP-MRI fusion biopsy and RALRP histopathology were evaluated by a single urologic pathologist.

This is a retrospective review of patient records; hence, subject contact and recruitment were not necessary.

The MP-MRI divided each prostate into six areas. Each area with a PIRADS score greater than 3 is considered an area with a possibility of clinically significant prostate cancer. The patient then underwent MP-MRI cognitive fusion biopsy, which directs the specimen collection to areas with possibility of clinically significant prostate cancer on MP-MRI.

For areas with negative MRI, the sample is taken systematically based on the Victorian trans-perineal template.

After having confirmed the presence of prostate cancer with the ultrasound fusion prostate biopsy in any of the six areas, the patient underwent RALRP. The prostate specimen was divided in the same manner as with the MP-MRI. The MP-MRI results and the MP-MRI ultrasound cognitive fusion biopsy results were then compared against the final histopathology of the whole specimen mount by same segment area.

Data were collated and analyzed using Microsoft Excel. For this study, the outcome measures were sensitivity, specificity, positive, negative predictive values and congruence. Histopathologic findings served as the reference standard, reported by the same expert uropathologist, blinded to all MR images and MP-MRI fusion biopsy findings. Significance of sensitivity, specificity, negative and positive predictive values were based on 95% confidence interval.

Ethical Considerations

A retrospective record review was done, hence no risks, or discomfort to subjects were anticipated. The hospital informed consent sufficed for the collection of data. All patient names were kept anonymous. All cases were identified by hospital patient identification number (PIN).

Results

Demographics

A total of 19 patients were included in the study with a total of 114 prostatic segments, all of which had representation in the MP-MRI, cognitive fusion biopsy, and final histopathology whole specimen mount. These patients underwent RALRP with no operative complications.

Age of patients ranged from 59 to 77 years, with mean and median of 66 and 65 years old respectively. PSA range was from 2.5 to 19.8 with a mean and median of 11.39 ng/dl and 9.96 ng/dl respectively. Prostate volume ranged from 18 grams to 74 grams with a mean and median of 37.80 grams and 34 grams, respectively; all patients had normal DRE.

Table 1. Patient demographics.

	Mean	Range
	Age 66 y/o	58 - 77 y/o
PSA	11.39 ng/dl	2.5 - 19.8 ng/dl
Prostate Volume	37.8 grams	18 - 70 grams

Imaging

The distribution of segment with corresponding PIRADS is shown in Figure 1. Majority of these cases were PIRADS 4 (56%), PIRADS 3 (32%) and PIRADS 5 (12%).

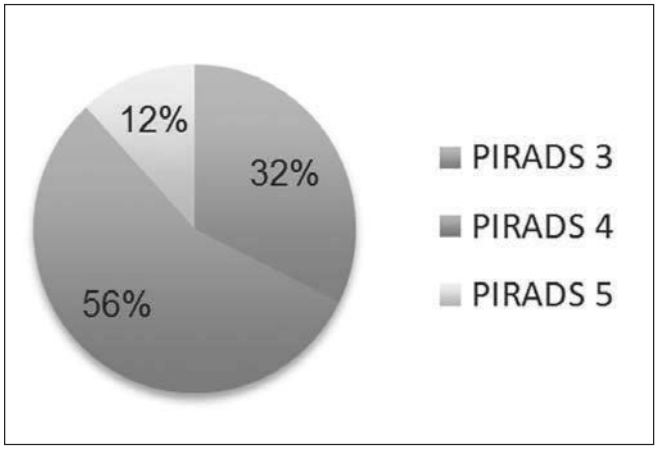

Figure 1. Distribution of PIRADS

Cognitive Fusion Biopsy Results

The distribution of clinically-significant prostate cancer by Gleason score on biopsy is shown in Figure 2. Majority (30%) were Gleason 7 (3+4). The left lobe, mid-region area of the prostate was most commonly identified to have a clinically-significant prostate adenocarcinoma.

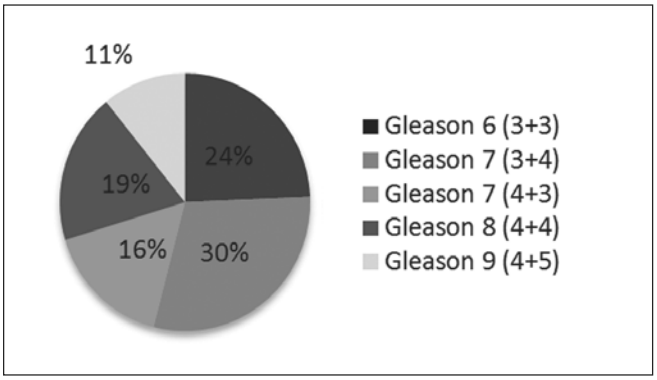

Figure 2. Distribution of biopsy results by Gleason score.

Final Histopathology Results

The distribution of prostate cancer by Gleason Score on final histopathology is shown in Figure 3. Majority (47%) were Gleason 7 (3+4). Both the left posterior and left mid-regions of the prostate were most commonly identified to have a clinically-significant prostate adenocarcinoma.

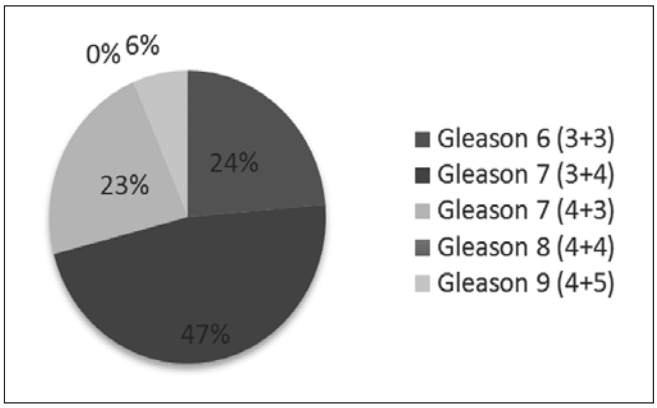

Figure 3. Distribution of final histopathology results by Gleason score

Outcome Measure

Table 2 shows the two by two table comparing MP-MRI with final histopathology of the whole mount specimen. The sensitivity of MP-MRI as compared with the final histopathology was 35.5% (C.I. 25.5% to 45.6%), while the specificity was 95.2% (C.I. 77.3% to 99.2%). The positive predictive value was computed at 97.1% (C.I. 82.70% to 99.5), while the negative predictive value was 25% (C.I. 21.80% to 28.49%).

Table 2. MP-MRI vs final histopathology.

	Positive MP-MRI	Negative MP-MRI	Total
Positive Histopathology	33	60	93
Negative Histopathology	1	20	21
Total	34	80	114

Table 3 shows the two by two table comparing MP-MRI ultrasound fusion biopsy results with that of final histopathology. The sensitivity of ultrasound fusion biopsy with the final histopathology was at 34.4% (C.I. 24.9% to 45.0%), while the specificity was 81.0% (C.I. 58.1% to 94.6%). With prevalence of 81.6%, the positive predictive value was 88.9% (C.I. 76.0% to 95.3%), while the negative predictive value was 21.8 % (C.I. 17.8% to 26.4%).

Table 3. MP-MRI ultrasound fusion biopsy vs final histopathology.

	Positive MP-MRI ultrasound fusion biopsy	Negative MP-MRI ultrasound fusion biopsy	Total
Positive Histopathology	32	61	93
Negative Histopathology	4	17	21
Total	36	78	114

Table 4 shows the total congruence of MP-MRI and the MP-MRI ultrasound fusion biopsy with positive results was at 50%, and 79.5% with negative results.

Discussion

Compared to results of previous studies which showed specificities of 50%-95%[12] and 60%-94%[13], this study revealed MP-MRI having a specificity of 95.2%. This implies that a positive result on MP-MRI has high likelihood of being a clinically-significant malignancy. The high specificity correlates well with its high positive predictive value of 97.1%. The high specificity and positive predictive value of MP-MRI support the use of this modality together with MP-MRI targeted fusion biopsy as means of identifying clinically-significant prostate cancer as the MP-MRI ultrasound cognitive fusion biopsy had similarly high specificity of 81.0% and high

Table 4. MP-MRI and fusion biopsy cross-tabulation

			Biopsy Positive	Negative	Total
MRI	Positive	Count	18	16	34
		% within MRI	52.9%	47.1%	100%
		% within Biopsy	50.0%	20.5%	29.8%
	Negative	Count	18	62	80
		%within MRI	22.5%	77.5%	100%
		%within Biopsy	50.0%	79.5%	70.2%
Total		Count	36	78	114
		%within MRI	31.6%	68.4%	100%
		%within Biopsy	100%	100%	100%

positive predictive value of 88.9%. The study confirms that international data are replicable in the local setting and encourages local Urologists, that a PIRADS scores on MP-MRI should be used as a prognosticating tool to objectively recommend to patients in need for biopsy regardless of risk factors or PSA value. MP-MRI and MP-MRI ultrasound cognitive fusion biopsy in the Philippine setting are capable of identifying presence of clinically significant prostate cancer at high specificity and high predictive values.

A striking difference of this study with other studies was that its focus went beyond the identification of mere presence of cancer. It also looked into the ability of MP-MRI to identify the actual location of all lesions with a high probability of a clinically-significant prostate cancer. This explains the low sensitivity of MP-MRI (35.5%) and MP-MRI cognitive fusion biopsy (34.4%). This however does not indicate that MP-MRI cannot identify the presence of cancer. It suggests that MP-MRI still has areas for improvement and not a reliable tool yet which can aid urologist in his surgical judgment.

It was also observed in the study, that a negative result on MP-MRI is not reliable in ruling out the possibility of a clinically-significant prostate cancer, since many lesions were missed out by this modality. This correlates well with the low negative predictive value of 25%. The practical application of this finding supports the practice that the researchers performed in combining targeted biopsy, with a systematic biopsy approach. Targeted biopsy alone could not be recommended as it misses out on many other potential areas of clinically-significant prostate cancer.

The low sensitivity could also possibly be due to the limitation of MP-MRI as a new modality and as a reader-dependent diagnostic modality. The short availability period of the machine and the limited experience of the local radiologist in using the modality may have contributed to the lower sensitivity in the local setting. Having the MP-MRI ultrasound cognitive fusion biopsy similar with a low sensitivity of 34.4% and low negative predictive value of 21.7%, the authors experience in the local setting on MP-MRI and MP-MRI ultrasound fusion biopsy both tend to miss out on a large percentage of areas with clinically significant prostate cancer.

With a positive congruence of only 50% and negative congruence of 79.5%, MP-MRI and fusion biopsy point out a low degree of factor similarity. Standardization of the fusion biopsy procedure is yet to be established since it is novel in the country. Further studies are needed to justify congruence before a strong conclusion can be made. This study however can be used as a basis of the initial results of congruence of MP-MRI with ultrasound fusion biopsy in the Philippines.

Conclusion

MP-MRI had high specificity and positive predictive value of 95.2% and 97.1% respectively, strong indication for the need for biopsy and support the utility of a targeted MP-MRI guided ultrasound cognitive fusion biopsy. However, the low sensitivity of 35.5% and negative predictive value of 25% show that MP-MRI guidance does not limit the number of biopsy samples only to visible MP-MRI lesions, since negative areas on MP-MRI still contain tumors in 75% of cases.

Recommendations

The low specificity and negative predictive value of MP-MRI warrants maintenance of high index of suspicion on the negative areas if the patient is clinically suspicious for prostate cancer. Thus, even on areas with negative MP-MRI, it is recommended that random biopsy samples should still be taken. For prostates with negative MP-MRI on all areas but with a high index of suspicion, further studies need to be made if MP-MRI can suffice justification for not proceeding with a random 12 core biopsy. The study also identifies with the claim that part of the strength of each study is reflected with the population involved, only 19 subjects were enrolled and the authors recommend that further studies with a bigger population be conducted.

Appendix I

(American College of Radiology, PI-RADS, Prostate Imaging Reporting and Data System version 2-2015)

PI-RADS assessment uses a 5-point scale based on the likelihood (probability) that a combination of mpMRI findings on T2W, DWI, and DCE correlates with the presence of a clinically significant cancer for each lesion in the prostate gland.

PI-RADS 1	Very low	Clinically significant cancer is highly unlikely to be present
PI-RADS 2	Low	Clinically significant cancer is unlikely to be present
PI-RADS 3	Intermediate	Clinically significant cancer is equivocal
PI-RADS 4	High	Clinically significant cancer is likely to be present
PI-RADS 5	Very high	Clinically significant cancer is highly likely to be present

Each modality has a specific means of assessing the probability that each lesion has a presence of significant cancer.

PI-RADS for DWI

Score	Peripheral Zone (PZ) or Transition Zone (TZ)
1	No abnormality (i.e., normal) on ADC and high b-value DWI
2	Indistinct hypointense on ADC
3	Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value DWI.
4	Focal markedly hypointense on ADC and markedly hyperintense on high b-value DWI; <1.5cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

PI-RADS for DCE

Score	Peripheral Zone (PZ) or Transition Zone (TZ)
(–)	no early enhancement, or diffuse enhancement not corresponding to a focal finding on T2W and/or DWI or focal enhancement corresponding to a lesion demonstrating features of BPH on T2WI
(+)	focal, and; earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues, and; correspnds to suspicious finding on T2W and/or DWI

PI-RADS Assessment for T2W

Score	Peripheral Zone (PZ)
1	Uniform hyperintense signal intensity (normal)
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity Includes others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

Score	Transition Zone (TZ)
1	Homogeneous intermediate signal intensity (normal)
2	Circumscribed hypointense or heterogeneous encapsulated nodule(s) (BPH)
3	Heterogeneous signal intensity with obscured margins Includes others that do not qualify as 2, 4, or 5
4	Lenticular or non-circumscribed, homogeneous, moderately hypointense, and <1.5 cm in greatest dimension
5	Same as 4, but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

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