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Clinical-Prostate cancer

The additive value of mpMRI on prostate cancer detection: Comparison between patients with and without a suspicious digital rectal examination (DRE)

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Abstract

Purpose: Diagnosis of prostate cancer (CaP) is based on digital rectal examination (DRE) and/or elevated prostate specific antigen (PSA) level. This approach lacks sensitivity and specificity and is associated with many negative biopsies, high rate of diagnosing clinically insignificant disease and lacks accuracy to predict clinically significant (CS) cancer. The addition of multiparametric magnetic resonance imaging (mpMRI) before prostate biopsy reduces the detection of low-grade tumors while improving the detection of CS CaP. Most studies that evaluated mpMRI performance did not separate the DRE status of the examined patients. Therefore, the aim of our study is to investigate whether mpMRI provides similar advantages in detection of CaP according to the DRE findings.

Materials and Methods: This prospective study included patients with clinically suspected CaP that were referred to MRI-fusion biopsy from 2014 to 2019. All patients had mpMRI of the prostate with an index lesion of PIRADS ≥3. Analysis was done comparing systemic and targeted biopsy. Patients were divided into two groups according to the DRE findings (positive or negative DRE) and the primary outcomes were compared between the 2 study groups: detection rate of CaP and the detection rate of CS disease defined as Gleason score ≥ 7.

Results: The final study cohort included 86 patients: 47 with negative DRE and 39 with positive DRE. Overall cancer detection rate was higher in patients with a positive DRE (70.3% vs 48.9%, P <0.05). In the region of interest a higher overall detection rate and of CS disease was found in those with abnormal DRE (51.3% vs. 40.4% and 48.6% vs. 34.0% respectively). The systematic biopsy analysis showed an overall lower detection rate in the negative DRE group (8.5% vs. 18.9 %). The targeted biopsies detected more cancer and significant tumors per core in patients with positive DRE (29.2% vs. 18.5% and 22.1% vs. 14.5% respectively).

Conclusions: Patients submitted to fusion biopsy and have a positive DRE are diagnosed more often with CaP, have higher grade disease and larger tumors. In patients suspicious for CaP and having a significant lesion on mpMRI one should combine targeted and systematic biopsy regardless of the DRE status.

Keywords: DRE; Prostate cancer; Clinically significant; Diagnosis; mpMRI

1. Introduction

Traditionally the clinical diagnosis of prostate cancer (CaP) is made on the basis of digital rectal examination (DRE) and/or elevated PSA level. Most cancers are located in the peripheral zone and as such may be detected by DRE especially when the tumor volume exceeds 0.2 cc. A suspicious DRE in patients with a PSA level < 2 ng/mL has a positive predictive value (PPV) of 5-30% [1]. An abnormal DRE is associated with an increased risk of detecting CaP, a higher ISUP Gleason grade group and is an indication for performing prostate biopsy regardless of the PSA level. For example, in the European randomized study of screening for CaP (ERSPC) at initial screening, the PPV of a suspicious DRE, in conjunction with an elevated PSA level, to detect CaP was 48.6% compared to 22.4% for men with a normal DRE. [2,3]. This diagnostic approach which

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is based on PSA and DRE is associates with many negative biopsies, high rate of diagnosing clinically insignificant disease and lack accuracy to predict more precisely clinically significant (CS) cancer [4]. To overcome these limitations the European Association of Urology (EAU) guidelines on CaP recommend performance of multiparametric magnetic resonance imaging (mpMRI) before prostate biopsy in patients suspected of having CaP both in biopsy-naïve and repeat-biopsy settings [5]. However, most studies that evaluated mpMRI performance did not separate the DRE status of the examined patients. Therefore, the aim of the current study was to investigate whether mpMRI provides similar advantages in detection of CaP in patients with or without a palpable nodule on DRE.

2. Material & methods

The study was approved by the local ethical committee and all patients signed a written informed consent (IRB: BNZ-053). We performed a prospective data collection for the study group which included patients with clinically suspected CaP (PSA >3 ng/ml and/or abnormal DRE) that were referred for MRI−TRUS fusion prostate biopsy in our hospital from 2014 to 2019.

2.1. Patients

We included patients referred to MRI−TRUS fusion prostate biopsy. All patients had mpMRI of the prostate with a discrete index lesion according to PIRADS V2 score ≥3. We used a pragmatic approach and included men undergoing either primary or repeated biopsy. We also included men who were previously diagnosed with low-risk CaP (Gleason Group 1) and are under active-surveillance (AS) protocol. For each participant we evaluated separately the performance of the procedure in the targeted vs. the systematic biopsy.

2.2. Navigo system

The 3D GS TRUS system (Navigo workstation) was incorporated side by side in the room with 2D ultrasound images transferred and displayed on the 3D TRUS screen. A 3D model of the prostate was built after prostate volume measurements and planimetry was done. The 3D model was built based on prostate segmentation in sections every 5 mm, navigation and targeting was done in real-time using electromagnetic sensors to detect probe location and patient movement. In real time using an electromagnetic system, the 12-core biopsy protocol was performed with tracking, displaying and recording of biopsy needle trajectory locations. Biopsy cores were fixed separately on six different cassettes (2 cores of apex, mid and base on both sides). In addition to the 12 systematic cores, targeted biopsies were collected − 2 cores per cassette. The previously marked regions of interest were shown with color indications on screen and sampled.

All the biopsies were done by a single experienced urologist who also determined the DRE status for each patient in the study. The biopsy specimens were sent to the local pathological lab and managed by the same standard tissue processing.

The detection rate is defined as the number of patients diagnosed with CaP by TRUS biopsy divided by the total number of the group. Because of different total core numbers for each patient and subsequently different average core numbers between the two groups the detection rate per core was also calculated by dividing the number of positive cores by the total number of cores for each group.

The following primary outcomes were compared between the two study groups: detection rate of CaP and the detection rate of CS disease defined as Gleason score ≥ 7.

2.3. Statistical analysis

Statistical analysis was performed using the SPSS ver. 20 (SPSS Inc. Chicago). Descriptive baseline continues variables of the two groups were presented as mean +/- standard deviation and compared using student t-test. The differences in percentage detection rate between the 2 groups were assessed by using the Chi-Square test. A P value of 0.05 or less was considered statistically significant in all analyses.

3. Results

The study group included 91 patients submitted for MRI-TRUS fusion biopsy of prostate in a single institution. Five of them were excluded because of insufficient information in our database, resulting in 86 participants. There were 47 and 39 patients in the negative and positive DRE cases respectively. With respect to baseline clinical characteristics (Table 1) no significant differences were recorded between the two groups.

When overall cancer detection rate was considered we observed a higher rate of positive biopsies in patients with a palpable nodule on DRE (70.3% vs. 48.9%, P <0.05). When we looked specifically at samples obtained from the region of interest as defined by the pre biopsy mpMRI we found a higher overall detection rate in those with abnormal DRE (51.3% vs. 40.4%). In this group the detection of CS disease was also more frequent in those with a positive rectal exam (48.6% vs. 34.0%). Analysis of the non-targeted biopsies revealed overall relatively lower detection rate of CaP (8.5% vs. 18.9%) in positive and negative cases respectively. Such magnitude of differences in positive biopsy remained unchanged also for tumors with Gleason score above Gleason 6(3+3) (8.1% and 4,2% for abnormal and normal DRE cases). These differences were not statistically significant probably due to the small number of cases (Table 2, Fig. 1).

We further compared the detection rate (per biopsy core) between targeted and systematic biopsies in the two studied

Table 1
Base line clinical characteristics of 91 patients submitted for prostate biopsy stratified by DRE status.

Patient characteristics	General	Negative DRE	Positive DRE	*P* value(Negative Vs. Positive DRE)
Number of patients	91	47	37	–
Suspected DRE	44%	0%	100%	–
Age	67.4±7.1	66.9±5.9	68.8±8.3	$P = 0.26$
PSA	9.6±7.9	9.3±4.9	9.4±10.9	$P = 0.93$
Prostate volume	74.6±42.6	74.4±41.9	68.9±36.6	$P = 0.5$
Number of cores	20.8±4.7	20.8±4.9	21.1±4.6	$P = 0.85$
Cores per ROI	5.3±1.6	5.3±1.4	5.5±1.8	$P = 0.77$
A.S.	27% (25/91)	28% (13/47)	24% (9/37)	$P = 0.73$

DRE = Digital rectal exam; PSA = Prostate specific antigen; ROI = Region of interest; A.S. = Active surveillance.

Table 2
Prostate cancer detection rate in 91 patients submitted for prostate biopsy stratified by DRE status.

	General	Negative DRE	Positive DRE	*P* value
Detection rate:	56%	48.9%	70.3%	$P < 0.05$
Positive in TB	41.7%	40.4%	51.3%	$P = 0.32$
Positive in TB: CS	38.4%	34.0%	48.6%	$P = 0.17$
Positive in SB	14.2%	8.5%	18.9%	$P = 0.16$
Positive in SB: CS	6.5%	4.2%	8.1%	$P = 0.45$

TB = Targeted biopsy; SB = Systematic biopsy; CS = Clinically significant.

groups. As expected, the overall detection rate and the diagnosis of CaP with Gleason score above 6(3+3) in the entire cohort was significantly higher in samples obtained from targeted lesions (22.5% vs. 8.7%, $P = 0.01$ and 17.2% vs. 5.9%, $P = 0.01$ respectively). In the targeted biopsies we were able to detect more cancer and significant tumors per core in patients with a palpable nodule than in those with a negative DRE (29.2% vs. 18.5% and 22.1% vs. 14.5% respectively). In the systematic specimens the detection rate was lower (13.9% and 5.2% respectively). Evaluation of the detection rate only in the systematic biopsies demonstrated 9.1% and 3.7% in cases with and without a palpable nodule respectively (Table 3).

4. Discussion

The exact role of DRE in CaP diagnosis is controversial. In the past DRE was the most widely used diagnostic test with approximately half of all palpable nodules turned to be CaP on subsequent biopsy [6]. Following the introduction of PSA testing, the number of men diagnosed with CaP due to an abnormal DRE alone has significantly decreased [7]. Some groups [3,8,9] have demonstrated that an abnormal DRE is an independent predictor of high-grade CaP. For example, Gosselaar et al. used data from the Rotterdam cohort of the European Randomized Study of Screening for CaP and found that the positive predictive value (PPV) of a positive DRE for the detection of CaP was 48.6%. An abnormal DRE was associated with a significantly increased risk of high-grade disease (Gleason score 8−10) during all 3 rounds of screening (P ≤0.002 for all rounds). Others, however, recommend against routine performance of DRE to diagnose CaP. For example, Naji et al. in a systematic review and meta-analysis (7 studies with 9,241 patients) reported a pooled PPV of 0.41 and pooled NPV of 0.64 and recommend against routine DRE for CaP diagnosis [10].

Due to the low performance of standard systematic biopsy the most recent version of the EAU guidelines on

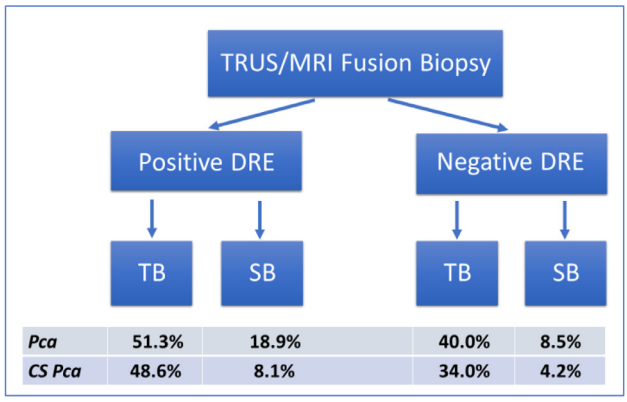

Fig. 1. Results of MRI-TRUS Fusion biopsy in patients suspicious for CaP with significant mpMRI prostate lesion with and without positive DRE. CaP = Prostate cancer; CS = Clinically significant; SB = Systematic biopsy; TB = Targeted biopsy.

Table 3
Prostate cancer detection rate per targeted and systematic biopsy cores in 91 patients submitted for prostate biopsy stratified by DRE status.

General	Targeted cores	Systematic cores	*P* value
Detection rate (per core)	22.5% (126/559)	8.7% (105/1204)	$P < 0.01$
Significant cores (>3+3) (out of all)	17.2% (96/559)	5.9% (71/1204)	$P < 0.01$
Significant cores (>3+3) (out of positive)	76.2% (96/126)	67.6% (71/105)	$P = 0.15$
Negative DRE			
Detection rate (per core)	18.5% (51/276)	5.3% (33/620)	$P < 0.01$
Significant cores (>3+3) (out of all)	14.5% (40/276)	3.7% (23/620)	$P < 0.01$
Significant cores (>3+3) (out of positive)	78.4% (40/51)	69.7% (23/33)	$P = 0.36$
Positive DRE			
Detection rate (per core)	29.2% (74/253)	13.9% (68/484)	$P < 0.01$
Significant cores (>3+3) (out of all)	22.1% (56/253)	9.1% (44/484)	$P < 0.01$
Significant cores (>3+3) (out of positive)	75.7% (56/74)	64.7% (44/68)	$P = 0.15$

DRE = Digital rectal examination.

CaP recommend performing mpMRI before prostate biopsy. This approach which can decrease the number of unnecessary biopsy procedures and reduce the detection of low-grade tumors while improving the detection of CS CaP [5], have not yet been adopted by all urological international guidelines

The data available in the literature on the advantage of mpMRI for CaP biopsy do not differentiate between patients with or without a palpable prostate nodule. While it seems reasonable to expect that incorporation of enhanced imaging modality for patients with negative DRE will be more helpful it was not clear if those with positive DRE may benefit as well from the "MRI pathway."

The main findings of our study indicate that as expected MRI-TRUS fusion biopsy detected more frequently CaP in patients with positive DRE (70.3% vs. 48.9%, $P = 0.05$). It should be mentioned that the incorporation of mpMRI into the diagnostic process significantly increased our ability to detect cancer compared with our standard systematic biopsy which was only 30.3% as recently reported by Masarwa et al. [11]. When targeted biopsies from the suspected MRI lesions were considered, similar differences in the detection rate were noted both for overall and for CS CaP. In the systematic biopsies the detection rate of CS CaP was nearly two-fold higher in the abnormal DRE group. However, such difference was not statistically significant probably due to the small sample size. Like previously reported in the literature we also observed correlation between positive DRE and high Gleason score cancers as well as a larger disease burden [3,8,9].

As have been described by others our results showed that targeted biopsies resulted in a higher overall and CS cancer detection compared to the systematic samples [12,13]. However, the contribution of mpMRI was more pronounced in patients with normal compared to those with abnormal DRE, who had 3-fold and 4-fold increase vs. 2-fold and 2.5-fold increase of overall and CS CaP detection rate (Table 3). This indicates the ability of mpMRI to better detect non-palpable cancer. Due to variations among biopsy sampling, the exact number of tissue cores obtained per each region of interest and the uncertainties regarding the exact size of each suspicious area we elected to analyze the detection rate also per number cores and not just for the individual patient.

The overall detection rate of CS disease in the systematic cores was relatively low but not insignificant in both groups, being approximately 4% and 8% for negative and positive DRE patients. Similar findings were also reported by Propiglia et al. who reported 3.8% detection rate of CS CaP in patients undergoing systematic biopsy in addition to targeted samples [14]. Taken together the results of the current study demonstrate that mpMRI before prostate biopsy is beneficial for patients with both positive and negative DRE.

Oure study has several limitations including the fact that there was no strict definition to characterize abnormal DRE. Only those with a suspicious DRE or elevated PSA underwent prostate biopsy, leading to underestimation of the false-negative rate. We have no data on those with low PSA level. This is a single institution study and the number of patients in each group is relatively small, and as such could affect differences between the groups. This may limit the generalization of our conclusions. Not all radiologists involved in this study were expert in prostate MRI and some were not reporting a high volume of mpMRIs per year. Finally, there was no correlation of the biopsy findings with radical prostatectomy pathologic specimen.

The study strength points are the facts that all the biopsies were obtained by a single experienced urologist and all the specimens were examined in the same pathologic laboratory. Moreover, the data on the study groups was collected prospectively.

5. Conclusion

We were able to demonstrate that patients submitted to fusion biopsy and have a palpable nodule on DRE are diagnosed more often with CaP, have higher grade disease and larger tumors. The value of mpMRI of the prostate is beneficial to both groups but more to those with a normal

palpable prostate gland. The practical implication from the data presented is that in patients suspected for CaP and having a significant lesion on mpMRI (PIRADS ≥ 3), one should combine targeted and systematic biopsy regardless of the DRE status. This approach which is only recommended by the EAU guidelines can decrease the number of unnecessary biopsy procedures and reduce the detection of low-grade tumors while improving the detection of CSCaP. Other international guidelines are encouraged to follow similar recommendations. Additional studies and larger number of patients are needed to verify our initial results.

Compliance with ethical standards

Ethical approval

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript. All the listed co-authors approve the submission of this manuscript, and the content of the manuscript has not been published, submitted for publication or is under consideration for publication with any other journal.

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