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Mpmri-Ultrasound Fusion Guided Prostate Cancer Biopsy Improves Staging Accuracy and Impacts Post Prostatectomy R1 Rates Compared to Standard Ultrasound Guided Biopsy

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1. Abstract

1.1. Background: Utilizing our specific institutional setup with patients coming from different urological referral centers using different prostate cancer biopsy techniques subsequently operated by only one robotic single surgeon we assessed:

- the staging accuracy of standard ultrasound-guided (US) biopsy compared to mpMRI-US fusion biopsy.

- the impact of an advanced preoperative cancer staging for postoperative pathological outcome in terms of positive cancer margins (R1).

1.2. Patients and Methods: Data from 140 patients after robotic assisted da Vinci radical prostatectomy including lymphadenectomy from 2018 through 05/2020 performed by a single surgeon was included.

Patients in group A were referred from one urological center A using standard ultrasound-based biopsy (n=79), while patients in group B were referred from a different urological center B and were diagnosed by mpMRI-US fusion biopsy. Each dataset pre- and postoperatively had to be complete and included all patients-, imaging and pathological information. Differences in staging accuracy as well as the difference in pathological outcome including positive surgical margins (R1) were evaluated.

1.3. Results: mpMRI-US fusion biopsy compared to ultrasound-only biopsy revealed:

- a significant understaging for uni- versus bilateral tumor growth after ultrasound only biopsy.

- a significant understaging for locally advanced tumor growth (>pT3) after ultrasound only biopsy.

- significantly higher rates of positive tumor margins (R1) after ultrasound only biopsy.

1.4. Conclusion: The specific setup in our institution with patient referrals from two different urological centers using two different biopsy techniques subsequently operated in a standardized surgical procedure by a single robotic surgeon allowed us to analyze the impact of ultrasound only versus mpMRI-US fusion biopsy and revealed a significant higher preoperative staging accuracy and postoperative significant lower R1 rates after fusion biopsy.

2. Introduction

The clinical stage of prostate cancer (PCa) before surgery is defined by digital-rectal examination (DRE), PSA value, multiparametric MRI (mpMRI) findings as well as the results of prostate biopsy [1]. For the latter the ultrasound-guided biopsy is still the most used technique despite its known limitations such as over-diagnosing clinically insignificant PCa as well as missing clinically significant PCa, especially PCa located in the anterior aspect of the prostate [2]. Using the advances of mpMRI in prostate cancer visualization has led to the development of mpMRI-Ultrasound (US) fusion biopsy (targeted biopsy) platforms in recent years, potentially allowing for a more precise preoperative mapping of the prostate before radical prostatectomy (RP). The goal of RP is the eradication of cancer while, whenever possible, preserving pelvic organ function [1]. Over the last decades technical progress led

to the widely accepted use of robotic systems (RARP) allowing for a better visualization of the anatomy including the urethra and cavernous nerves to possibly improve the rates of continence and erectile function. Nerve sparing is usually performed on the non-tumor-bearing side of the prostate in order to decrease the chance of a tumor positive margin (R1-situation) [3]. Therefore, preoperative knowledge about the clinical tumor stage (cT) including localization of the tumor(s) within the prostate appears to be mandatory, especially since prostate cancer is often a multifocal disease. However, mpMRI reports often focus on one or two leading lesions, which might be the main focus of interest during ultrasound-guided biopsy while underrating template biopsies.

We therefore assessed the staging accuracy of standard ultrasound guided biopsy compared to mpMRI-US fusion biopsy results using pre- and postradical prostatectomy data. Moreover, we evaluated whether an advanced preoperative knowledge of tumor localization within the prostate may result in lower rates of positive surgical margins (R1).

Typically, the RARP procedure has a much higher impact on these questions compared to the preoperative diagnostic technique due to different surgeons with different levels of expertise and different intraoperative strategies. To overcome this limitation in this series all analyzed patients were operated by the same experienced senior robotic surgeon in a standardized manner.

3. Material and Methods

3.1. Ethical Approval and Consent to Participate

All patients gave written consent. The study was approved by the local ethical review board (IRB).

3.2. Patients

Patients in group A were referred from one urological center (A) using standard ultrasound-based biopsy (n=79), while patients in group B were referred from a different urological center (B) and were diagnosed by mpMRI-US fusion biopsy. Patients were referred to both urological centers (A and B) for prostate biopsy due to a clinical suspicion of prostate cancer on the basis of an elevated PSA level, an abnormal digital rectal examination, or both.

In order to be included all participants had to be >18years and to provide written informed consent. Moreover, all pre- and postoperative data had to be available and all datasets had to be complete.

3.3. Pre-biopsy MRI

All patients from both urological centers (A and B) underwent a pre-biopsy multiparametric magnetic resonance imaging (mpMRI) utilizing a 3.0-T scanner without an endorectal coil. Importantly all MRIs were performed in the same department of Radiology, Klinik St. Anna, Lucerne, Switzerland. Appropriate sequences (T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences) were acquired and analyzed by one of the two MRI experienced consultant of the department of radiology. Interpretation and reporting of the mpMRI followed the Reporting and Data System Version 2 (PI-RADS™ v2).

3.4. Ultrasound Guided Prostate Biopsy (group A)

In case of a PIRADS ≥3 lesion or the persistent suspicion of a significant prostate cancer despite PIRADS 2 scoring, patients in group A (from center A) received a standard 10-12x transrectal ultrasound guided prostate biopsy. Cores were obtained from the lesion as described in the mpMRI ± additional cores of the residual prostate tissue (template biopsy). Tissue cores were analyzed by the local department of pathology.

3.5. mpMR-Ultrasound Fusion Biopsy (group B)

All biopsies were performed in center B via the transrectal approach by one senior consultant of urology experienced in the Artemis system (Eigen, Grass Valley, California, USA). The usage of the Artemis system has been described previously [4]. Contouring of the prostate margins and the target lesions was done by a radiologist using the transverse T2 TSE-images. A maximum of 3 lesions with a PIRADS 3 minimum were electronically loaded into the Artemis and contours were fused with real-time TRUS during the biopsy session. For targeted biopsy, 2 cores were obtained from each lesion and tissue of each lesion separately sent for histology. Systematic biopsy sampling with ≥8 cores was then performed as pre-selected by the Artemis device, independent of the MRI results. Systematic biopsies were sent separately for histology according to its site of origin (apex left/right, midlevel left/right, base left/right). Tissue cores were analyzed by the local department of pathology.

3.6. Robot-Assisted Laparoscopic Radical Prostatectomy with the da Vinci Xi

All 140 patients (group A and B) underwent subsequently robot-assisted laparoscopic radical prostatectomy using the da Vinci Xi system. The procedure was performed by a single open and robotic experienced surgeon in a standardized manner including lymphadenectomy at the Klinik St. Anna, Lucerne, Switzerland. Nerve sparing was performed whenever possible according to preoperative tumor characteristics including clinical stage according to mpMRI and prostate biopsy results as well as patient characteristics (erectile function / continence). Patients of both groups (A and B) were operated between 2018 and 05/2020 in a non-consecutive manner. The surgeon was already highly experienced in open and robotic assisted prostatectomy before study time. All specimens were analyzed by the local department of pathology.

3.7. Data Analysis

Patient data included age, prostate size, preoperative PSA value, digital-rectal examination (DRE), and staging results. For each patient every mpMRI described lesion as well as the template biopsies were evaluated for its size, localization, number of positive and negative biopsy cores and the corresponding Gleason score.

A preoperative clinical staging according to the EAU-guidelines included all above-mentioned findings. Postoperative data included side of nerve sparing, tumor size and location, Gleason score, R- and pT-status and resulted in a pathological staging similar to the preoperative staging.

3.8. Comparison of pre- and Postoperative Staging Accuracy

For both groups (A and B) each preoperative clinical stage (cT) was defined by DRE, PSA-Level, MRI lesion, biopsy location and Gleason socre. Postoperative pathological stage was defined according to final histology after radical prostatectomy including whole mount sections. TNM information including uni- vs. bilateral tumor growth, status of surgical margins, Gleason score was statistically analyzed using the unpaired t-test and Mann-Whitney-U test.

3.9. Postoperative Positive Surgical Margins in Pt2 Prostate Cancer

Patients with a pT2 postoperative pathological tumor stage were filtered in both groups (A and B) and analyzed according to their R-status. Moreover, patients with a pT2 stage were differentiated according to their preoperative clinical stage. The exact location of the positive surgical margin was documented according to postoperative pathology reports. Data was statistically analyzed using the unpaired t-test.

4. Results

4.1. Trial Population

Patients in group A were referred from one urological center (A) using standard ultrasound-based biopsy (n=79), while patients in group B were referred from a different urological center (B) and were diagnosed by mpMRI-US fusion biopsy (n=61). The characteristics of the participants in at baseline (age, prostate size, DRE findings and PSA) were similar in the two groups (Table 1).

All 140 patients subsequently underwent robotic assisted da Vinci radical prostatectomy including lymphadenectomy from 2018 through 05/2020 performed by a single surgeon in the same institution.

Table 1: Baseline patients characteristics

	Group A (Ultrasound only)	Group B (MRI-US Fusion)	p-value
Patients (n)	79	61	
Age (yrs)	64.2 yrs	65.5 yrs	*p= 0.15*
Median PSA at diagnosis (ug/l))	9ug/l	8.7ug/l	*p= 0.94*
Median Prostate size (ml)	45.7 ml	42.8 ml	*p= 0.37*
DRE (% positive/negative)	29% / 71%	34% / 66%	*p= 0.21*
Number of MRI lesions (n)	1.4	1.2	*p= 0.63*
Number of biopsies	10	13	*p= <0.05*
PIRADS score (mean)	4	4	*p= 0.86*

4.2. Number of Biopsies

In patients diagnosed with prostate cancer using standard ultrasound a medium of 10.1 cores were taken (group A from center A) while a medium of 13.2 cores were taken in patients undergoing mpMRI-US fusion biopsy (group B from center B) (p= <0.05).

4.3. Pre-operative Clinical Stages (cT)

Using standard ultrasound biopsy group A classified significantly more prostate cancer to be unilateral compared to group B using targeted mpMRI-US fusion biopsy (group A: 45 (56% of all diagnosed cancers) patients versus group B: 7 patients (11% of all diagnosed cancers) (p=<0.05). An organ confined bilateral prostate tumor (cT2c) was significantly less diagnosed in group A compared to group B (group A: n=27 (34% of all diagnosed cancers) patients versus group B n=34 patients (56% of all diagnosed cancers, p= <0.05). Group A classified significantly less locally advanced tumor stages compared to group B (group A: 8 patients (10% of all diagnosed cancers) versus group B: 20 patients (32% of all diagnosed cancers, p= <0.05).

4.4. Comparison of pre- and Postoperative Staging Accuracy (cT versus pT)

Group A classified 45 patients preoperatively with unilateral tumor. Of these 9 (20%) were also postoperatively classified as unilateral, while 36 patients (80%) were upstaged as follows: bilateral tumor (pT2c): 23 patients (51%) or pT3a/b: 13 patients (29%). Group B classified 7 patients preoperatively with unilateral tumor. Of these 4 (57%) were also postoperatively classified as unilateral, while 3 patients (43%) were upstaged as follows: bilateral tumor (pT2c): 2 patients (28.61%), pT3a/b: 1 patient (14%).

MpMRI-US fusion biopsy demonstrated a significantly improved staging accuracy compared to diagnostic using ultrasound only in patients with unilateral tumors. Additionally, ultrasound only biopsies resulted in a significant overestimation of unilateral tumors while missing the true bilateral tumor extension.

Group A classified 27 patients preoperatively with bilateral prostate cancer (cT2c). These classified postoperatively: unilateral tumor: 0 patients (0%), bilateral tumor (pT2c): 13 patients (48,1%),

pT3a/b: 14 patients (51%). Group B classified 34 patients for bilateral tumor (cT2c), their postoperative stages were: unilateral tumor: 0 patients (0%), bilateral tumor (pT2c): 23 patients (68 %), pT3a/b: 11 patients (32%).

Both biopsy strategies revealed comparable results for the correct staging of bilateral tumor growth. However, again ultrasound only biopsy led to a significant underestimation of the true cancer extension, diagnosing cT2c while missing the advanced prostate cancer.

Preoperatively locally advanced tumor stages (cT3a/b) appeared also to be locally advanced in the postoperative classification with almost no downstaging in both groups (all data including p-values shown in Table 2).

4.5. Postoperative Positive Surgical Margins in pT2 Prostate Cancer

45 prostate cancer patients diagnosed with standard ultrasound-based biopsy (group A) were classified as pT2. Of these 38 were diagnosed to be R0 (85%) after surgery, while 7 patients revealed positive surgical margins leading to a pT2 R1 (15,5%) rate (Table 3).

29 prostate cancer patients diagnosed with targeted mpMRI-US fusion biopsy (group B) were classified as pT2. Of these 28 appeared to be R0 (96%). In 1 patients of this group a cancer positive surgical margin was found, leading to a pT2 R1 (3.4%) rate (Table 3).

Of the 7 patients with a R1 margin in group A, 5 were previously classified as unilateral tumors but turned out to be understaged compared to bilateral tumors (pT2c) on final histopathology, while 2 patients with R1 status were already pre-surgery correctly classified as bilateral tumors (cT2c), which was proven on final histopathology (pT2c) (Table 3). In 4 of the 5 patients that were preoperatively underestimated as unilateral tumors the positive surgical margin was located contralateral to the pre-surgery known tumor lesion.

Table 2: Correlation of preoperative clinical (cT) and postoperative pathological tumor stage (pT) after ultrasound only prostate biopsy (group A) and MRI-US fusion biopsy (group B).

	Overall	p12a/b	p12c	p13a/b
Group A c T2a/b (%)	n=45/79 (57%)	9/45 (20%)	23/45 (51%)	13/45 (29%)
Group B cT2a/b (%)	n=7/61 (11%)	4/7 (57%)	2/7 (29%)	1/7 (14%)
p-value	p<= 0.05	p<=0.05	p<= 0.05	p<= 0.05
Group A cT2c (%)	n=27/79 (34%)	0/27 (0%)	13/27 (48%)	14/27 (51 %)
Group B c12c (%)	n=34/61(56%)	0/34 (0%)	23/34 (68%)	11/34 (32 %)
p-value	p< = 0.05	p=1	p = 0.51	p<= 0.05
Group A cT3a/b (%)	n=8/79 (10%)	0/8 (0%)	1/8 (12%)	7/8 (88%)
Group B cT3a/b (%)	n=20/61 (33%)	0/20 (0%)	0/20(0%)	20/20 (100%)
p-value	p<= 0.05	p=1	p<=0.05	P= 0.48

Table 3: Correlation of preoperative clinical (cT), postoperative pathological tumor stage (pT) and tumor positive surgical margins (R-status) after ultrasound only prostate biopsy (group A) and MRI-US fusion biopsy (group B).

	pT2a/b R0	**pT2a/b R1**	**pT2c R0**	**pT2c R1**
Group A cT2a/b (n=32)	9/32 (28%)	0/32 (0%)	18/32 (56%)	5/32 (16%)
Group B cT2a/b (n=6)	4/6 (67%)	0 (0%)	2/6 (33%)	0 (0%)
Group A cT2c (n=13)	0 (0%)	0 (0%)	11 (85%)	2 (15%)
Group B cT2c (n=23)	0 (0%)	0 (0%)	22/23 (96%)	1/23 (4%)

5. Discussion

The goal of the RP is the eradication of cancer while, whenever possible, preserving pelvic organ function [1].

In order to decrease the rates of postoperative urinary incontinence and erectile dysfunction the intraoperative strategy often includes a preservation of anatomic structures such as cavernous nerves, urethra and bladder neck. Despite recent advantages in technology and the usage of robotic systems the preservation strategy bears a risk of tumor positive surgical margins [5]. However, postoperative outcome depends not only on the performance of the surgical process alone, it is rather a result of an optimal diagnostic-therapeutic chain. Therefore, an optimal preoperative tumor mapping including its exact localization in relationship to the surrounding anatomic structures appears to be a mandatory requisite for prostate cancer diagnostic. We therefore thought to evaluate the difference in the accuracy of prostate cancer staging according to the used biopsy technique. Moreover we assessed the meaning of a better preoperative cancer staging for postoperative pathological outcome in terms of R1 rates.

In the current literature as well as in the urological community the process of surgery performed by different surgeons with different surgical experience and intraoperative strategies appears to have a much greater influence on the postoperative tumor stage and R-rates compared to the used techniques of the preoperative diagnostic evaluation. However, the specific setup in our institution with one experienced open and robotic surgeon operating patients coming from two different urological centers using different biopsy strategies allowed us to evaluate the difference of the two different diagnostic backgrounds (ultrasound versus mpMRI-US fusion biopsy). Importantly patients from both urological centers (A and B) had comparable patient and tumor characteristic, all patients received preoperative MRI in the same department of radiology, all biopsies were performed by senior consultants of urology and specimen were analyzed by the same department of pathology in order to minimize additional bias. Conventional ultrasound guided biopsy resulted in a significantly higher number of unilateral classified tumors compared to mpMRI-US fusion biopsy (group A: 45 patients (56,9 %) versus group B: 7 patients (11,4%)).

However, the classification of a unilateral tumor using ultrasound guided biopsy was only in 20% of the cases correct. In 80% final histopathology revealed a bilateral tumor stage (≥ pT2c), therefore substantially understaging the true tumor localization and dimension. In contrast the problem of understaging an unilateral tumor was significantly less after MRI-Ultrasound fusion biopsy as 57% resulted correctly in a postoperative unilateral tumor stage, while 28% of the unilateral tumor were understaged and appeared to be bilateral tumors (pT2c). The reason for substantial understaging after ultrasound only biopsy is most probably the consultants focusing on the MRI described lesion during prostate biopsy while the surrounding tissue and especially the contralateral side is bioptically underrepresented. The significant less tumor cores taken during ultrasound only diagnostics compared to the mpMRI-US fusion biopsy could back up this assumption. The same pattern of underestimation was found in the group with bilateral tumor growth (pT2c). Both techniques revealed statistically comparable results for the correct tumor stage prediction. However, ultrasound only biopsies again revealed a significant underestimation of the true tumor extend, in this case locally advanced cancer involving the seminal vesicles (pT3a/b), which is an information of utmost importance for the surgical strategy. The difference might be explainable by the template biopsies pre-selected by the Artemis device including the prostatic base allowing for a more precise diagnostic of a possible cT3b stage. Interestingly, ultrasound guided biopsy missed 11% of locally advance prostate cancer involving the seminal vesicles (pT3b), while all these cases were correctly staged in the mpMRI-US fusion biopsy group (0%). This underestimation might be due to the known limitations of ultrasound only biopsies at the base and anterior aspect of the prostate. The correct classification of a uni- versus bilateral tumor stage or even locally advanced tumor instead of a localized tumor is a valuable preoperative information that certainly leads to change of the nerve sparing strategy.

Most important postoperative surgical margins appeared to be significantly higher in the ultrasound only group (15.5%) compared mpMRI-US fusion biopsy group (4%). In detail 5 out of 7 patients with a positive surgical margin appeared to be underestimated in the previous biopsy by using ultrasound only as they were classified with unilateral tumor but revealed bilateral tumor growth in final histology (pT2c). The positive margins in 4 out of these 5 patients were on the contralateral side of the pre-surgery describe tumor lesion. We postulate that a more accurate preoperative knowledge of a bilateral tumor instead the presumed unilateral tumor could have prevented the R1 situation during the attempt of the maximal contralateral nerve sparing in order to achieve optimal clinical outcome.

Of course, the retrospective and non-randomized nature of the study limits the conclusion. Moreover, the low numbers of the analyzed also limits statistical power. Nevertheless, our institutional quality analysis indicates that the technique used for the pre-operative diagnostic of prostatic cancer may not only have an impact on preoperative staging accuracy but also on postoperative R-status. As a consequence, it dramatically influenced our diagnostic-therapeutic pathway. We now almost exclusively perform mpMRI-US fusion biopsy. In case of an ultrasound only diagnostic template biopsies including the base and anterior aspect of the prostate sent separately for histopathology are mandatory. Especially unilateral tumor cases are reviewed according to the quality of the preoperative biopsies before surgery as there is a greater chance of underestimation the real tumor dimension and number of lesions in this typically multifocal tumor. Whether this strategy will in future decrease accidental R1 rates while trying to achieve maximal nerve sparing is up to a planned prospective randomized trial.

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